STAVROS·NIARCHOS·FOUNDATION
BIOETHICS·ACADEMY

2019
Course Materials

JOHNS HOPKINS
BERMAN INSTITUTE
of BIOETHICS

ETH zürich

TABLE OF CONTENTS

Agenda

Day 1: Thursday, June 20, 2019

8:30-9:00	**Registration**
9:00-9:15	**Welcome** **Jeffrey Kahn and Effy Vayena**
9:15-9:45	**Introduction of participants**
9:45-10:15	**Bioethics in Greece** **Ismini Kriari, PhD** Panteion University
10:15-11:15	**Principles of Bioethics** **Tom Beauchamp, PhD** Georgetown University (Emeritus)
11:15-11:30	**COFFEE BREAK**
11:30-12:30	**Ethics and Research with Human Subjects** **Ruth Faden, PhD, MPH** Johns Hopkins Berman Institute of Bioethics
12:30-13:30	**Small Group Discussion**
13:30-14:30	**LUNCH BREAK**
14:30-15:30	**Ethics and Research on Laboratory Animals** **Jeffrey Kahn, PhD, MPH** Johns Hopkins Berman Institute of Bioethics
15:30-15:40	**Regulatory Framework of Laboratory Animal Use in Greece** **Nikolaos Kostomitsopoulos, DVM, PhD** Biomedical Research Foundation of the Academy of Athens
15:40-16:40	**Small Group Discussion**
17:00-18:00	**Digital Tool Demonstration** **Joanna Sleigh,** ETH Zurich

WELCOME RECEPTION AND DINNER AT SNFCC

Day 2: Friday, June 21, 2019

9:00-10:00 **Ethics and Genetics Research**
Effy Vayena, PhD Health Ethics and Policy Lab, Swiss Federal Institute of Technology, Zurich

10:00-10:10 **Biobanking Landscape in Greece**
Olga Tzortzatou, PhD Biomedical Research Foundation of the Academy of Athens

10:10-11:10 **Small Group Discussion**

11:10-11:30 **COFFEE BREAK**

11:30-12:30 **Ethics and Stem Cell Research**
Jeremy Sugarman, MD, MA, MPH Johns Hopkins Berman Institute of Bioethics

12:30-13:30 **Small Group Discussion**

13:30-15:00 **LUNCH BREAK**

15:00-17:30 **Film Screening and Discussion**

17:30 **Reception**
Buffet Dinner and Networking

Day 3: Saturday, June 22, 2019

Panel Presentations—Late-Breaking Topics

9:00-10:30 **Mitochondria Replacement Techniques/CRISPR** (Jeffrey Kahn and Jeremy Sugarman)**/Digital Health Information** (Effy Vayena/Alessandro Blasimme)

11:00-12:00 **Infectious Disease Research Involving Pregnant Women** (Ruth Faden)**/Payments for Research Participants** (Tom Beauchamp)

12:00-12:45 **Panel and Final Plenary Discussion**
Research Ethics in Greece—Needs and Next Steps
Panelists: Stavroula Tsinorema, Helen Rethimiotaki, Evangelos Protopapadakis
Moderator: Effy Vayena

CLOSING AND AWARDING OF CERTIFICATES

Course Materials

Principles of Bioethics

Tom Beauchamp

Required Reading

Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics*, 7th edition (Oxford University Press, 2013), especially chaps. 1-2, 10.

John-Stewart Gordon, Oliver Rauprich, and Jochen Vollman, "Applying the Four-Principle Approach," *Bioethics* 25 (2011): 293–300, with a reply by Tom Beauchamp, "Making Principlism Practical: A Commentary on Gordon, Rauprich, and Vollmann," *Bioethics* 25 (2011): 301–03.

Søren Holm, "Not Just Autonomy—The Principles of American Biomedical Ethics," *Journal of Medical Ethics* 21 (1994): 332-38.

Suggested Further Reading

John Arras, "Theory and Bioethics," *The Stanford Encyclopedia of Philosophy* (Winter 2016 edition; first published 2010), ed. Edward N. Zalta, available at https://plato.stanford.edu/archives/win2016/entries/theory-bioethics/ (retrieved April 27, 2018).

Tom L. Beauchamp, "Principlism and Its Alleged Competitors," *Kennedy Institute of Ethics Journal* 5 (1995): 181-198.

Tom L. Beauchamp, *Standing on Principles: Collected Essays* (New York: Oxford University Press, 2010), especially chaps. 1–2.

David DeGrazia, "Common Morality, Coherence, and the Principles of Biomedical Ethics," *Kennedy Institute of Ethics Journal* 13 (2003): 219–30.

David DeGrazia and Tom L. Beauchamp, "Philosophical Methods," in *Methods of Bioethics,* 2nd edition, ed. Daniel Sulmasy and Jeremy Sugarman (Washington, DC: Georgetown University Press, 2010), pp. 37-53.

Bernard Gert (and subsequently revised by Joshua Gert), "The Definition of Morality," *The Stanford Encyclopedia of Philosophy* (Fall 2017 Edition), ed. Edward N. Zalta, available at https://plato.stanford.edu/archives/fall2017/entries/morality-definition/ (accessed April 20, 2018).

Bernard Gert, Charles M. Culver, and K. Danner Clouser, *Bioethics: A Return to Fundamentals,* 2nd ed. (New York: Oxford University Press, 2006), chap. 4.

Peter Herissone-Kelly, “The Principlist Approach to Bioethics, and Its Stormy Journey Overseas,” in *Scratching the Surface of Bioethics,* ed. Matti Häyry and Tuija Takala (Amsterdam: Rodopi, 2003), pp. 65–77.

Rebecca Kukla, “Living with Pirates: Common Morality and Embodied Practice,” *Cambridge Quarterly of Healthcare Ethics* 23 (2014): 75-85.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (Washington, DC: DHEW Publication OS 78–0012, 1978).

Oliver Rauprich, “Common Morality: Comment on Beauchamp and Childress,” *Theoretical Medicine and Bioethics* 29 (2008): 43-71.

Henry S. Richardson, “Specifying, Balancing, and Interpreting Bioethical Principles,” *Journal of Medicine and Philosophy* 25 (2000): 285–307, also in *Belmont Revisited: Ethical Principles for Research with Human Subjects,* ed. James F. Childress, Eric M. Meslin, and Harold T. Shapiro (Washington, DC: Georgetown University Press, 2005), pp. 205–27.

Outline

UNIVERSAL PRINCIPLES AND COMMON MORALITY IN BIOMEDICAL ETHICS

Tom L. Beauchamp

1. Principlism as a Theory about Universal Moral Principles

A. My collaborative work on moral principles with James Childress
B. Principles are not absolute or categorical imperatives
C. What is universal morality? The main areas in which it is found are:
    i. Principles of obligation
    ii. Human rights
    iii. Virtues
D. Universal standards are not mere cultural standards

2. Principlism's Framework of Universal Principles

Four clusters of basic moral principles serve as the moral framework:

1. Respect for autonomy (a principle requiring respect for the decisions and decision-making capacities of autonomous persons),
2. Nonmaleficence (a principle requiring the avoidance of causing harm to others),
3. Beneficence (a group of principles requiring both lessening of and prevention of harm as well as provision of benefits to others and balancing benefits, burdens, and risks), and
4. Justice (a group of principles requiring fair distribution of benefits and burdens across all affected parties).

3. Common Morality as the Source of Universal Principles

A. The Larger Body of Universal Moral Requirements: Common Morality
B. All impartial and morally committed persons accept these norms.
C. Principlism Identifies only a slice of the universal common morality
D. Principlism *draws its principles from* the common morality to construct a normative framework *for biomedical ethics*.
E. By contrast, Bernard Gert and Rebecca Kukla, present truly bold universalist theories for bioethics.
F. Childress and I defend the Thesis that universal common morality *includes* our principles, whatever else it may contain.

4. Does European Bioethics Need a Different Framework of Principles?

A. The Question: Are frameworks of general principles relative to *cultures*?

B. Some European critics see a quaintly American point of view at work.

i) Søren Holm's theory of cultural moralities in Europe

ii) Peter Kemp and Jacob Rendtorff's theory of basic European Principles [a competitor framework of principles for bioethics]:

1. Respect for Autonomy
2. Dignity
3. Integrity
4. Vulnerability

C. Conclusion: These proposed European principles are not well-conceived for Europe or for any other cultural context—although Holm's view that the principles can be applied in different ways in different countries in Europe is correct.

1. Does "Eastern Ethics" Rest on Different Cultural Principles than "Western Ethics"?

A. Does Asia have fundamentally different moral traditions of principles?

B. Amartya Sen's views on "Human Rights and Asian Values."

C. Do any "quintessential [moral] values" *differentiate* Asians as a group?

D. Are community and family relationships valued more highly in Asia?

2. The Global Reach of Principles & Rules of Research Ethics

A. 40 years ago no universally accepted principles of research ethics existed.

B. Today we find a sea of similarity in countries on every continent.

C. Today's rules are grounded in universal moral principles.

D. Examples: Requirements to disclose all material information to subjects; requirements to obtain individual, voluntary, informed consent; requirements to protect subjects in research against excessive and unnecessary risk; and requirements that ethics review committees critically assess and approve research protocols.

3. Conclusion

More than any other part of moral discourse, universal principles and their correlative human rights cross international boundaries and form the basis of a global bioethics.

<PN>Part I</PN>

<PT>Moral Foundations</PT>

<CN>1</CN>

<CT>Moral Norms</CT>

In the last third of the twentieth century, major developments in the biological and health sciences and in biomedical technology strikingly challenged traditional professional ethics in much of clinical medicine, nursing, and biomedical and behavioral research.[1] Despite a remarkable continuity in medical ethics across millennia, the widely-revered Hippocratic tradition could not adequately address many modern concerns such as informed consent, privacy, access to health care, communal and public health responsibilities, and research involving human subjects. Professional ethics was also ill equipped to provide an adequate framework for public policy in a pluralistic society.

In this book we acknowledge and draw from the great traditions of medical ethics,[2] but we also draw from philosophical reflections on morality. This approach helps us to examine and, where appropriate, challenge common assumptions in the biomedical sciences, health care, and public health.

<1>NORMATIVE AND NONNORMATIVE ETHICS</1>

The term *ethics* needs attention before we turn to the meanings of *morality* and *professional ethics. Ethics* is a generic term covering several different ways of examining and interpreting the moral life. Some approaches to ethics are normative, others nonnormative.

<2>Normative Ethics</2>

General normative ethics addresses the question, "Which general moral norms should we use to guide and evaluate conduct, and why?" Ethical theories seek to identify and justify these norms, which are often referred to as principles, rules, rights, or virtues. In Chapter 9 we examine several types of general normative ethical theory and offer criteria for assessing them.

Many practical questions would remain unanswered even if a fully satisfactory general ethical theory were available. The term *practical ethics,* as used here, is synonymous with *applied ethics* and stands in contrast to *theoretical ethics*.[3] It refers to the use of moral concepts and norms when deliberating about moral problems, practices, and policies in professions, institutions, and public policy. Often no direct movement from general norms,

precedents, or theories to particular judgments is possible. General norms are usually only starting points for the development of more specific norms of conduct suitable for contexts such as clinical medicine and biomedical research. Throughout this book we address how to move from general norms to specific norms and particular judgments and from theory to practice.

<*2*>**Nonnormative Ethics**<*/2*>

Two types of nonnormative ethics are distinguishable. The first is *descriptive ethics,* which is the factual investigation of moral beliefs and conduct. It often uses scientific techniques to study how people reason and act. For example, anthropologists, sociologists, psychologists, and historians determine which moral norms are expressed in professional practice, in professional codes, in institutional mission statements and rules, and in public policies. They study phenomena such as surrogate decision making, treatment of the dying, the use of vulnerable populations in research, how consents are obtained from patients, and refusal of treatment by patients.

The second type of nonnormative ethics is *metaethics,* which involves analysis of the language, concepts, and methods of reasoning in normative ethics.[4] For example, metaethics addresses the meanings of terms such as *right,*

obligation, virtue, justification, morality, and *responsibility.* It is also concerned with moral epistemology (the theory of moral knowledge), the logic and patterns of moral reasoning and justification, and the nature and possibility of moral truth. Whether morality is objective or subjective, relative or nonrelative, and rational or nonrational are prominent questions in metaethics.

Descriptive ethics and metaethics are nonnormative because their objective is to establish what factually or conceptually *is* the case, not what ethically *ought to be* the case or what is ethically *valuable.* For example, in this book we often rely on reports in descriptive ethics when investigating the nature of professional conduct and codes of ethics, current forms of access to health care, and physician attitudes toward hastening the deaths of patients who have requested aid in dying. In these investigations we are interested in how such descriptive information assists in determining which practices are morally justifiable as well as in resolving other normative issues.

<1>THE COMMON MORALITY AS UNIVERSAL MORALITY</1>

In its most familiar sense, the word *morality* (a broader term than *common morality,* which is discussed immediately below in the section on "The Nature of the Common Morality," and in more detail in Chapter 10, pp. •••–•••) refers

to norms about right and wrong human conduct that are widely shared and form a stable societal compact. As a social institution, morality encompasses many standards of conduct, including moral principles, rules, ideals, rights, and virtues. We learn about morality as we grow up, and we learn to distinguish between the part of morality that holds for everyone and moral norms that bind only members of specific communities or special groups such as physicians, nurses, or public health officials.

<2>**The Nature of the Common Morality**</2>

Some core tenets found in every acceptable particular morality are not relative to cultures, groups, or individuals. All persons living a moral life know and accept rules such as not to lie, not to steal others' property, not to punish innocent persons, not to kill or cause harm to others, to keep promises, and to respect the rights of others. All persons committed to morality do not doubt the relevance and importance of these universally valid rules. Violation of these norms is unethical and will generate feelings of remorse. The literature of biomedical ethics virtually never debates the merit or acceptability of these central moral norms. Debates do occur, however, about their precise meaning, scope, weight, and strength, often in regard to hard moral cases or current

practices that merit careful scrutiny—such as when, if ever, physicians may justifiably withhold some aspects of a diagnostic finding from their patients.

We call the set of universal norms shared by all persons committed to morality *the common morality.* This morality is not merely *a* morality, in contrast to other moralities.[5] It is applicable to all persons in all places, and we appropriately judge all human conduct by its standards. The following norms are examples (far from a complete list) of generally binding *standards of action* (that is, rules of obligation) found in the common morality: (1) Do not kill, (2) Do not cause pain or suffering to others, (3) Prevent evil or harm from occurring, (4) Rescue persons in danger, (5) Tell the truth, (6) Nurture the young and dependent, (7) Keep your promises, (8) Do not steal, (9) Do not punish the innocent, and (10) Obey just laws.

The common morality also contains standards other than obligatory rules of conduct. Here are ten examples of *moral character traits,* or virtues, recognized in the common morality (again, not a complete list): (1) nonmalevolence (not harboring ill will toward others), (2) honesty, (3) integrity, (4) conscientiousness, (5) trustworthiness, (6) fidelity, (7) gratitude, (8) truthfulness, (9) lovingness, and (10) kindness. These virtues are universally admired traits of character.[6] A person is deficient in moral character if he or she

lacks such traits. Negative traits that are the opposite of these virtues are *vices* (for example, malevolence, dishonesty, lack of integrity, cruelty, etc.). They are universally recognized as substantial moral defects. In this chapter we will say nothing further about moral character and the virtues and vices, because they are investigated in both Chapter 2 and a major section of Chapter 9 (pp. •••–•••,•••–•••).

In addition to the obligations and virtues just mentioned, the common morality supports *human rights* and endorses *moral ideals* such as charity and generosity. Philosophers debate whether one of these regions of the moral life—obligations, rights, or virtues—is more basic or more valuable than another, but in the common morality there is no reason to give primacy to any one area or type of norm. For example, human rights are not more basic than moral virtues in universal morality, and moral ideals should not be downgraded morally merely because people are not obligated to conform to them. An undue emphasis on any one of these areas or types of norms disregards the full scope of morality.[7]

Our account of universal morality in this chapter and Chapter 10 does not conceive of the common morality as ahistorical or a priori.[8] This problem in moral theory cannot be adequately engaged until our discussions in Chapter 10,

and we offer now only three clarifications of our position: First, the common morality is a product of human experience and history and is a universally shared product. The origin of the norms of the common morality is no different in principle from the origin of the norms of a particular morality for a medical or other profession. Both are learned and transmitted in communities. The primary difference is that the common morality has authority in all communities, whereas particular moralities are authoritative only for specific groups. Second, we accept moral pluralism in *particular* moralities, as discussed later in this chapter (pp. •••–•••), but we reject moral pluralism, understood as relativism, in the *common* morality. (See the section in Chapter 10 on "Moral Change" for further clarification.) No particular moral way of life qualifies as morally acceptable unless it conforms to the standards in the common morality. Third, the common morality comprises moral *beliefs* (what all morally committed persons believe), not timeless, detached standards that exist independently of moral beliefs. Every *theory* of the common morality likewise has a history of development by the author(s) of the theory.

<*2*>**Ways to Examine the Common Morality**</*2*>

Various statements about or references to the common morality might be

understood as normative, nonnormative, or possibly both. If the appeals are normative, the claim is that the common morality has normative force: It establishes moral standards for everyone, and violating these standards is unethical. If the references are nonnormative, the claim is that we can empirically study whether the common morality is present in all cultures. We accept both the normative force of the common morality and the objective of studying it empirically.

Some critics of our theory of the common morality (see Chapter 10) have asserted that scant anthropological or historical evidence supports the empirical hypothesis that a universal common morality exists.[9] Accordingly, they think we need to consider how good the evidence is both for and against the existence of a universal common morality. This problem is multifaceted and difficult to address, but in principle, scientific research could either confirm or falsify the hypothesis of a universal morality. It would be absurd to assert that all persons do in fact accept the norms of the common morality, because many amoral, immoral, or selectively moral persons do not care about or identify with its moral demands. Our hypothesis is that all persons *committed to morality* accept the standards in the common morality.

We explore this hypothesis about the empirical study of the common

morality in Chapter 10 (pp. •••–•••). Here we note only that when we claim that the normative judgments found in many parts of this book are derived from the common morality, we are not asserting that our theory of the common morality gets the common morality perfectly right or that it interprets or extends the common morality in just the right ways. No doubt, there are dimensions of the common morality that we do not correctly capture or depict; and there are many parts of the common morality that we do not even address.[10] When we attempt to build on the common morality in this book by using it as a basis for critically examining problems of biomedical ethics, we do not mean to imply that our extensions can validly claim the authority of the common morality at every level of our interpretation of this morality.

<1>PARTICULAR MORALITIES AS NONUNIVERSAL</1>

We shift now from universal morality (the common morality) to particular moralities, which contain moral norms that are not shared by all cultures, groups, and individuals who are committed to morality.

<2>The Nature of Particular Moralities</2>

Whereas the common morality contains moral norms that are abstract,

universal, and content-thin (such as "Tell the truth"), particular moralities present concrete, nonuniversal, and content-rich norms (such as "Make conscientious oral disclosures to, and obtain a written informed consent from, all human research subjects"). Particular moralities are distinguished by the specificity of their norms, but these norms are not morally justified if they violate norms in the common morality. Specific moralities include the many responsibilities, aspirations, ideals, sentiments, attitudes, and sensitivities found in diverse cultural traditions, religious traditions, professional practice, and institutional guides. Explication of the values in these moralities sometimes requires a special knowledge and may involve refinement by experts or scholars over centuries—as, for example, in the body of Jewish religious, legal, and moral norms in the Talmudic tradition; well-structured moral systems to provide methods for judgments and to adjudicate conflicts in Roman Catholic casuistry; and Islamic reliance on Shari'ah-based principles. Each tradition continues today to elaborate its commitments through the development of detailed, and hopefully coherent systems of medical ethics. These elaborations are often derived from the common morality, not merely from the scriptures of a particular religious tradition.

Professional moralities, which include moral codes and standards of

practice, are also particular moralities. They may legitimately vary from other moralities in the ways they handle certain conflicts of interest, research protocol reviews, advance directives, and similar matters. (See the next section below on "Professional and Public Moralities.") *Moral ideals* such as charitable goals and aspirations to rescue suffering persons in dangerous situations provide another instructive example of facets of particular moralities. By definition, moral ideals such as charitable beneficence are not morally *required* of all persons; indeed, they are not required of any person.[11] Persons who fail to fulfill even their own personal ideals cannot be blamed or criticized by others. These ideals may nonetheless be critically important features of personal or communal moralities. Examples are found in physicians' individual commitments or physician codes that call for assumption of a significant level of risk in circumstances of communicable disease. It is reasonable to presume that all morally committed persons share an admiration of and endorsement of moral ideals of generosity and service, and in this respect these ideals are part of shared moral beliefs in the common morality; they are universally *praiseworthy* even though not universally *required* or universally *practiced*. When such ideals are regarded by those who embrace them as obligations (as they are, for example, in some monastic traditions), the obligations are still parts of a

particular morality, not of universal morality.

Persons who accept a particular morality sometimes presume that they can use this morality to speak with an authoritative moral voice for all persons. They operate under the false belief that their particular convictions have the authority of the common morality. These persons may have morally acceptable and even praiseworthy beliefs, but their particular beliefs do not bind other persons or communities. For example, persons who believe that scarce medical resources, such as transplantable organs, should be distributed by lottery rather than by medical need may have good moral reasons for their views, but they cannot claim that their views are supported by the common morality.

<*2*>**Professional and Public Moralities**<*/2*>

Just as the common morality is accepted by all morally committed persons, most professions have, at least implicitly, a professional morality with standards of conduct that are generally acknowledged and encouraged by those in the profession who are serious about their moral responsibilities. In medicine, professional morality specifies general moral norms for the institutions and practices of medicine. Special roles and relationships in medicine derive from rules or traditions that other professions will likely not need or accept. As we

argue in Chapters 4 and 8, rules of informed consent and medical confidentiality may not be serviceable or appropriate outside of medicine, nursing, biomedical research, and public health, but these rules are justified by general moral requirements of respecting the autonomy of persons and protecting them from harm.

Members of professions often adhere to moral guidelines such as rules prohibiting discrimination against colleagues on the basis of gender, race, religion, or national origin (some of these guidelines now have legal backing). In recent years formal codifications of and instruction in professional morality have increased through codes of medical and nursing ethics, codes of research ethics, corporate policies of bioethics, institutional guidelines governing conflict of interest, and the reports and recommendations of public commissions. Before we assess these guidelines, the nature of professions in general needs brief discussion.

In a classic work on the subject, Talcott Parsons defines a profession as "a cluster of occupational roles, that is, roles in which the incumbents perform certain functions valued in the society in general, and, by these activities, typically earn a living at a full-time job."[12] Under this definition, circus performers, exterminators, and garbage collectors are professionals. It is not

surprising to find all such activities characterized as professions, inasmuch as the word *profession* has come, in common use, to mean almost any occupation by which a person earns a living. The once honorific sense of *profession* is now better reflected in the term *learned profession,* which assumes an extensive education in the arts, humanities, law, sciences, or technologies.

Professionals are usually distinguished by their specialized knowledge and training as well as by their commitment to provide important services or information to patients, clients, students, or consumers. Professions maintain self-regulating organizations that control entry into occupational roles by formally certifying that candidates have acquired the necessary knowledge and skills. In learned professions such as medicine, nursing, and public health, a professional's background knowledge is partly acquired through closely supervised training, and the professional is committed to providing a service to others.

Health care professions specify and enforce obligations for their members, thereby seeking to ensure that persons who enter into relationships with these professionals will find them competent and trustworthy.[13] The obligations that professions attempt to enforce are determined by an accepted role. These obligations comprise the "ethics" of the profession, although there

may also be role-specific customs such as self-effacement that are not obligatory. Problems of professional ethics commonly arise either from conflicts over appropriate professional standards or conflicts between professional commitments and the commitments professionals have outside the profession.

Because traditional standards of professional morality are often vague, some professions codify their standards in detailed statements aimed at reducing vagueness and improving adherence. Their codes sometimes specify rules of etiquette in addition to rules of ethics. For example, a historically significant version of the code of the American Medical Association (AMA) dating from 1847 instructed physicians not to criticize fellow physicians who had previously been in charge of a case.[14] Such professional codes tend to foster and reinforce member identification with the prevailing values of the profession. These codes are beneficial when they effectively incorporate defensible moral norms, but some codes oversimplify moral requirements, make them indefensibly rigid, or make excessive and unwarranted claims about their completeness and authoritativeness. As a consequence, professionals may mistakenly suppose that they are satisfying all relevant moral requirements by scrupulously following the rules of the code, just as some people believe that

they fully discharge their moral obligations when they meet all relevant legal requirements.

We can and should ask whether the codes specific to areas of science, medicine, nursing, health care, and public health are coherent, defensible, and comprehensive within their domain. Historically, few codes had much to say about the implications of several pivotal moral principles and rules such as veracity, respect for autonomy, and social justice that have been the subjects of intense discussion in recent biomedical ethics. From ancient medicine to the present, physicians have generated codes without determining their acceptability to patients and the public. These codes have rarely appealed to general ethical standards or to a source of moral authority beyond the traditions and judgments of physicians themselves.[15] The articulation of such professional norms has often served more to protect the profession's interests than to offer a broad and impartial moral viewpoint or to address issues of importance to patients and society.[16]

Psychiatrist Jay Katz poignantly expressed reservations about traditional principles and codes of medical ethics. Initially inspired by his outrage over the fate of Holocaust victims at the hands of German physicians, Katz became convinced that a professional ethics that reaches beyond traditional codes is

indispensable:

> <EXT>As I became increasingly involved in the world of law, I learned much that was new to me from my colleagues and students about such complex issues as the right to self-determination and privacy and the extent of the authority of governmental, professional, and other institutions to intrude into private life. . . . These issues . . . had rarely been discussed in my medical education. Instead it had been all too uncritically assumed that they could be resolved by fidelity to such undefined principles as *primum non nocere* ["First, do no harm"] or to visionary codes of ethics.[17]</EXT>

<*2*>**The Regulation and Oversight of Professional Conduct**<*/2*>

Additional moral direction for health professionals and scientists comes through the public policy process, which includes regulations and guidelines promulgated by governmental bodies. The term *public policy* refers to a set of normative, enforceable guidelines adopted by an official public body, such as an agency of government or a legislature, to govern a particular area of conduct. The policies of corporations, hospitals, trade groups, and professional societies are private, not public, even if these bodies are regulated to some degree by

public policies and sometimes have an impact on public policy.

A close connection exists between law and public policy: All laws constitute public policies, but not all public policies are, in the conventional sense, laws. In contrast to laws, public policies need not be explicitly formulated or codified. For example, an official who decides not to fund a newly recommended government program with no prior history of funding is formulating a public policy. Decisions not to act, as well as decisions to act, can constitute policies.

Policies such as those that fund health care for the indigent or that protect subjects of biomedical research regularly incorporate moral considerations. Moral analysis is part of good policy formation, not merely a method for evaluating existing policy. Efforts to protect the rights of patients and research subjects are instructive examples. Over the past few decades many governments have created national commissions, national review committees, advisory committees, and councils to formulate guidelines for research involving human subjects, for the distribution of health care, and for addressing moral mistakes made in the health professions. Morally informed policies have guided decision making about other areas of practice as well. The relevance of bioethics to public policy is now recognized in most countries, some of which have

influential standing bioethics committees.[18]

Many courts have developed case law that sets standards for science, medicine, and health care. Legal decisions often express communal moral norms and stimulate ethical reflection that over time alters those norms. For example, the lines of court decisions in many countries about how dying patients may be or must be treated have constituted nascent traditions of moral reflection that have been influenced by, and in turn have influenced, literature in biomedical ethics on topics such as when artificial devices that sustain life may be withdrawn, whether medically administered nutrition and hydration is a medical treatment that may be discontinued, and whether physicians may be actively involved in hastening a patient's death at the patient's request.

Policy formation and criticism generally involve more specific moral judgments than the judgments found in general ethical theories, principles, and rules.[19] Public policy is often formulated in contexts that are marked by profound social disagreements, uncertainties, and differing interpretations of history. No body of abstract moral principles and rules can fix policy in such circumstances, because abstract norms do not contain enough specific information to provide direct and discerning guidance. The implementation of moral principles and rules, through specification and balancing, must take into

account factors such as feasibility, efficiency, cultural pluralism, political procedures, pertinent legal requirements, uncertainty about risk, and noncompliance by patients. Moral principles and rules provide a normative structure for policy formation and evaluation, but policies are also shaped by empirical data and information generated in fields such as medicine, nursing, public health, veterinary science, economics, law, biotechnology, and psychology.

When using moral norms to formulate or criticize public policies, one cannot move with assurance from a judgment that an *act* is morally right (or wrong) to a judgment that a corresponding *law* or *policy* is morally right (or wrong). Considerations such as the symbolic value of law and the costs of a publicly funded program and its enforcement often may have substantial importance for law and policy. The judgment that an act is morally wrong does not entail the judgment that the government should prohibit it or refuse to allocate funds to support it. For example, one can argue without any inconsistency that sterilization and abortion are morally wrong but that the law should not prohibit them, because they are fundamentally matters of personal choice beyond the legitimate reach of government (or, alternatively, because many persons would seek dangerous and unsanitary procedures from unlicensed

practitioners). Similarly, the judgment that an act is morally acceptable does not imply that the law should permit it. For example, the belief that euthanasia is morally justified for some terminally ill infants who face uncontrollable pain and suffering is consistent with the belief that the government should legally prohibit such euthanasia on grounds that it would not be possible to control abuses if it were legalized.

We are not defending any of these moral judgments. We are maintaining only that the connections between moral norms and judgments about policy or law are complicated and that a judgment about the morality of particular actions does not entail a comparable judgment about law or policy.

<1>Moral Dilemmas</1>

Common to all forms of practical ethics is reasoning through difficult cases, some of which constitute dilemmas. This is a familiar feature of decision making in morality, law, and public policy. Consider a classic case[20] in which judges on the California Supreme Court had to reach a decision about the legal force and limits of medical confidentiality. A man had killed a woman after confiding to a therapist his intention to do so. The therapist had attempted unsuccessfully to have the man committed but, in accordance with his duty of

medical confidentiality to the patient, did not communicate the threat to the woman when the commitment attempt failed.

The majority opinion of the Court held that "When a therapist determines, or pursuant to the standards of his profession should determine, that his patient presents a serious danger of violence to another, he incurs an obligation to use reasonable care to protect the intended victim against such danger." This obligation extends to notifying the police and also to warning the intended victim. The justices in the majority opinion argued that therapists generally ought to observe the rule of medical confidentiality, but that the rule must yield in this case to the "public interest in safety from violent assault." These justices recognized that rules of professional ethics have substantial public value, but they held that matters of greater importance, such as protecting persons against violent assault, can override these rules.

In a minority opinion, a judge disagreed and argued that doctors violate patients' rights if they fail to observe standard rules of confidentiality. If it were to become common practice to break these rules, he reasoned, the fiduciary nature of the relationship between physicians and patients would erode. Persons who are mentally ill would refrain from seeking aid or divulging critical information because of the loss of trust that is essential for effective treatment.

This case presents moral and legal dilemmas in which the judges cite relevant reasons to support their conflicting judgments.[21] Moral dilemmas are circumstances in which moral obligations demand or appear to demand that a person adopt each of two (or more) alternative but incompatible actions, such that the person cannot perform all the required actions. These dilemmas occur in at least two forms.[22] (1) Some evidence or argument indicates that an act is morally permissible and some evidence or argument indicates that it is morally wrong, but the evidence or strength of argument on both sides is inconclusive. Abortion, for example, may present a terrible dilemma for women who see the evidence in this way. (2) An agent believes that, on moral grounds, he or she is obligated to perform two or more mutually exclusive actions. In a moral dilemma of this form, one or more moral norms obligate an agent to do *x* and one or more moral norms obligate the agent to do *y,* but the agent cannot do both in the circumstance. The reasons behind alternatives *x* and *y* are weighty and neither set of reasons is overriding. If one acts on either set of reasons, one's actions will be morally acceptable in some respects and morally unacceptable in others. The withdrawal of life-prolonging therapies from patients suffering from a wakeful unconscious state (formerly called a persistent, continuing, or continuous vegetative state) is sometimes regarded as

an instance of this second form of dilemma.

Popular literature, novels, and films often illustrate how conflicting moral principles and rules create difficult dilemmas. For example, an impoverished person who steals from a grocery store to save a family from starvation confronts such a dilemma. The only way to comply with one obligation is to contravene another obligation. Some obligation must be overridden or compromised no matter which course is chosen. From the perspective we defend, it is confusing to say that we are obligated to perform both actions in these dilemmatic circumstances. Instead, we should discharge the obligation that we judge to override what we would have been firmly obligated to perform were it not for the conflict.

Conflicts between moral requirements and self-interest sometimes create a *practical* dilemma, but not, strictly speaking, a *moral* dilemma. If moral reasons compete with nonmoral reasons, such as self-interest, questions about priority can still arise even though no moral dilemma is present. When a moral reason conflicts with a personal reason, the moral reason is not always overriding. If, for example, a physician must choose between saving his or her own life or that of a patient, in a situation of extreme scarcity of available drugs, the moral obligation to take care of the patient may not be overriding.

Some moral philosophers and theologians have argued that although many practical dilemmas involving moral reasons exist, no irresolvable moral dilemmas exist. They do not deny that agents experience moral perplexity or conflict in difficult cases. However, they claim that the purpose of a moral theory is to provide a principled procedure for resolving deep conflicts. Some philosophers have defended this conclusion because they accept one supreme moral value as overriding all other conflicting values (moral and nonmoral) and because they regard it as incoherent to allow contradictory obligations in a properly structured moral theory. The only *ought,* they maintain, is the one generated by the supreme value.[23] (We examine such theories, including both utilitarian and Kantian theories, in Chapter 9.)

In contrast to the account of moral obligation offered by these theories, we maintain throughout this book that various moral principles, rules, and rights can and do conflict in the moral life. These conflicts sometimes produce irresolvable moral dilemmas. When forced to a choice, we may "resolve" the situation by choosing one option over another, but we also may believe that neither option is morally preferable. A physician with a limited supply of medicine may have to choose to save the life of one patient rather than another and still find his or her moral dilemma irresolvable. Explicit acknowledgment

of such dilemmas helps deflate unwarranted expectations about what moral principles and theories can do. Although we find ways of reasoning about what we should do, we may not be able to reach a reasoned resolution in many instances. In some cases the dilemma becomes more difficult and remains unresolved even after the most careful reflection.

<1>A FRAMEWORK OF MORAL PRINCIPLES</1>

Moral norms central to biomedical ethics rely on the common morality, but they do not exhaust the common morality. Some types of basic moral norms are treated in this section, especially principles, rules, and rights. The virtues are the subject of Chapter 2, and the principles of primary importance for biomedical ethics are treated individually in Part II of this book. Most classical ethical theories accept these norms in some form, and traditional medical codes incorporate or presuppose at least some of them.

*<2>***Principles***</2>*

The set of pivotal moral principles defended in this book functions as an analytical framework of general norms derived from the common morality that form a suitable starting point for reflection on moral problems in biomedical

ethics.[24] These principles are general guidelines for the formulation of more specific rules. In Chapters 4 through 7 we defend four clusters of moral principles: (1) *respect for autonomy* (a norm of respecting and supporting autonomous decisions), (2) *nonmaleficence* (a norm of avoiding the causation of harm), (3) *beneficence* (a group of norms pertaining to relieving, lessening, or preventing harm and providing benefits and balancing benefits against risks and costs), and (4) *justice* (a cluster of norms for fairly distributing benefits, risks, and costs).

Nonmaleficence and beneficence have played central roles in the history of medical ethics. By contrast, respect for autonomy and justice were neglected in traditional medical ethics and have risen to prominence in this field only recently. In 1803, British physician Thomas Percival published *Medical Ethics,* the first comprehensive account of medical ethics in the long history of the subject. This book served as the backbone of British medical ethics and as the prototype for the American Medical Association's first code of ethics in 1847. Percival argued, using somewhat different language, that nonmaleficence and beneficence fix the physician's primary obligations and triumph over the patient's preferences and decision-making rights in circumstances of conflict.[25] Percival understated the critically important place of principles of respect for

autonomy and distributive justice for physician conduct, but, in fairness to him, these considerations are now prominent in discussions of ethics in medicine in a way they were not when he wrote *Medical Ethics*.

That these four clusters of moral principles are central to biomedical ethics is a conclusion the authors of this work have reached by examining *considered moral judgments* and the *coherence of moral beliefs,* two notions analyzed in Chapter 10. The selection of these four principles, rather than some other clusters of principles, does not receive an argued defense in Chapters 1 through 3. However, in Chapters 4 through 7, we defend the vital role of each principle in biomedical ethics.

<*2*>**Rules**<*/2*>

The framework of moral norms in this book encompasses several types of normative guidance, most notably principles, rules, rights, and virtues. Principles are more comprehensive and less specific than rules, but we draw only a loose distinction between them. Both are norms of obligation, but rules are more specific in content and more restricted in scope. Principles do not function as precise guides in each circumstance in the way that more detailed rules and judgments do. Principles and rules of obligation have correlative

rights and often corresponding virtues. (See the discussion of rights in Chapter 9 and of virtues in Chapter 2.)

We defend several types of rules, the most important being substantive rules, authority rules, and procedural rules.

<3>Substantive rules.</3> Rules of truth telling, confidentiality, privacy, forgoing treatment, informed consent, and rationing health care provide more specific guides to action than abstract principles provide. An example of a rule that sharpens the requirements of the principle of respect for autonomy in certain contexts is "Follow an incompetent patient's advance directive whenever it is clear and relevant." To indicate how this rule *specifies* the principle of respect for autonomy, it needs to be stated in full as "Respect the autonomy of incompetent patients by following all clear and relevant formulations in their advance directives." This specification shows how the initial norm of respect for autonomy endures even while becoming specified. (See the subsection "Specifying Principles and Rules" in the next section of this chapter.)

*<3>**Authority rules.**</3>* We also defend rules of decisional authority—

that is, rules regarding who may and should make decisions and perform actions. For example, *rules of surrogate authority* determine who should serve as surrogate agents when making decisions for incompetent persons; *rules of professional authority* determine who in professional ranks should make decisions to accept or to override a patient's decisions; and *rules of distributional authority* determine who should make decisions about allocating scarce medical resources such as new and expensive medical technologies.

Authority rules do not delineate substantive standards or criteria for making decisions. However, authority rules and substantive rules interact in some situations. For instance, authority rules are justified, in part, by how well particular authorities can be expected to respect and comply with substantive rules and principles.

<*3*>***Procedural rules.***</*3*> We also defend rules that establish procedures to be followed. Procedures for determining eligibility for organ transplantation and procedures for reporting grievances to higher authorities are typical examples. We often resort to procedural rules when we run out of substantive rules and when authority rules are incomplete or inconclusive. For example, if substantive or authority rules are inadequate to determine which

patients should receive scarce medical resources, a resort to procedural rules such as queuing and lottery may be justifiable.[26]

<1>CONFLICTING MORAL NORMS</1>

<2>Prima Facie Obligations and Rights</2>

Principles, rules, obligations, and rights are not rigid or absolute standards that allow no compromise. Although "a person of principle" is sometimes depicted as strict and unyielding, principles must be balanced and specified so they can function practically. It is no objection to moral norms that, in some circumstances, they can be justifiably overridden by other norms with which they conflict. All general moral norms are justifiably overridden in some circumstances. For example, we might justifiably not tell the truth to prevent someone from killing another person; and we might justifiably disclose confidential information about a person to protect the rights of another person.

Actions that harm individuals, cause basic needs to go unmet, or limit liberties are often said to be either wrong *prima facie* (i.e., wrongness is upheld unless the act is justifiable because of norms that are more stringent in the circumstances) or wrong *pro tanto* (i.e., wrong to a certain extent or wrong

unless there is a compelling justification)—which is to say that the action is wrong in the absence of other moral considerations that supply a compelling justification.[27] Compelling justifications are sometimes available. For example, in circumstances of a severe swine flu pandemic, the forced confinement of persons through isolation and quarantine orders might be justified. Here a justifiable infringement of liberty rights occurs.

W. D. Ross's distinction between *prima facie* and *actual* obligations clarifies this idea. A *prima facie* obligation must be fulfilled unless it conflicts with an equal or stronger obligation. Likewise, a *prima facie* right (here we extend Ross's theory) must prevail unless it conflicts with an equal or stronger right (or conflicts with some other morally compelling alternative). Obligations and rights always constrain us unless a competing moral obligation or right can be shown to be overriding in a particular circumstance. As Ross put it, agents can determine their *actual* obligations in situations of conflict by examining the respective weights of the competing prima facie obligations. What agents ought to do is determined by what they ought to do all things considered.[28]

Imagine that a psychiatrist has confidential medical information about a patient who also happens to be an employee in the hospital where the psychiatrist practices. The employee seeks advancement in a stress-filled

position, but the psychiatrist has good reason to believe that this advancement would be devastating for both the employee and the hospital. The psychiatrist has several prima facie duties in these circumstances, including those of confidentiality, nonmaleficence, beneficence, and respect for autonomy. Should the psychiatrist break confidence in this circumstance to meet these other duties? Could the psychiatrist make "confidential" disclosures to a hospital administrator and not to the personnel office? Addressing such questions through moral deliberation and justification is required to establish an agent's actual duty in the face of the conflicting prima facie duties.

These matters are more complicated than Ross suggests, particularly when rights come into conflict. We may need to develop a structured moral system or set of guidelines in which (1) some rights in a certain class of rights (for example, rights of individuals while alive to decide whether to donate their tissues and organs after death) have a fixed priority over others in another class of rights (for example, rights of family members to make decisions about the donation of their deceased relatives' tissues and organs) and (2) morally compelling social objectives such as gathering information in biomedical research can almost always be overridden by basic human rights such as the right to give an informed consent or refusal.

No moral theory or professional code of ethics has successfully presented a system of moral rules free of conflicts and exceptions, but this observation should not generate either skepticism or alarm about ethical reflection, argument, and theory. The distinction between prima facie and actual obligations conforms closely to our experience as moral agents and provides indispensable categories for biomedical ethics. Almost daily we confront situations that force us to choose among conflicting values in our personal lives. For example, a person's financial situation might require that he or she choose between buying books for school and buying a train ticket to see friends. Not having the books will be an inconvenience and a loss, whereas not visiting with friends will disappoint the friends. Such choices do not come effortlessly, but we are usually able to think through the alternatives, deliberate, and reach a conclusion.

<*2*>**Moral Regret and Residual Obligation**<*/2*>

An agent who determines that a particular act is the best one to perform in a situation of conflicting obligations may still not be able to discharge all aspects of moral obligation by performing that act. Even the morally best action in the circumstances may still be regrettable and may leave a moral residue, also

called a moral trace.[29] Regret and residue over what is not done can arise even if the right action is clear and uncontested.

This point is about continuing obligation, not merely about feelings of regret and residue. Moral residue results because a prima facie obligation does not simply disappear when overridden. Often we have residual obligations because the obligations we were unable to discharge create new obligations. We may feel deep regret and a sting of conscience, but we also realize that we have a duty to bring closure to the situation.[30] We can sometimes make up for not fulfilling an obligation in one or more of several ways. For example, we may be able to notify persons in advance that we will not be able to keep a promise; we may be able to apologize in a way that heals a relationship; we may be able to change circumstances so that the conflict does not occur again; and we may be able to provide adequate compensation.

<*2*>**Specifying Principles and Rules**<*/2*>

The four clusters of principles we present in this book do not by themselves constitute a general ethical theory. They provide only a framework of norms with which to get started in biomedical ethics. These principles must be specified in order to achieve more concrete guidance. Specification is a process

of reducing the indeterminacy of abstract norms and generating rules with action-guiding content.[31] For example, without further specification, "do no harm" is too bare for thinking through problems such as whether it is permissible to hasten the death of a terminally ill patient.

Specification is not a process of producing or defending general norms such as those in the common morality; it assumes that the relevant general norms are available. Specifying the norms with which one starts—whether those in the common morality or norms previously specified—is accomplished by narrowing the scope of the norms, not by explaining what the general norms mean. We narrow the scope, as Henry Richardson puts it, by "spelling out where, when, why, how, by what means, to whom, or by whom the action is to be done or avoided."[32] For example, the norm that we are obligated to "respect the autonomy of persons" cannot, unless specified, handle complicated problems in clinical medicine and research involving human subjects. A definition of "respect for autonomy" (e.g., as "allowing competent persons to exercise their liberty rights") clarifies one's meaning in using the norm, but it does not narrow the scope of the general norm or render it more specific in guiding actions.

Specification adds content. For example, as noted previously, one

possible specification of "respect the autonomy of patients" is "respect the autonomy of competent patients by following their advance directives when they become incompetent." This specification will work well in some medical contexts, but it will confront limits in others, where additional specification will be needed. Progressive specification can continue indefinitely, but to qualify all along the way as a specification some transparent connection must be maintained to the initial general norm that gives moral authority to the resulting string of specifications. This process is a prime way in which general principles become practical instruments for moral reasoning; and it also helps explain why the four-principles approach is not merely an abstract theory limited to four general principles.[33]

An example of specification arises when psychiatrists conduct forensic evaluations of patients in a legal context. Psychiatrists cannot always obtain an informed consent, but they then risk violating their obligations to respect autonomy, a central imperative of medical ethics. A specification aimed at handling this problem is "Respect the autonomy of persons who are the subjects of forensic evaluations, where consent is not legally required, by disclosing to the evaluee the nature and purpose of the evaluation." We do not claim that this formulation is the best specification, but it approximates the provision

recommended in the "Ethical Guidelines for the Practice of Forensic Psychiatry" of the American Academy of Psychiatry and the Law.[34] This specification attempts to guide forensic psychiatrists in discharging their diverse moral obligations.

Another example of specification derives from the oft-cited rule "Doctors should put their patients' interests first." In some countries patients are able to receive the best treatment available only if their physicians falsify information on insurance forms. The rule of patient priority does not imply that a physician should act illegally by lying or distorting the description of a patient's problem on an insurance form. Rules against deception, on the one hand, and for patient priority, on the other, are not categorical imperatives. When they conflict, we need some form of specification to know what we can and cannot do.

A survey of practicing physicians' attitudes toward deception illustrates how some physicians reconcile their dual commitment to patients and to nondeception. Dennis H. Novack and several colleagues used a questionnaire to obtain physicians' responses to difficult ethical problems that potentially could be resolved by use of deception. In one scenario, a physician recommends an annual screening mammography for a fifty-two-year-old woman who protests that her insurance company will not cover the test. The insurance company will

cover the costs if the physician states (deceptively in this scenario) that the reason is "rule out cancer" rather than "screening mammography." The insurance company understands "rule out cancer" to apply only if there is a breast mass or other objective clinical evidence of the possibility of cancer, neither of which is present in this case. Almost 70% of the physicians responding to this survey indicated that they would state that they were seeking to "rule out cancer," and 85% of this group (85% of the 70%) insisted that their act would not involve "deception."[35]

These physicians' decisions are rudimentary attempts to specify the rule that "Doctors should put their patients' interests first." Some doctors seem to think that it is properly specified as follows: "Doctors should put their patients' interests first by withholding information from or misleading someone who has no *right* to that information, including an insurance company that, through unjust policies of coverage, forfeits its right to accurate information." In addition, most physicians in the study apparently did not operate with the definition of "deception" favored by the researchers, which is "to deceive is to make another believe what is not true, to mislead." Some physicians apparently believed that "deception" occurs when one person unjustifiably misleads another, and that it was justifiable to mislead the insurance company in these

circumstances. It appears that these physicians would not agree on how to specify rules against deception or rules assigning priority to patients' interests.

All moral rules are, in principle, subject to specification. All will need additional content, because, as Richardson puts it, "the complexity of the moral phenomena always outruns our ability to capture them in general norms."[36] Many already specified rules will need further specification to handle new circumstances of conflict. These conclusions are connected to our earlier discussion of particular moralities. Different persons and groups will offer conflicting specifications, potentially creating multiple particular moralities. In any problematic case, competing specifications are likely to be offered by reasonable and fair-minded parties, all of whom are committed to the common morality.

To say that a problem or conflict is resolved or dissolved by specification is to say that norms have been made sufficiently determinate in content that, when cases fall under them, we know what must be done. Obviously some proposed specifications will fail to provide the most adequate or justified resolution. When competing specifications emerge, the proposed specifications should be based on deliberative processes of reasoning. Specification as a method can be connected to a model of justification that will support some

specifications and not others, as we argue in Chapter 10 (pp. •••–•••).

Some specified norms are virtually absolute and need no further specification, though they are rare. Examples include prohibitions of cruelty that involve unnecessary infliction of pain and suffering.[37] "Do not rape" is a comparable example. More interesting are norms that are intentionally formulated with the goal of including all legitimate exceptions. An example is, "Always obtain oral or written informed consent for medical interventions with competent patients, *except* in emergencies, in forensic examinations, in low-risk situations, or when patients have waived their right to adequate information." This norm needs further interpretation, including an analysis of what constitutes an informed consent, an emergency, a waiver, a forensic examination, and a low risk. This rule would be absolute if all legitimate exceptions had been successfully incorporated into its formulation, but such rules are rare. In light of the range of possibilities for contingent conflicts among rules, even the firmest and most detailed rules are likely to encounter exceptive cases.

<*2*>**Weighing and Balancing**<*/2*>

Principles, rules, obligations, and rights often must be balanced in circumstances of contingent conflict. Does balancing differ from specification,

or are they identical?

<3>***The process of weighing and balancing.***</3> Balancing occurs in the process of reasoning about which moral norms should prevail when two or more of them come into conflict. Balancing is concerned with the relative weights and strengths of different moral norms, whereas specification is concerned primarily with their range and scope, i.e., their reach when narrowing the scope of pre-existing general norms (while adding content). Balancing consists of deliberation and judgment about these weights and strengths. It is well suited for reaching judgments in *particular cases*, whereas specification is especially useful for developing more *specific policies* from already accepted general norms.

The metaphor of larger and smaller weights moving a scale up and down has often been invoked to depict the balancing process, but this metaphor can obscure what happens in balancing. Justified acts of balancing are supported by good reasons. They need not rest merely on intuition or feeling, although intuitive balancing is one form of balancing. Suppose a physician encounters an emergency case that would require her to extend an already long day, making her unable to keep a promise to take her son to the local library. She engages in

a process of deliberation that leads her to consider how urgently her son needs to get to the library, whether they could go to the library later, whether another physician could handle the emergency case, and the like. If she determines to stay deep into the night with the patient, she has judged this obligation to be overriding because she has found a good and sufficient reason for her action. The reason might be that a life hangs in the balance and she alone may have the knowledge to deal adequately with the circumstances. Canceling her evening with her son, distressing as it will be, could be justified by the significance of her reasons for doing what she does.

One way of approaching balancing merges it with specification. In our example, the physician's reasons can be generalized to similar cases: "If a patient's life hangs in the balance and the attending physician alone has the knowledge to deal adequately with the full array of the circumstances, then the physician's conflicting domestic obligations must yield." Even if we do not always state the way we balance considerations in the form of a specification, might not all deliberative judgments be made to conform to this model? If so, then deliberative balancing would be nothing but deliberative specification.

The goal of merging specification and balancing is appealing, but it is not well-suited to handle all situations in which balancing occurs. Specification

requires that a moral agent extend norms by both narrowing their scope and generalizing to relevantly similar circumstances. Accordingly, "respect the autonomy of competent patients when they become incompetent by following their advance directives" is a rule suited for all incompetent patients with advance directives. However, the responses of caring moral agents, such as physicians and nurses, are often highly specific to the needs of *this* patient or *this* family in *this* particular circumstance. Numerous considerations must be weighed and balanced, and any generalizations that could be formed might not hold even in remarkably similar cases.

Generalizations conceived as policies might even be dangerous. For example, cases in which risk of harm and burden are involved for a patient are often circumstances unlikely to be decided by expressing, by a rule, how much risk is allowable or how heavy the burden can be to secure a certain stated benefit. After levels of risk and burden are determined, these considerations must be balanced with the likelihood of the success of a procedure, the uncertainties involved, whether an adequately informed consent can be obtained, whether the family has a role to play, and the like. In this way, balancing allows for a due consideration of all the factors bearing on a complex particular circumstance, including all relevant moral norms.

Consider the following discussion with a young woman who has just been told that she is HIV-infected, as recorded by physician Timothy Quill and nurse Penelope Townsend:[38]

<DIA>PATIENT: Please don't tell me that. Oh my God. Oh my children. Oh Lord have mercy. Oh God, why did He do this to me? . . .

DR. QUILL: First thing we have to do is learn as much as we can about it, because right now you are okay.

PATIENT: I don't even have a future. Everything I know is that you gonna die anytime. What is there to do? What if I'm a walking time bomb? People will be scared to even touch me or say anything to me.

DR. QUILL: No, that's not so.

PATIENT: Yes they will, 'cause I feel that way . . .

DR. QUILL: There is a future for you . . .

PATIENT: Okay, alright. I'm so scared. I don't want to die. I don't want to die, Dr. Quill, not yet. I know I got to die, but I don't want to die.

DR. QUILL: We've got to think about a couple of things.</DIA>

Quill and Townsend work to calm down and reassure this patient, while engaging sympathetically with her feelings and conveying the presence of knowledgeable medical authorities. Their emotional investment in the patient's feelings is joined with a detached evaluation of the patient. Too much compassion and emotional investment may doom the task at hand; too much detachment will be cold and may destroy the patient's trust and hope. A balance in the sense of a right mixture between engagement and detachment must be found.

Quill and Townsend could try to specify norms of respect and beneficence to indicate how caring physicians and nurses should respond to patients who are desperately upset. However, specification will ring hollow and will not be sufficiently nuanced to provide practical guidance for this patient and certainly not for all desperately upset patients. Each encounter calls for a response inadequately captured by general principles and rules and their specifications. Behavior that is a caring response for one desperate patient may intrude on privacy or irritate another desperate patient. A physician may, for example, find it appropriate to touch or caress a patient, while appreciating that such behavior would be entirely inappropriate for another patient in a similar circumstance.

How physicians and nurses balance different moral considerations often involves sympathetic insight, humane responsiveness, and the practical wisdom of discerning a particular patient's circumstance and needs.[39] Balancing is often a more complex set of activities than those involved in a straightforward case of balancing two conflicting principles or rules. Considerations of trust, compassion, objective assessment, caring responsiveness, reassurance, and the like may all be involved in the process of balancing.

In many clinical contexts it may be hopelessly complicated and unproductive to engage in specification. For example, in cases of balancing harms of treatment against the benefits of treatment for incompetent patients, the cases are often so exceptional that it is perilous to generalize a conclusion that would reach out to other cases. These problems are sometimes further complicated by disagreements among family members about what constitutes a benefit, poor decisions and indecision by a marginally competent patient, limitations of time and resources, and the like.[40]

We do not suggest that balancing is inescapably intuitive and unreflective. Instead, we propose a model of moral judgment that focuses on how balancing and judgment occur through practical astuteness, discriminating intelligence, and sympathetic responsiveness that are not reducible to the

specification of norms. The capacity to balance many moral considerations is connected to what we discuss in Chapter 2 as capacities of moral character. Capacities in the form of virtues of compassion, attentiveness, discernment, caring, and kindness are integral to the way wise moral agents balance diverse, sometimes competing, moral considerations.

Practicability supplies another reason why the model of specification needs supplementation by the model of balancing. Progressive specification covering all areas of the moral life would eventually mushroom into a body of norms so bulky that the normative system would become unwieldy. A scheme of comprehensive specification would constitute a package of potentially hundreds, thousands, or millions of rules, each suited to a narrow range of conduct. In the model of specification, every type of action in a circumstance of the contingent conflict of norms would be covered by a rule, but the formulation of rules for every circumstance of contingent conflict would be a body of rules too cumbersome to be helpful.

<*3*>***Conditions that constrain balancing.***</*3*>To allay concerns that the model of balancing is too intuitive or too open-ended and lacks a commitment to firm principles and rigorous reasoning, we propose six conditions that should

help reduce intuition, partiality, and arbitrariness. These conditions must be met to justify infringing one prima facie norm in order to adhere to another.

<NL>1. Good reasons are offered to act on the overriding norm rather than the infringed norm.

2. The moral objective justifying the infringement has a realistic prospect of achievement.

3. No morally preferable alternative actions are available.[41]

4. The lowest level of infringement, commensurate with achieving the primary goal of the action, has been selected.

5. All negative effects of the infringement have been minimized.

6. All affected parties have been treated impartially.</NL>

Although some of these conditions are obvious and noncontroversial, some are often overlooked in moral deliberation and would lead to different conclusions were they observed. For example, some decisions to use futile life-extending technologies over the objections of patients or their surrogates violate condition 2 by endorsing actions in which no realistic prospect exists of achieving the goals of a proposed intervention. Typically, these decisions are made when health professionals regard the intervention as legally required, but in some cases the standard invoked is merely traditional or deeply entrenched.

Condition 3 is more commonly violated. Actions are regularly performed in some settings without serious consideration of alternative actions that might be performed. As a result, agents fail to identify a morally preferable alternative. For example, in animal care and use committees a common conflict involves the obligation to approve a good scientific protocol and the obligation to protect animals against unnecessary suffering. A protocol may be approved if it proposes a standard form of anesthesia. However, standard forms of anesthesia are not always the best way to protect the animal, and further inquiry is needed to determine the best anesthetic for the particular interventions proposed. In our schema of conditions, it is unjustifiable to approve the protocol or to conduct the experiment without this additional inquiry, which affects conditions 4 and 5 as well as 3.

Finally, consider this example: The principle of respect for autonomy and the principle of beneficence (which requires acts intended to prevent harm to others) sometimes come into contingent conflict when addressing situations that arise in governmental and professional responses to serious infectious-disease outbreaks, such as Severe Acquired Respiratory Syndrome (SARS). Persons exposed to SARS may put other persons at risk. The government, under its public health responsibilities, and various health professionals have an

obligation based on beneficence and justice to protect unexposed persons whenever possible. However, respect for autonomy often sets a prima facie barrier to infringements of liberty and privacy even in the context of public health concerns. To justify overriding respect for autonomy, one must show that mandatory quarantine of exposed individuals is necessary to prevent harm to others and has a reasonable prospect of preventing such harm. If it meets these conditions, mandatory quarantine still must pass the least-infringement test (condition 4), and public health officials should seek to minimize the negative effects of the quarantine, including the loss of income and the inability to care for dependent family members (condition 5). Finally, impartial application of the quarantine rules is essential for both fairness and public trust (condition 6).[42]

In our judgment, these six constraining conditions are morally demanding, at least in some circumstances. When conjoined with requirements of coherence presented in Chapter 10 (pp. •••–•••), these conditions provide protections against purely intuitive, subjective, or biased balancing judgments. We could introduce further criteria or safeguards, such as "rights override nonrights" and "liberty principles override nonliberty principles," but these provisions are certain to fail in circumstances in which rights claims and liberty interests are relatively minor.

<2>**Moral Diversity and Moral Disagreement**</2>

Sometimes conscientious and reasonable moral agents understandably disagree over moral priorities in circumstances of a contingent conflict of norms. Morally conscientious persons may disagree, for example, about whether disclosure of a life-threatening condition to a fragile patient is appropriate, whether religious values about brain death have a place in secular biomedical ethics, whether teenagers should be permitted to refuse life-sustaining treatments, and other issues. Disagreement does not indicate moral ignorance or moral defect. We simply lack a single, entirely reliable way to resolve many disagreements, despite methods of specifying and balancing.

Moral disagreement can emerge because of (1) factual disagreements (e.g., about the level of suffering that an intervention will cause), (2) disagreements resulting from insufficient information or evidence, (3) disagreements about which norms are applicable or relevant in the circumstances, (4) disagreements about the relative weights or rankings of the relevant norms, (5) disagreements about appropriate forms of specification or balancing, (6) the presence of a genuine moral dilemma, (7) scope and moral status disagreements about who should be protected by a moral norm (e.g.,

whether embryos, fetuses, and sentient animals are protected; see Chapter 3), and (8) conceptual disagreements about a crucial moral concept such as whether removal of nutrition and hydration from a dying patient at a family's request constitutes *killing*.

Different parties may emphasize different principles or assign different weights to principles even when they agree on which principles and concepts are relevant. Disagreement may persist among morally committed persons who appropriately appreciate the basic demands that morality makes on them. If evidence is incomplete and different items of evidence are available to different parties, one individual or group may be justified in reaching a conclusion that another individual or group is justified in rejecting. Even if both parties have some incorrect beliefs, each party may have good reasons for holding those beliefs. We cannot hold persons to a higher practical standard than to make judgments conscientiously in light of the available norms and evidence.

When moral disagreements arise, a moral agent can—and usually should—defend his or her decision without disparaging or reproaching others who reach different decisions. Recognition of legitimate diversity—by contrast to moral violations that warrant criticism—is vital in the evaluation of the actions of others. One person's conscientious assessment of his or her

obligations may differ from another's when they confront the same moral problem, and both evaluations may be appropriately grounded in the common morality. Similarly, what one institution or government determines it should do may differ from what another institution or government determines it should do. In such cases we can assess one position as morally preferable to another only if we can show that the position rests on a more coherent set of specifications and interpretations of the common morality.[43]

<1>CONCLUSION</1>

In this chapter we have presented what is sometimes called the *four-principles approach* to biomedical ethics, now commonly called *principlism.*[44] The four clusters of principles in our moral framework descend from the common morality, but when specifying and balancing these principles in later chapters we will also call on historical experience in formulating professional obligations and virtues in health care, public health, biomedical research, and health policy. Although various assumptions in traditional medical ethics, current medical and research codes, and other parts of contemporary bioethics need further reform, we are deeply indebted to their insights and commitments. Our goal in later chapters is to develop, specify, and balance the normative

content of the four clusters of principles, and we will often seek to render our views consistent with professional traditions, practices, and codes.

Principlism is not merely a list of four abstract principles. It is a theory about how these principles are linked to and guide practice. In the nine chapters hereafter we will show how principles and other moral norms are connected to an array of understandings, practices, and transactions in healthcare settings, research institutions, and public health policies.

<N-1>**Notes**</N-1>

<N>[1] See Albert Jonsen, *The Birth of Bioethics* (New York: Oxford University Press, 1998), pp. 3ff; Jonsen, *A Short History of Medical Ethics* (New York: Oxford University Press, 2000); John-Stewart Gordon, "Bioethics," in the *Internet Encyclopedia of Philosophy*, especially section 2, available at https://www.iep.utm.edu/bioethics/ (accessed March 23, 2018); and Edmund D. Pellegrino and David C. Thomasma, *The Virtues in Medical Practice* (New York: Oxford University Press, 1993), pp. 184–89.

[2] A comprehensive treatment of this history that ranges worldwide is Robert B. Baker and Laurence McCullough, eds. *The Cambridge World History of Medical Ethics* (Cambridge and New York: Cambridge University Press, 2009).

[3] The language of "applied ethics" can be misleading insofar as it suggests one-way traffic from ethical theory and principles and rules to particular judgments about cases. In fact, particular case judgments interact dialectically with and may lead to modifications of theories, principles, and rules. See our discussion in Chapter 10, pp. , pp. •••–•••.

[4] These distinctions should be used with caution. Metaethics frequently takes a turn toward the normative, and normative ethics often relies on metaethics. Just as no sharp distinction should be drawn between practical ethics and general normative ethics, no bright line should be drawn to distinguish normative ethics and metaethics.

[5] Although there is only one universal common morality, there is more than one theory of the common morality. For a diverse group of theories, see Alan Donagan, *The Theory of Morality* (Chicago: University of Chicago Press, 1977); Bernard Gert, *Common Morality: Deciding What to Do* (New York: Oxford University Press, 2007); Bernard Gert, Charles M. Culver, and K. Danner Clouser, *Bioethics: A Return to Fundamentals,* 2nd ed. (New York: Oxford University Press, 2006); W. D. Ross, *The Foundations of Ethics* (Oxford: Oxford University Press, 1939); and the special issue of the *Kennedy Institute of Ethics Journal* 13 (2003), especially the introductory article by Robert Veatch, pp. 189–92.

For challenges to these theories and their place in bioethics, see John D. Arras, "The Hedgehog and the Borg: Common Morality in Bioethics," *Theoretical Medicine and Bioethics* 30 (2009): 11-30; Arras, "A Common Morality for Hedgehogs: Bernard Gert's Method," in Arras, *Methods in Bioethics: The Way We Reason Now*, ed. James F. Childress and Matthew Adams (New York: Oxford University Press, 2017), pp. 27-44; B. Bautz, "What is the Common Morality, Really?" *Kennedy Institute of Ethics Journal* 26 (2016): 29-45; Carson Strong, "Is There No Common Morality?" *Medical Humanities Review* 11 (1997): 39-45; and Andrew Alexandra and Seumas Miller, "Ethical Theory, 'Common Morality,' and Professional Obligations," *Theoretical Medicine and Bioethics* 30 (2009): 69-80.

[6] See Martha Nussbaum's thesis that, in Aristotle's philosophy, certain "non-relative virtues" are objective and universal. "Non-Relative Virtues: An Aristotelian Approach," in *Ethical Theory, Character, and Virtue,* ed. Peter French et al. (Notre Dame, IN: University of Notre Dame Press, 1988), pp. 32–53, especially pp. 33–4, 46–50. In another classic work in philosophical ethics, David Hume presents a theory of the virtues as objective and universal, though his theory is somewhat different from Aristotle's. See Hume's *An Enquiry concerning the Principles of Morals*, ed. Tom L. Beauchamp, in the series "Oxford Philosophical Texts Editions" (Oxford: Oxford University Press, 1998).

[7] For a broad and engaging account of common morality, see Rebecca Kukla, "Living with Pirates: Common Morality and Embodied Practice," *Cambridge Quarterly of Healthcare Ethics* 23 (2014): 75-85. See also Bernard Gert's insistence on the role of the *whole moral system* (not merely rules of obligation) and the perils of neglecting it, an often overlooked point with which we agree. See Gert's *Morality: Its Nature and Justification* (New York: Oxford University Press, 2005), pp. 3, 159–61, 246–47; and see also his "The Definition of Morality," in *The Stanford Encyclopedia of Philosophy*; revision of Feb. 8, 2016, available at https://plato.stanford.edu/entries/morality-definition/ (accessed February 9, 2018).

[8] This mistaken interpretation of our theory is found in Leigh Turner, "Zones of Consensus and Zones of Conflict: Questioning the 'Common Morality' Presumption in Bioethics," *Kennedy Institute of Ethics Journal* 13 (2003): 193–218; and Turner, "An Anthropological Exploration of Contemporary Bioethics: The Varieties of Common Sense," *Journal of Medical Ethics* 24 (1998): 127–33.

[9] See David DeGrazia, "Common Morality, Coherence, and the Principles of Biomedical Ethics," *Kennedy Institute of Ethics Journal* 13 (2003): 219–30; Turner, "Zones of Consensus and Zones of Conflict"; Donald C. Ainslee, "Bioethics and the Problem of Pluralism," *Social Philosophy and Policy* 19 (2002): 1–28; Oliver Rauprich, "Common Morality: Comment on Beauchamp and Childress," *Theoretical Medicine and Bioethics* 29 (2008): 43–71; and Letícia Erig Osório de Azambuja and Volnei Garrafa, "The Common Morality Theory in the Work of Beauchamp and Childress," *Revista Bioética* 23 (2015), available at http://www.scielo.br/scielo.php?pid=S1983-80422015000300634&script=sci_arttext&tlng=en (accessed March 22, 2018). For a related, but distinguishable, criticism, see Anna E. Westra, Dick L. Willems, and Bert J. Smit, "Communicating with Muslim Parents: 'The Four Principles' are not as Culturally Neutral as Suggested," *European Journal of Pediatrics* 168 (2009): 1383-1387; this article is published together with a beautifully correct interpretation of our position by Voo Teck Chuan, "Editorial Comment: The Four Principles and Cultural Specification," *European Journal of Pediatrics* 168 (2009): 1389.

[10] Kukla reaches this conclusion in "Living with Pirates." See, in response, Tom L. Beauchamp, "On Common Morality as Embodied Practice: A Reply To Kukla," *Cambridge Quarterly of Healthcare Ethics* 23 (2014): 86-93; Carson Strong, "Kukla's Argument against Common Morality as a Set of Precepts: On Stranger Tides," *Cambridge Quarterly of Healthcare Ethics* 23 (2014): 93–99; and Kukla, "Response to Strong and Beauchamp–at World's End," *Cambridge Quarterly of Healthcare Ethics* 23 (2014): 99-102.

[11] See Richard B. Brandt, "Morality and Its Critics," in his *Morality, Utilitarianism, and Rights* (Cambridge: Cambridge University Press, 1992), chap. 5; and Gregory Mellema, "Moral Ideals and Virtue Ethics," *The Journal of Ethics* 14 (2010): 173-180. See also our discussion of moral ideals and supererogation in Chapter 2, pp. •••–•••.

[12] Talcott Parsons, *Essays in Sociological Theory,* rev. ed. (Glencoe, IL: Free Press, 1954), p. 372. See further Jan Nolin, *In Search of a New Theory of Professions* (Borås, Sweden: University of Borås, 2008).

[13] See the excellent introduction to this subject in Edmund D. Pellegrino, "Codes, Virtues, and Professionalism," in *Methods of Bioethics,* ed. Daniel Sulmasy and Jeremy Sugarman, 2nd ed. (Washington, DC: Georgetown University Press, 2010), pp. 91-108. For an overview of codes of medical ethics, see Robert Baker, "Medical Codes and Oaths," *Bioethics* [Formerly *Encyclopedia of Bioethics*], 4th edition, ed. Bruce Jennings (Farmington Hills, MI: Gale, Cengage Learning, Macmillan Reference USA, 2014), Vol. 4, pp. 1935-1946. For a history and assessment of the Code of Ethics for Nurses of the American Nurses Association, see Beth Epstein and Martha Turner, "The Nursing Code of Ethics: Its Value, Its History," *The Online Journal of Issues in Nursing* 20, No. 2 (May

2015), available at http://ojin.nursingworld.org/MainMenuCategories/ANAMarketplace/ANAPeriodicals/OJIN/TableofContents/Vol-20-2015/No2-May-2015/The-Nursing-Code-of-Ethics-Its-Value-Its-History.html (accessed June 3, 2018).

[14] The American Medical Association Code of Ethics of 1847 was largely adapted from Thomas Percival's *Medical Ethics; or a Code of Institutes and Precepts, Adapted to the Professional Conduct of Physicians and Surgeons* (Manchester, England: S. Russell, 1803). See Donald E. Konold, *A History of American Medical Ethics 1847–1912* (Madison, WI: State Historical Society of Wisconsin, 1962), chaps. 1–3; Chester Burns, "Reciprocity in the Development of Anglo-American Medical Ethics," in *Legacies in Medical Ethics,* ed. Burns (New York: Science History Publications, 1977); and American Medical Association, "History of the Code," available at https://www.ama-assn.org/sites/default/files/media-browser/public/ethics/ama-code-ethics-history.pdf (accessed March 23, 2018).

[15] For a related and rigorous critical analysis of Hippocratic and other medical codes, see Robert M. Veatch's influential views in his *Hippocratic, Religious, and Secular Medical Ethics: The Points of Conflict* (Washington, DC: Georgetown University Press, 2012).

[16] Cf. the conclusions reached about medicine in N. D. Berkman, M. K. Wynia, and L. R. Churchill, "Gaps, Conflicts, and Consensus in the Ethics Statements of Professional Associations, Medical Groups, and Health Plans," *Journal of Medical Ethics* 30 (2004): 395–401; Ryan M. Antiel, Farr A. Curlin, C. Christopher Hook, and Jon C. Tilburt, "The Impact of Medical School Oaths and other Professional Codes of Ethics: Results of a National Physician Survey," *Archives of Internal Medicine* 171 (2011): 469-71; Robert D. Orr, Norman Pang, Edmund D. Pellegrino, and Mark Siegler, "Use of the Hippocratic Oath: A Review of Twentieth Century Practice and a Content Analysis of Oaths Administered in Medical Schools in the U.S. and Canada in 1993," *Journal of Clinical Ethics* 8 (1997): 377–88; and A. C. Kao and K. P. Parsi, "Content Analyses of Oaths Administered at U.S. Medical Schools in 2000," *Academic Medicine* 79 (2004): 882–87.

[17] Jay Katz, ed., *Experimentation with Human Beings* (New York: Russell Sage Foundation, 1972), pp. ix–x.

[18] For an examination of different models of public bioethics, see James F. Childress, "Reflections on the National Bioethics Advisory Commission and Models of Public Bioethics," *Goals and Practice of Public Bioethics: Reflections on National Bioethics Commissions*, special report, *Hastings Center Report* 47, no. 3 (2017): S20-S23, and several other essays in this special report. See also *Society's Choices: Social and Ethical Decision Making in Biomedicine*, ed. Ruth Ellen Bulger, Elizabeth Meyer Bobby, and Harvey V. Fineberg, for the Committee on the Social and Ethical Impacts of Developments in Biomedicine, Division of Health Sciences Policy, Institute of Medicine

(Washington, DC: National Academies Press, 1995).

[19] See Allen Buchanan, "Philosophy and Public Policy: A Role for Social Moral Epistemology," *Journal of Applied Philosophy* 26 (2009): 276-90; Will Kymlicka, "Moral Philosophy and Public Policy: The Case of New Reproductive Technologies," in *Philosophical Perspectives on Bioethics,* ed. L. W. Sumner and Joseph Boyle (Toronto: University of Toronto Press, 1996); Dennis Thompson, "Philosophy and Policy," *Philosophy & Public Affairs* 14 (Spring 1985): 205–18; Andrew I. Cohen, *Philosophy, Ethics, and Public Policy* (London and New York: Routledge, 2015); and a symposium on "The Role of Philosophers in the Public Policy Process: A View from the President's Commission," with essays by Alan Weisbard and Dan Brock, in *Ethics* 97 (July 1987): 775–95.

[20] *Tarasoff v. Regents of the University of California,* 17 Cal. 3d 425, 551 P.2d 334, 131 Cal. Rptr. 14 (Cal. 1976).

[21] On the interactions of ethical and legal judgments (and the reasons for their interactions) on bioethical issues, see Stephen W. Smith, John Coggan, Clark Hobson, et al., eds., *Ethical Judgments: Re-Writing Medical Law* (Oxford U.K. and Portland, OR: Hart Publishing, 2016).

[22] See John Lemmon, "Moral Dilemmas," *Philosophical Review* 71 (1962): 139–58; Daniel Statman, "Hard Cases and Moral Dilemmas," *Law and Philosophy* 15 (1996): 117–48; Terrance McConnell, "Moral Dilemmas," *Stanford Encyclopedia of Philosophy* (Fall 2014 Edition), ed. Edward N. Zalta, available at https://plato.stanford.edu/archives/fall2014/entries/moral-dilemmas/ (accessed March 23, 2018); H. E. Mason, "Responsibilities and Principles: Reflections on the Sources of Moral Dilemmas," in *Moral Dilemmas and Moral Theory,* ed. H. E. Mason (New York: Oxford University Press, 1996).

[23] Christopher W. Gowans, ed., *Moral Dilemmas* (New York: Oxford University Press, 1987); Walter Sinnott-Armstrong, *Moral Dilemmas* (Oxford: Basil Blackwell, 1988); Edmund N. Santurri, *Perplexity in the Moral Life: Philosophical and Theological Considerations* (Charlottesville, VA: University Press of Virginia, 1987). For an approach to dilemmas offered as an addition to our account in this chapter, see Joseph P. DeMarco, "Principlism and Moral Dilemmas: A New Principle," *Journal of Medical Ethics* 31 (2005): 101–5.

[24] Some writers in biomedical ethics express reservations about the place of the particular principles we propose in this book. See Pierre Mallia, *The Nature of the Doctor–Patient Relationship*: *Health Care Principles Through the Phenomenology of Relationships with Patients* (Springer Netherlands, Springer Briefs in Ethics, 2013), esp. Chapter 2, "Critical Overview of Principlist Theories"; K. Danner Clouser and Bernard Gert, "A Critique of Principlism," *Journal of Medicine and Philosophy* 15 (April 1990): 219–36;

Søren Holm, "Not Just Autonomy—The Principles of American Biomedical Ethics," *Journal of Medical Ethics* 21 (1994): 332-38; Peter Herissone-Kelly, "The Principlist Approach to Bioethics, and Its Stormy Journey Overseas," in *Scratching the Surface of Bioethics,* ed. Matti Häyry and Tuija Takala (Amsterdam: Rodopi, 2003), pp. 65–77; and numerous essays in *Principles of Health Care Ethics,* ed. Raanan Gillon and Ann Lloyd (London: Wiley, 1994); and *Principles of Health Care Ethics,* 2nd ed., ed. Richard E. Ashcroft, et al. (Chichester, England: Wiley, 2007) .

[25] Thomas Percival, *Medical Ethics; or a Code of Institutes and Precepts, Adapted to the Professional Interests of Physicians and Surgeons* (Manchester: S. Russell, 1803 (and numerous later editions). For commentary on this classic work and its influence, see Edmund D. Pellegrino, "Percival's Medical Ethics: The Moral Philosophy of an 18th-Century English Gentleman," *Archives of Internal Medicine* 146 (1986): 2265-2269; Pellegrino, "Thomas Percival's Ethics: The Ethics Beneath The Etiquette" (Washington DC: Georgetown University, Kennedy Institute of Ethics, 1984), available at https://repository.library.georgetown.edu/bitstream/handle/10822/712018/Pellegrino_M269.pdf?sequence=1&isAllowed=n (accessed March 24, 2018); Robert B. Baker, Arthur L. Caplan, Linda L. Emanuel, and Stephen R. Latham (eds.), *The American Medical Ethics Revolution: How the AMA's Code of Ethics Has Transformed Physicians' Relationships to Patients, Professionals, and Society* (Baltimore: Johns Hopkins University Press, 1999).

[26] Procedural rules might also be interpreted as grounded in substantive rules of equality. If so interpreted, the procedural rules could be said to have a justification in substantive rules.

[27] For a discussion of the distinction between *pro tanto* and *prima facie,* see Shelly Kagan, *The Limits of Morality* (Oxford: Clarendon Press, 1989), p. 17. Kagan prefers *pro tanto,* rather than prima facie, and notes that Ross used *prima facie* with effectively the same meaning, which some writers classify as a mistake on Ross's part. See further Andrew E. Reisner, "Prima Facie and Pro Tanto Oughts," *International Encyclopedia of Ethics* [online], first published: 1 February 2013, available at https://onlinelibrary.wiley.com/doi/full/10.1002/9781444367072.wbiee406 (accessed March 24, 2018)

[28] W. D. Ross, *The Right and the Good* (Oxford: Clarendon Press, 1930), esp. pp. 19–36, 88. On important cautions about both the meaning and use of the related notion of "prima facie rights," see Joel Feinberg, *Rights, Justice, and the Bounds of Liberty* (Princeton, NJ: Princeton University Press, 1980), pp. 226–29, 232; and Judith Jarvis Thomson, *The Realm of Rights* (Cambridge, MA: Harvard University Press, 1990), pp. 118–29.

[29] Robert Nozick, "Moral Complications and Moral Structures," *Natural Law Forum* 13 (1968): 1–50, available at https://scholarship.law.nd.edu/cgi/viewcontent.cgi?article=1136...naturallaw_forum

(accessed March 26, 2018); James J. Brummer, "Ross and the Ambiguity of Prima Facie Duty," *History of Philosophy Quarterly* 19 (2002): 401–22. See also Thomas E. Hill, Jr., "Moral Dilemmas, Gaps, and Residues: A Kantian Perspective"; Walter Sinnott-Armstrong, "Moral Dilemmas and Rights"; and Terrance C. McConnell, "Moral Residue and Dilemmas"—all in *Moral Dilemmas and Moral Theory,* ed. Mason.

[30] For a similar view, see Ross, *The Right and the Good,* p. 28.

[31] Henry S. Richardson, "Specifying Norms as a Way to Resolve Concrete Ethical Problems," *Philosophy & Public Affairs* 19 (Fall 1990): 279–310; and Richardson, "Specifying, Balancing, and Interpreting Bioethical Principles," *Journal of Medicine and Philosophy* 25 (2000): 285–307, also in *Belmont Revisited: Ethical Principles for Research with Human Subjects,* ed. James F. Childress, Eric M. Meslin, and Harold T. Shapiro (Washington, DC: Georgetown University Press, 2005), pp. 205–27. See also David DeGrazia, "Moving Forward in Bioethical Theory: Theories, Cases, and Specified Principlism," *Journal of Medicine and Philosophy* 17 (1992): 511–39.

[32] Richardson, "Specifying, Balancing, and Interpreting Bioethical Principles," p. 289.

[33] For an excellent critical examination and case study of how the four-principles approach can and should be used as a practical instrument, see John-Stewart Gordon, Oliver Rauprich, and Jochen Vollman, "Applying the Four-Principle Approach," *Bioethics* 25 (2011): 293–300, with a reply by Tom Beauchamp, "Making Principlism Practical: A Commentary on Gordon, Rauprich, and Vollmann," *Bioethics* 25 (2011): 301–03.

[34] American Academy of Psychiatry and the Law, "Ethical Guidelines for the Practice of Forensic Psychiatry," as revised and adopted May 2005, section III: "The informed consent of the person undergoing the forensic evaluation should be obtained when necessary and feasible. If the evaluee is not competent to give consent, the evaluator should follow the appropriate laws of the jurisdiction. . . . [P]sychiatrists should inform the evaluee that if the evaluee refuses to participate in the evaluation, this fact may be included in any report or testimony. If the evaluee does not appear capable of understanding the information provided regarding the evaluation, this impression should also be included in any report and, when feasible, in testimony." Available at http://www.aapl.org/ethics.htm (accessed February 19, 2018).

[35] Dennis H. Novack et al., "Physicians' Attitudes Toward Using Deception to Resolve Difficult Ethical Problems," *Journal of the American Medical Association* 261 (May 26, 1989): 2980–85. We return to these problems in Chapter 8 (pp. •••–•••).

[36] Richardson, "Specifying Norms," p. 294. The word "always" in this formulation should be understood to mean "in principle always." Specification may, in some cases, reach

a final form.

[37] Other prohibitions, such as rules against murder and rape, may be absolute only because of the meaning of their terms. For example, to say "murder is categorically wrong" may be only to say "unjustified killing is unjustified."

[38] Timothy Quill and Penelope Townsend, "Bad News: Delivery, Dialogue, and Dilemmas," *Archives of Internal Medicine* 151 (March 1991): 463–64.

[39] See Alisa Carse, "Impartial Principle and Moral Context: Securing a Place for the Particular in Ethical Theory," *Journal of Medicine and Philosophy* 23 (1998): 153–69. For a defense of balancing as the best method in such situations, see Joseph P. DeMarco and Paul J. Ford, "Balancing in Ethical Deliberations: Superior to Specification and Casuistry," *Journal of Medicine and Philosophy* 31 (2006): 483–97, esp. 491–93.

[40] See similar reflections in Lawrence Blum, *Moral Perception and Particularity* (New York: Cambridge, 1994), p. 204.

[41] To the extent these six conditions incorporate moral norms, the norms are prima facie, not absolute. Condition 3 is redundant if it cannot be violated when all of the other conditions are satisfied; but it is best to be clear on this point, even if redundant.

[42] See James F. Childress and Ruth Gaare Bernheim, "Public Health Ethics: Public Justification and Public Trust," *Bundesgundheitsblat: Gusundheitsforschung, Gesundheitsschutz* 51, No. 2 (February 2008): 158-63; and Ruth Gaare Bernheim, James F. Childress, Richard J. Bonnie, and Alan L. Melnick, *Essentials of Public Health Ethics: Foundations, Tools, and Interventions* (Boston: Jones and Bartlett, 2014), esp. chaps. 1, 2, & 8.

[43] For a criticism of our conclusion in this paragraph, see Marvin J. H. Lee, "The Problem of 'Thick in Status, Thin in Content' in Beauchamp and Childress' Principlism," *Journal of Medical Ethics* 36 (2010): 525–28. See further Angus Dawson and E. Garrard, "In Defence of Moral Imperialism: Four Equal and Universal Prima Facie Principles," *Journal of Medical Ethics* 32 (2006): 200–4; Walter Sinnott-Armstrong, *Moral Dilemmas,* pp. 216–27; and D. D. Raphael, *Moral Philosophy* (Oxford: Oxford University Press, 1981), pp. 64–65.

[44] See Bernard Gert, Charles M. Culver, and K. Danner Clouser, *Bioethics: A Return to Fundamentals,* 2nd ed. (New York: Oxford University Press, 2006), chap. 4; Clouser and Gert, "A Critique of Principlism," pp. 219–36; Carson Strong, "Specified Principlism," *Journal of Medicine and Philosophy* 25 (2000): 285–307; John H. Evans, "A Sociological Account of the Growth of Principlism," *Hastings Center Report* 30 (September–October 2000): 31–38; Evans, *Playing God: Human Genetic Engineering and the Rationalization of Public Bioethical Debate* (Chicago: University of Chicago

Press, 2002); and Evans, *The History and Future of Bioethics: A Sociological View* (New York: Oxford University Press, 2011). For a critical analysis of Evans' arguments, particularly in *Playing God*, see James F. Childress, "Comments," *Journal of the Society of Christian Ethics* 24, no. 1 (2004): 195-204.</N>

<CN>2</CN>

<CT>Moral Character</CT>

Chapter 1 concentrated on moral norms in the form of principles, rules, obligations, and rights. This chapter focuses on moral character, especially moral virtues, moral ideals, and moral excellence. These categories complement those in the previous chapter. The moral norms discussed in Chapter 1 chiefly govern right and wrong *action*. By contrast, character ethics and virtue ethics concentrate on the *agent* who performs actions and the virtues that make agents morally worthy persons.[1]

The goals and structure of medicine, health care, public health, and research call for a deep appreciation of moral virtues. What often matters most in healthcare interactions and in the moral life generally is not adherence to moral rules, but having a reliable character, good moral sense, and appropriate emotional responsiveness. Even carefully specified principles and rules do not convey what occurs when parents lovingly play with and nurture their children or when physicians and nurses exhibit compassion, patience, and responsiveness in their encounters with patients and families. The feelings and concerns for others that motivate us to take actions often cannot be reduced to a sense of obligation to

follow rules. Morality would be a cold and uninspiring practice without appropriate sympathy, emotional responsiveness, excellence of character, and heartfelt ideals that reach beyond principles and rules.

Some philosophers have questioned the place of virtues in moral theory. They see virtues as less central than action-guiding norms and as difficult to unify in a systematic theory, in part because there are many independent virtues to be considered. Utilitarian Jeremy Bentham famously complained that there is "no marshaling" the virtues and vices because "they are susceptible of no arrangement; they are a disorderly body, whose members are frequently in hostility with one another. . . . Most of them are characterized by that vagueness which is a convenient instrument for the poetical, but dangerous or useless to the practical moralist."[2]

Although principles and virtues are different and learned in different ways, virtues are no less important in the moral life, and in some contexts are probably more important. In Chapter 9, we examine virtue ethics as a type of moral theory and address challenges and criticisms such as Bentham's. In the first few sections of the present chapter, we analyze the concept of virtue; examine virtues in professional roles; treat

the moral virtues of care, caregiving, and caring in health care; and explicate five other focal virtues in both healthcare and research.

<1>THE CONCEPT OF MORAL VIRTUE</1>

A *virtue* is a dispositional trait of character that is socially valuable and reliably present in a person, and a *moral virtue* is a dispositional trait of character that is morally valuable and reliably present. If cultures or social groups approve a trait and regard it as moral, their approval is not sufficient to qualify the trait as a moral virtue. Moral virtue is more than a personal, dispositional trait that is socially approved in a particular group or culture.[3] This approach to the moral virtues accords with our conclusion in Chapter 1 that the common morality excludes provisions found in so-called cultural moralities and individual moralities. The moral virtues, like moral principles, are part of the common morality.

Some define the term *moral virtue* as a disposition to act or a habit of acting in accordance with, and with the aim of following, moral principles, obligations, or ideals.[4] For example, they understand the moral virtue of nonmalevolence as the trait of abstaining from causing harm to others when it would be wrong to cause harm. However, this definition unjustifiably views

virtues as merely derivative from and dependent on principles and fails to capture the importance of moral motives. We care morally about people's motives, and we care especially about their characteristic motives and dispositions, that is, the motivational structures embedded in their character. Persons who are motivated through impartial sympathy and personal affection, for example, are likely to meet our moral approval, whereas persons who act similarly, but are motivated merely by personal ambition, do not.

Consider a person who discharges moral obligations only because they are moral requirements, while intensely disliking being obligated to place the interests of others above his or her personal interests and projects. This person does not feel friendly toward or cherish others and respects their wishes only because moral obligation requires it. If this person's motive is improper, a critical moral ingredient is missing even though he or she consistently performs morally right actions and has a disposition to perform right actions. When a person characteristically lacks an appropriate motivational structure, a necessary condition of virtuous character is absent. The act may be right and the actor blameless, but neither the act nor the actor is *virtuous.* People may be disposed to do what

is right, intend to do it, and do it, while simultaneously yearning to avoid doing it. Persons who characteristically perform morally right actions from such a motivational structure are not morally virtuous even if they invariably perform the morally right action.

Such a person has a morally deficient character, and he or she performs morally right actions for reasons or feelings disconnected from moral motivation. A philanthropist's gift of a new wing of a hospital will be recognized by hospital officials and by the general public as a generous gift, but if the philanthropist is motivated only by a felt need for public praise and only makes the gift to gain such praise, there is a discordance between those feelings and the performance of the praised action. Feelings, intentions, and motives are morally important in a virtue theory in a way that may be lost or obscured in an obligation-based theory.[5]

<1>Virtues in Professional Roles</1>

Persons differ in their sets of character traits. Most individuals have some virtues and some vices while lacking other virtues and vices. However, all persons with normal moral capacities can cultivate the character traits centrally important to morality such as honesty, fairness, fidelity, truthfulness, and benevolence. In professional life in healthcare and research the traits that warrant encouragement

and admiration often derive from role responsibilities. Some virtues are essential for enacting these professional roles, and certain vices are intolerable in professional life. Accordingly, we turn now to virtues that are critically important in professional and institutional roles and practices in biomedical fields.

<2>**Virtues in Roles and Practices**</2>

Professional roles are grounded in institutional expectations and governed by established standards of professional practice. Roles internalize conventions, customs, and procedures of teaching, nursing, doctoring, and the like. Professional practice has traditions that require professionals to cultivate certain virtues. Standards of virtue incorporate criteria of professional merit, and possession of these virtues disposes persons to act in accordance with the objectives of the practices.

In the practice of medicine several goods internal to the profession are appropriately associated with being a good physician. These goods include specific moral and nonmoral skills in the care of patients, the application of specific forms of knowledge, and the teaching of health behaviors. They are achievable only if one lives up to the standards of the good physician, standards that in part define the practice. A practice is not merely a set of technical skills.

Practices should be understood in terms of the respect that practitioners have for the goods internal to the practices. Although these practices sometimes need to be revised, the historical development of a body of standards has established many practices now found at the heart of medicine, nursing, and public health.[6]

Roles, practices, and virtues in medicine, nursing, and other health care and research professions reflect social expectations as well as standards and ideals internal to these professions.[7] The virtues we highlight in this chapter are care—a fundamental virtue for health care relationships—along with five focal virtues found in all health-care professions: compassion, discernment, trustworthiness, integrity, and conscientiousness, all of which support and promote caring and caregiving. Elsewhere in this chapter and in later chapters, we discuss other virtues, including respectfulness, nonmalevolence, benevolence, justice, truthfulness, and fidelity.

To illustrate the difference between standards of moral character in a profession and standards of technical performance in a profession, we begin with an instructive study of surgical error. Charles L. Bosk's influential *Forgive and Remember: Managing Medical Failure* presents an ethnographic study of the way two surgical services handle medical failure, especially failures by surgical residents in "Pacific Hospital" (a name substituted for the hospitals actually

studied).[8] Bosk found that both surgical services distinguish, at least implicitly, between several different forms of error or mistake. The first form is *technical*: A professional discharges role responsibilities conscientiously, but his or her technical training or information still falls short of what the task requires. Every surgeon will occasionally make this sort of mistake. A second form of error is *judgmental*: A conscientious professional develops and follows an incorrect strategy. These errors are also to be expected. Attending surgeons forgive momentary technical and judgmental errors but remember them when a pattern develops indicating that a surgical resident lacks the technical and judgmental skills to be a competent surgeon. A third form of error is *normative:* A physician violates a norm of conduct or fails to possess a moral skill, particularly by failing to discharge moral obligations conscientiously or by failing to acquire and exercise critical moral virtues such as conscientiousness. Bosk concludes that surgeons regard technical and judgmental errors as less important than moral errors, because every conscientious person can be expected to make "honest errors" or "good faith errors," whereas moral errors such as failures of conscientiousness are considered profoundly serious when a pattern indicates a defect of character.

Bosk's study indicates that persons of high moral character acquire a reservoir of goodwill in assessments of either the praiseworthiness or the blameworthiness of their actions. If a conscientious surgeon and another surgeon who is not adequately conscientious make the same technical or judgmental errors, the conscientious surgeon will not be subjected to moral blame to the same degree as the other surgeon.

<2>**Virtues in Different Professional Models**</2>

Professional virtues were historically integrated with professional obligations and ideals in codes of health care ethics. Insisting that the medical profession's "prime objective" is to render service to humanity, an American Medical Association (AMA) code in effect from 1957 to 1980 urged the physician to be "upright" and "pure in character and . . . diligent and conscientious in caring for the sick." It endorsed the virtues that Hippocrates commended: modesty, sobriety, patience, promptness, and piety. However, in contrast to its first code of 1847, the AMA over the years has increasingly de-emphasized virtues in its codes. The 1980 version for the first time eliminated all trace of the virtues except for the admonition to expose "those physicians deficient in character or competence." This pattern of de-emphasis regrettably still continues.

Thomas Percival's 1803 book, *Medical Ethics,* is a classic example of an attempt to establish the proper set of virtues in medicine. Starting from the assumption that the patient's best medical interest is the proper goal of medicine, Percival reached conclusions about the good physician's traits of character, which were primarily tied to responsibility for the patient's medical welfare.[9] This model of medical ethics supported medical paternalism with effectively no attention paid to respect for patients' autonomous choices.

In traditional nursing, where the nurse was often viewed as the "handmaiden" of the physician, the nurse was counseled to cultivate the passive virtues of obedience and submission. In contemporary models in nursing, by contrast, active virtues have become more prominent. For example, the nurse's role is now often regarded as one of advocacy for patients.[10] Prominent virtues include respectfulness, considerateness, justice, persistence, and courage.[11] Attention to patients' rights and preservation of the nurse's integrity also have become increasingly prominent in some contemporary models.

The conditions under which ordinarily praiseworthy virtues become morally unworthy present thorny ethical issues. Virtues such as loyalty, courage, generosity, kindness, respectfulness, and benevolence at times lead persons to act inappropriately and unacceptably. For instance, the physician who acts kindly and

loyally by not reporting the incompetence of a fellow physician acts unethically. This failure to report misconduct does not suggest that loyalty and kindness are not virtues. It indicates only that the virtues need to be accompanied by an understanding of what is right and good and of what deserves loyalty, kindness, generosity, and the like.

<1>The Central Virtue of Caring</1>

As the language of *health care, medical care,* and *nursing care* suggests, the virtue of care, or caring, is prominent in professional ethics. We treat this virtue as fundamental in relationships, practices, and actions in health care. In explicating this family of virtues we draw on what has been called the *ethics of care,* which we interpret as a form of virtue ethics.[12] The ethics of care emphasizes traits valued in intimate personal relationships such as sympathy, compassion, fidelity, and love. *Caring* refers to care for, emotional commitment to, and willingness to act on behalf of persons with whom one has a significant relationship. *Caring for* is expressed in actions of "caregiving," "taking care of," and "due care." The nurse's or physician's trustworthiness and quality of care and sensitivity in the face of patients' problems, needs, and vulnerabilities are integral to their professional moral lives.

The ethics of care emphasizes what physicians and nurses do—for example, whether they break or maintain confidentiality—and how they perform those actions, which motives and feelings underlie them, and whether their actions promote or thwart positive relationships.

<2>**The Origins of the Ethics of Care**</2>

The ethics of care, understood as a form of philosophical ethics, originated and continues to flourish in feminist writings. The earliest works emphasized how women display an ethic of care, by contrast to men, who predominantly exhibit an ethic of rights and obligations. Psychologist Carol Gilligan advanced the influential hypothesis that "women speak in a different voice"—a voice that traditional ethical theory failed to appreciate. She discovered "the voice of care" through empirical research involving interviews with girls and women. This voice, she maintained, stresses empathic association with others, not based on "the primacy and universality of individual rights, but rather on . . . a very strong sense of being responsible."[13]

Gilligan identified two modes of moral thinking: an ethic of care and an ethic of rights and justice. She did not claim that these two modes of thinking strictly correlate with gender or that all women or all men speak in the same moral

voice.[14] She maintained only that men tend to embrace an ethic of rights and justice that uses quasi-legal terminology and impartial principles, accompanied by dispassionate balancing and conflict resolution, whereas women tend to affirm an ethic of care that centers on responsiveness in an interconnected network of needs, care, and prevention of harm.[15]

<2>**Criticisms of Traditional Theories by Proponents of an Ethics of Care**</2>

Proponents of the care perspective often criticize traditional ethical theories that tend to de-emphasize virtues of caring. Two criticisms merit consideration here.[16]

<3>***Challenging impartiality.***</3> Some proponents of the care perspective argue that theories of obligation unduly telescope morality by overemphasizing detached fairness. This orientation is suitable for some moral relationships, especially those in which persons interact as equals in a public context of impersonal justice and institutional constraints, but moral detachment also may reflect a lack of caring responsiveness. In the extreme case, detachment becomes uncaring indifference. Lost in the *detachment* of impartiality is an *attachment* to what we care about most and is closest to us—for example, our loyalty to family,

friends, and groups. Here partiality toward others is morally permissible and is an expected form of interaction. This kind of partiality is a feature of the human condition without which we might impair or sever our most important relationships.[17]

Proponents of a care ethics do not recommend complete abandonment of principles if principles are understood to allow room for discretionary and contextual judgment. However, some defenders of the ethics of care find principles largely irrelevant, ineffectual, or unduly constrictive in the moral life. A defender of principles could hold that principles of care, compassion, and kindness tutor our responses in caring, compassionate, and kind ways. But this attempt to rescue principles seems rather empty. Moral experience confirms that we often do rely on our emotions, capacity for sympathy, sense of friendship, and sensitivity to find appropriate moral responses. We could produce rough generalizations about how caring clinicians should respond to patients, but such generalizations cannot provide adequate guidance for all interactions. Each situation calls for responses beyond following rules, and actions that are caring in one context may be offensive or even harmful in another.

<3>***Relationships and emotion.***</3> The ethics of care places special emphasis

on mutual interdependence and emotional responsiveness. Many human relationships in health care and research involve persons who are vulnerable, dependent, ill, and frail. Feeling for and being immersed in the other person are vital aspects of a moral relationship with them.[18] A person seems morally deficient if he or she acts according to norms of obligation without appropriately aligned feelings, such as concern and sympathy for a patient who is suffering. Good health care often involves insight into the needs of patients and considerate attentiveness to their circumstances.[19]

In the history of human experimentation, those who first recognized that some subjects of research were brutalized, subjected to misery, or placed at unjustifiable risk were persons able to feel sympathy, compassion, disgust, and outrage about the situation of these research subjects. They exhibited perception of and sensitivity to the feelings of subjects where others lacked comparable perceptions, sensitivities, and responses. This emotional sensitivity does not reduce moral response to emotional response. Caring has a cognitive dimension and requires a range of moral skills that involve insight into and understanding of another's circumstances, needs, and feelings.

One proponent of the ethics of care argues that action is sometimes appropriately principle-guided, but not necessarily always governed by or derived

from principles.[20] This statement moves in the right direction for construction of a comprehensive moral framework. We need not reject principles of obligation in favor of virtues of caring, but moral judgment clearly involves moral skills beyond those of specifying and balancing general principles. An ethic that emphasizes the virtues of caring can serve health care well because it is close to the relationships and processes of decision making found in clinical contexts, and provides insights into basic commitments of caring and caretaking. It also liberates health professionals from the narrow conceptions of role responsibilities that have been delineated in some professional codes of ethics.

<1>Five Focal Virtues</1>

We now turn to five focal virtues for health professionals: compassion, discernment, trustworthiness, integrity, and conscientiousness. These virtues are important for the development and expression of caring, which we have presented as a fundamental orienting virtue in health care. These five additional virtues provide a moral compass of character for health professionals that builds on centuries of thought about health care ethics.[21]

<2>**Compassion**</2>

Compassion, says Edmund Pellegrino, is a "prelude to caring."[22] The virtue of compassion combines an attitude of active regard for another's welfare together with sympathy, tenderness, and discomfort at another's misfortune or suffering.[23] Compassion presupposes sympathy, has affinities with mercy, and is expressed in acts of beneficence that attempt to alleviate the misfortune or suffering of another person.

Nurses and physicians must understand the feelings and experiences of patients to respond appropriately to them and their illnesses and injuries—hence the importance of empathy, which involves sensing or even reconstructing another person's mental experience, whether that experience is negative or positive.[24] As important as empathy is for compassion and other virtues, the two are different and empathy does not always lead to compassion. Some literature on professionalism in medicine and health care now often focuses on empathy rather than compassion, but this literature risks making the mistake of viewing empathy alone as sufficient for humanizing medicine and health care while overlooking its potential dangers.[25]

Compassion generally focuses on others' pain, suffering, disability, or misery—the typical occasions for compassionate response in health care. Using the language of *sympathy,* eighteenth-century philosopher David Hume pointed to

a typical circumstance of compassion in surgery and explained how such feelings arise:

> <EXT>Were I present at any of the more terrible operations of surgery, 'tis certain, that even before it begun, the preparation of the instruments, the laying of the bandages in order, the heating of the irons, with all the signs of anxiety and concern in the patient and assistants, wou'd have a great effect upon my mind, and excite the strongest sentiments of pity and terror. No passion of another discovers itself immediately to the mind. We are only sensible of its causes or effects. From *these* we infer the passion: And consequently *these* give rise to our sympathy.[26]</EXT>

Physicians and nurses who express little or no compassion in their behavior may fail to provide what patients need most. The physician, nurse, or social worker altogether lacking in the appropriate display of compassion has a moral weakness. However, compassion also can cloud judgment and preclude rational and effective responses. In one reported case, a long-alienated son wanted to continue a futile and painful treatment for his near-comatose father in an intensive care unit (ICU) to have time to "make his peace" with his father. Although the son understood that his alienated father had no cognitive capacity, the son wanted to work through his sense of regret and say a proper good-bye. Some hospital staff

argued that the patient's grim prognosis and pain, combined with the needs of others waiting to receive care in the ICU, justified stopping the treatment, as had been requested by the patient's close cousin and informal guardian. Another group in the unit regarded continued treatment as an appropriate act of compassion toward the son, who they thought should have time to express his farewells and regrets to make himself feel better about his father's death. The first group, by contrast, viewed this expression of compassion as misplaced because of the patient's prolonged agony and dying. In effect, those in the first group believed that the second group's compassion prevented clear thinking about primary obligations to this patient.[27]

Numerous writers in the history of ethical theory have proposed a cautious approach to compassion. They argue that a passionate, or even a compassionate, engagement with others can blind reason and prevent impartial reflection. Health care professionals understand and appreciate this phenomenon. Constant contact with suffering can overwhelm and even paralyze a compassionate physician or nurse. Impartial judgment sometimes gives way to impassioned decisions, and emotional burnout can arise. To counteract this problem, medical education and nursing education are well designed when they inculcate detachment alongside

compassion. The language of *detached concern* and *compassionate detachment* came to the fore in this context.

<2>**Discernment**</2>

The virtue of discernment brings sensitive insight, astute judgment, and understanding to bear on action. Discernment involves the ability to make fitting judgments and reach decisions without being unduly influenced by extraneous considerations, fears, personal attachments, and the like. Some writers closely associate discernment with practical wisdom, or *phronesis,* to use Aristotle's term. A person of practical wisdom knows which ends to choose, knows how to realize them in particular circumstances, and carefully selects from among the range of possible actions, while keeping emotions within proper bounds. In Aristotle's model, the practically wise person understands how to act with the right intensity of feeling, in just the right way, at just the right time, with a proper balance of reason and desire.[28]

A discerning person is disposed to understand and perceive what circumstances demand in the way of human responsiveness. For example, a discerning physician will see when a despairing patient needs comfort rather than privacy, and vice versa. If comfort is the right choice, the discerning physician

will find the right type and level of consolation to be helpful rather than intrusive. If a rule guides action in a particular case, seeing *how* to best follow the rule involves a form of discernment that is independent of seeing *that* the rule applies.

The virtue of discernment thus involves understanding both that and how principles and rules apply. For instance, acts of respect for autonomy and beneficence will vary in health care contexts, and the ways in which clinicians discerningly implement these principles in the care of patients will be as different as the many ways in which devoted parents care for their children.

<2>**Trustworthiness**</2>

Virtues, Annette Baier maintains, "are personal traits that contribute to a good climate of trust between people, when trust is taken to be acceptance of being, to some degree and in some respects, in another's power."[29] Trust is a confident belief in and reliance on the moral character and competence of another person, often a person with whom one has an intimate or established relationship. Trust entails a confidence that another will reliably act with the right motives and feelings and in accordance with appropriate moral norms.[30] To be *trustworthy* is to warrant another's confidence in one's character and conduct.

Traditional ethical theories rarely mention either trust or trustworthiness. However, Aristotle took note of one important aspect of trust and trustworthiness. He maintained that when relationships are voluntary and among intimates, by contrast to legal relationships among strangers, it is appropriate for the law to forbid lawsuits for harms that occur. Aristotle reasoned that intimate relationships involving "dealings with one another as good and trustworthy" hold persons together more than "bonds of justice" do.[31]

Nothing is more valuable in health care organizations than the maintenance of a culture of trust. Trust and trustworthiness are essential when patients are vulnerable and place their hope and their confidence in health care professionals. A true climate of trust is endangered in contemporary health care institutions, as evidenced by the number of medical malpractice suits and adversarial relations between health care professionals and the public. Overt distrust has been engendered by mechanisms of managed care, because of the incentives some health care organizations create for physicians to limit the amount and kinds of care they provide to patients. Appeals have increased for ombudsmen, patient advocates, legally binding "directives" to physicians, and the like. Among the contributing causes of the erosion of a climate of trust are the loss of intimate contact between physicians and patients, the increased use of specialists, the lack

of adequate access to adequate healthcare insurance, and the growth of large, impersonal, and bureaucratic medical institutions.[32]

<2>**Integrity**</2>

Some writers in bioethics hold that the primary virtue in health care is integrity.[33] People often justify their actions or refusals to act on grounds that they would otherwise compromise or sacrifice their integrity. Later in this chapter we discuss appeals to integrity as invocations of *conscience,* but we confine attention at present to the virtue of integrity.

The central place of integrity in the moral life is beyond dispute, but what the term means is less clear. In its most general sense, "moral integrity" means soundness, reliability, wholeness, and integration of moral character. In a more restricted sense, the term refers to objectivity, impartiality, and fidelity in adherence to moral norms. Accordingly, the virtue of integrity represents two aspects of a person's character. The first is a coherent integration of aspects of the self—emotions, aspirations, knowledge, and the like—so that each complements and does not frustrate the others. The second is the character trait of being faithful to moral values and standing up in their defense when necessary. A person can lack moral integrity in several respects—for example, through hypocrisy,

insincerity, bad faith, and self-deception. These vices represent breaks in the connections among a person's moral convictions, emotions, and actions. The most common deficiency is probably a lack of sincerely and firmly held moral convictions, but no less important is the failure to act consistently on the moral beliefs that one does hold.

Problems in maintaining integrity may also arise from a conflict of moral norms, or from moral demands that require persons to halt or abandon personal goals and projects. Persons may experience a sense of loss of their autonomy and feel violated by the demand to sacrifice their personal commitments and objectives.[34] For example, if a nurse is the only person in her family who can properly manage her mother's health, health care, prescription medications, nursing home arrangements, explanations to relatives, and negotiations with physicians, little time may be left for her personal projects and commitments. Such situations can deprive persons of the liberty to structure and integrate their lives as they choose. If a person has structured his or her life around personal goals that are ripped away by the needs and agendas of others, a loss of personal integrity occurs.

Problems of professional integrity often center on wrongful conduct in professional life. Because breaches of professional integrity involve violations of

professional standards, they are often viewed as violations of the rules of professional associations, codes of medical ethics, or medical traditions,[35] but this vision needs to be broadened. Breaches of professional integrity also occur when a physician prescribes a drug that is no longer recommended for the outcome needed, enters into a sexual relationship with a patient, or follows a living will that calls for a medically inappropriate intervention.

Sometimes conflicts arise between a person's sense of moral integrity and what is required for professional integrity. Consider medical practitioners who, because of their religious commitments to the sanctity of life, find it difficult to participate in decisions not to do everything possible to prolong life. To them, participating in removing ventilators and intravenous fluids from patients, even from patients with a clear advance directive, violates their moral integrity. Their commitments may create morally troublesome situations in which they must either compromise their fundamental commitments or withdraw from the care of the patient. Yet compromise seems what a person, or an organization, of integrity cannot do, because it involves the sacrifice of deep moral commitments.[36]

Health care facilities cannot entirely eliminate these and other problems of staff disagreement and conflicting commitments, but persons with the virtues of patience, humility, and tolerance can help reduce the problems. Situations that

compromise integrity can be ameliorated if participants anticipate the problem before it arises and recognize the limits and fallibility of their personal moral views. Participants in a dispute may also have recourse to consultative institutional processes, such as hospital ethics committees. However, it would be ill-advised to recommend that a person of integrity can and should always negotiate and compromise his or her values in an intrainstitutional confrontation. There is something ennobling and admirable about the person or organization that refuses to compromise beyond a certain carefully considered moral threshold. To compromise below the threshold of integrity is simply to lose it.

<2>**Conscientiousness**</2>

The subject of integrity and compromise leads directly to a discussion of the virtue of conscientiousness and accounts of conscience. An individual acts conscientiously if he or she is motivated to do what is right because it is right, has worked with due diligence to determine what is right, intends to do what is right, and exerts appropriate effort to do so. Conscientiousness is the character trait of acting in this way.

<3>***Conscience and conscientiousness.***</3> *Conscience* has often been viewed as a mental faculty of, and authority for, moral decision making.[37] Slogans such as, "Let your conscience be your guide" suggest that conscience is the final authority in moral justification. However, such a view fails to capture the nature of either conscience or conscientiousness, as the following case presented by Bernard Williams helps us see: Having recently completed his Ph.D. in chemistry, George has not been able to find a job. His family has suffered from his failure: They are short of money, his wife has had to take additional work, and their small children have been subjected to considerable strain, uncertainty, and instability. An established chemist can get George a position in a laboratory that pursues research on chemical and biological weapons. Despite his perilous financial and familial circumstances, George concludes that he cannot accept this position because of his conscientious opposition to chemical and biological warfare. The senior chemist notes that the research will continue no matter what George decides. Furthermore, if George does not take this position, it will be offered to another young man who would vigorously pursue the research. Indeed, the senior chemist confides, his concern about the other candidate's nationalistic fervor and uncritical zeal for research in chemical and biological warfare motivated him to recommend George for the job. George's wife is puzzled and hurt by George's

reaction. She sees nothing wrong with the research. She is profoundly concerned about their children's problems and the instability of their family. Nonetheless, George forgoes this opportunity both to help his family and to prevent a destructive fanatic from obtaining the position. He says his conscience stands in the way.[38]

Conscience, as this example suggests, is not a special moral faculty or a self-justifying moral authority. It is a form of self-reflection about whether one's acts are obligatory or prohibited, right or wrong, good or bad, virtuous or vicious. It also involves an internal sanction that comes into play through critical reflection. When individuals recognize their acts as violations of an appropriate standard, this sanction often appears as a bad conscience in the form of feelings of remorse, guilt, shame, disunity, or disharmony. A conscience that sanctions conduct in this way does not signify bad moral character. To the contrary, this experience of conscience is most likely to occur in persons of strong moral character and may even be a necessary condition of morally good character.[39] Kidney donors have been known to say, "I had to do it. I couldn't have backed out, not that I had the feeling of being trapped, because the doctors offered to get me out. I just had to do it."[40] Such judgments derive from ethical standards that are sufficiently powerful that violating them would diminish integrity and result in

guilt or shame.[41]

When people claim that their actions are conscientious, they sometimes feel compelled by conscience to resist others' authoritative demands. Instructive examples are found in military physicians who believe they must answer first to their consciences and cannot plead "superior orders" when commanded by a superior officer to commit what they believe to be a moral wrong. Agents sometimes act out of character in order to perform what they judge to be the morally appropriate action. For example, a normally cooperative and agreeable physician may indignantly, but justifiably, protest an insurance company's decision not to cover the costs of a patient's treatment. Such moral indignation and outrage can be appropriate and admirable.

<3>***Conscientious refusals.***</3> Conscientious objections and refusals by physicians, nurses, pharmacists, and other health care professionals raise difficult issues for public policy, professional organizations, and health care institutions. Examples are found in a physician's refusal to honor a patient's legally valid advance directive to withdraw artificial nutrition and hydration, a nurse's refusal to participate in an abortion or sterilization procedure, and a pharmacist's refusal to fill a prescription for an emergency contraception.

There are good reasons to promote conscientiousness and to respect acts of conscience.

Respecting conscientious refusals in health care is an important value, and these refusals should be accommodated unless there are overriding conflicting values. Banning or greatly restricting conscientious refusals in health care could have several negative consequences. It could, according to one analysis, negatively affect the type of people who choose medicine as their vocation and how practicing physicians view and discharge professional responsibilities. It could also foster "callousness" and encourage physicians' "intolerance" of diverse moral beliefs among their patients (and perhaps among their colleagues as well).[42] These possible negative effects are somewhat speculative, but they merit consideration in forming institutional and public policies.

Also meriting consideration is that some conscientious refusals adversely affect patients' and others' legitimate interests in (1) timely access, (2) safe and effective care, (3) respectful care, (4) nondiscriminatory treatment, (5) care that is not unduly burdensome, and (5) privacy and confidentiality. Hence, public policy, professional associations, and healthcare institutions should seek to recognize and accommodate conscientious refusals as long as they can do so without seriously

compromising patients' rights and interests. The metaphor of *balancing* professionals' and patients' rights and interests is commonly used to guide efforts to resolve such conflicts, but it offers limited guidance and no single model of appropriate response covers all cases.[43]

Institutions such as hospitals and pharmacies can often ensure the timely performance of needed or requested services while allowing conscientious objectors not to perform those services.[44] However, ethical problems arise when, for example, a pharmacist refuses, on grounds of complicity in moral wrongdoing, to transfer a consumer's prescription or to inform the consumer of pharmacies that would fill the prescription. According to one study, only 86% of U.S. physicians surveyed regard themselves as obligated to disclose information about morally controversial medical procedures to patients, and only 71% of U.S. physicians recognize an obligation to refer patients to another physician for such controversial procedures.[45] Given these results, millions of patients in the U.S. may be under the care of physicians who do not recognize these obligations or are undecided about them.

At a minimum, in our view, health care professionals have an ethical duty to inform prospective employers and prospective patients, clients, and consumers in advance of their personal conscientious objections to performing vital services.

Likewise, they have an ethical duty to disclose options for obtaining legal, albeit morally controversial, services; and sometimes they have a duty to provide a referral for those services. They also may have a duty to perform the services in emergency circumstances when the patient is at risk of adverse health effects and a timely referral is not possible.[46]

Determining the appropriate scope of protectable conscientious refusals is a vexing problem, particularly when those refusals involve expansive notions of what counts as assisting or participating in the performance of a personally objectionable action. Such expansive notions sometimes include actions that are only indirectly related to the objectionable procedure. For example, some nurses have claimed conscientious exemption from all forms of participation in the care of patients having an abortion or sterilization, including filling out admission forms or providing post-procedure care. It is often difficult and sometimes impractical for institutions to pursue their mission while exempting objectors to such broadly delineated forms of participation in a procedure.

<1>Moral Ideals</1>

We argued in Chapter 1 that norms of obligation in the common morality constitute a moral minimum of requirements that govern everyone. These

standards differ from extraordinary moral standards that are not *required* of any person. Moral ideals such as extraordinary generosity are rightly admired and approved by all morally committed persons, and in this respect they are part of the common morality. Extraordinary moral standards come from a morality of aspiration in which individuals, communities, or institutions adopt high ideals not required of others. We can praise and admire those who live up to these ideals, but we cannot blame or criticize persons who do not pursue the ideals.

A straightforward example of a moral ideal in biomedical ethics is found in "expanded access" or "compassionate use" programs that—prior to regulatory approval—authorize access to an investigational drug or device for patients with a serious or immediately life-threatening disease or condition. These patients have exhausted available therapeutic options and are situated so that they cannot participate in a clinical trial of a comparable investigational product. Although it is compassionate and justified to provide some investigational products for therapeutic use, it is generally not obligatory to do so. These programs are compassionate, nonobligatory, and motivated by a goal of providing a good to these patients. The self-imposed moral commitment by the sponsors of the investigational product usually springs from moral ideals of communal service or

providing a benefit to individual patients. (See Chapter 6, pp. •••–•••, for additional discussion of expanded access programs.)

With the addition of moral ideals, we now have four categories pertaining to moral action: (1) actions that are right and obligatory (e.g., truth-telling); (2) actions that are wrong and prohibited (e.g., murder and rape); (3) actions that are optional and morally neutral, and so neither wrong nor obligatory (e.g., playing chess with a friend); and (4) actions that are optional but morally meritorious and praiseworthy (e.g., sending flowers to a hospitalized friend). We concentrated on the first two in Chapter 1, occasionally mentioning the third. We now focus exclusively on the fourth.

<2>**Supererogation and Virtue**</2>

Supererogation is a category of moral ideals pertaining principally to ideals of action, but it has important links both to virtues and to Aristotelian ideals of moral excellence.[47] The etymological root of *supererogation* means paying or performing beyond what is owed or, more generally, doing more than is required. This notion has four essential conditions. First, supererogatory acts are optional and neither required nor forbidden by common-morality standards of obligation. Second, supererogatory acts exceed what the common morality of obligation

demands, but at least some moral ideals are *endorsed* by all persons committed to the common morality. Third, supererogatory acts are intentionally undertaken to promote the welfare interests of others. Fourth, supererogatory acts are morally good and praiseworthy in themselves and are not merely acts undertaken with good intentions.

Despite the first condition, individuals who act on moral ideals do not always *consider* their actions to be morally optional. Many heroes and saints describe their actions in the language of *ought, duty,* and *necessity:* "I had to do it." "I had no choice." "It was my duty." The point of this language is to express a personal sense of obligation, not to state a general obligation. The agent accepts, as a pledge or assignment of personal responsibility, a norm that lays down what ought to be done. At the end of Albert Camus's *The Plague,* Dr. Rieux decides to make a record of those who fought the pestilence. It is to be a record, he says, of "what *had to be done* . . . despite their personal afflictions, by all who, while unable to be saints but refusing to bow down to pestilences, strive their utmost to be healers."[48] Such healers accept exceptional risks and thereby exceed the obligations of the common morality and of professional associations and traditions.

Many supererogatory acts would be morally obligatory were it not for some abnormal adversity or risk in the face of which the individual elects not to invoke an allowed exemption based on the adversity or risk.[49] If persons have the strength of character that enables them to resist extreme adversity or assume additional risk to fulfill their own conception of their obligations, it makes sense to accept their view that they are under a self-imposed obligation. The hero who says, "I was only doing my duty," is speaking as one who accepts a standard of moral excellence. This hero does not make a mistake in regarding the action as personally required and can view failure as grounds for guilt, although no one else is free to evaluate the act as a moral failure.

Despite the language of "exceptional" and "extreme adversity," not all supererogatory acts are extraordinarily arduous, costly, or risky. Examples of less demanding forms of supererogation include generous gift-giving, volunteering for public service, forgiving another's costly error, and acting from exceptional kindness. Many everyday actions exceed obligation without reaching the highest levels of supererogation. For example, a nurse may put in extra hours of work during the day and return to the hospital at night to visit patients. This nurse's actions are morally excellent, but he or she does not thereby qualify as a saint or hero.

Often we are uncertain whether an action exceeds obligation because the boundaries of obligation and supererogation are ill defined. There may be no clear norm of action, only a virtue of character at work. For example, what is a nurse's role obligation to desperate, terminally ill patients who cling to the nurse for comfort in their few remaining days? If the obligation is that of spending forty hours a week conscientiously fulfilling a job description, the nurse exceeds that obligation by just a few off-duty visits to patients. If the obligation is simply to help patients overcome burdens and meet a series of challenges, a nurse who does so while displaying extraordinary patience, fortitude, and friendliness well exceeds the demands of obligation. Health care professionals sometimes live up to what would ordinarily be a role obligation (such as complying with basic standards of care), while making a sacrifice or taking an additional risk. These cases exceed obligation, but they may not qualify as supererogatory actions.

<2>**The Continuum from Obligation to Supererogation**</2>

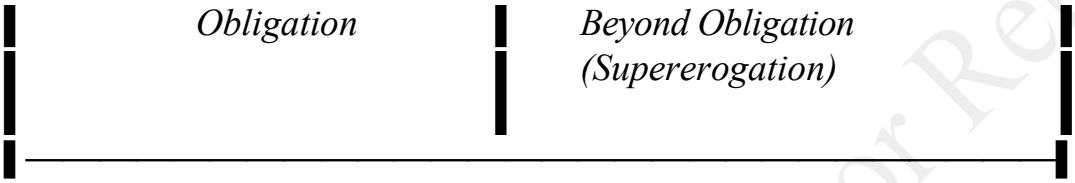
Our analysis may seem to suggest that actions should be classified as either obligatory or beyond the obligatory. The better view, however, is that actions sometimes do not fit neatly into these categories because they fall between the two. Common morality distinctions and ethical theory are not precise enough to

determine whether all actions are morally required or morally elective. This problem is compounded in professional ethics, because professional roles engender obligations that do not bind persons who do not occupy the relevant professional roles. Hence, the two "levels" of the obligatory and the supererogatory lack sharp boundaries both in the common morality and in professional ethics.

Actions may be strictly obligatory, beyond the obligatory, or somewhere between these two classifications. A continuum runs from strict obligation (such as the obligations in the core principles and rules in the common morality) through weaker obligations that are still within the scope of the morally required (such as double checking one's professional work to be sure that no medical errors have occurred), and on to the domain of the morally nonrequired and the exceptionally virtuous. The nonrequired starts with low-level supererogation, such as walking a visitor lost in a hospital's corridors to a doctor's office. Here an absence of generosity or kindness in helping someone may constitute a small defect in the moral life, rather than a failure of obligation. The continuum ends with high-level supererogation, such as heroic acts of self-sacrifice, as in highly risky

medical self-experimentation. A continuum exists on each level. The following diagram represents the continuum.

<Comp: set diagram below as per design in 7/e, p. 47, using all solid lines with no breaks.>



<end>

This continuum moves from strict obligation to the most arduous and elective moral ideal. The horizontal line represents a continuum with rough, not sharply defined, breaks. The middle vertical line divides the two general categories, but is not meant to indicate a sharp break. Accordingly, the horizontal line expresses a continuum across the four lower categories and expresses the scope of the common morality's reach into the domains of both moral obligation and nonobligatory moral ideals.

Joel Feinberg argues that supererogatory acts are "located on an altogether different scale than obligations."[50] The preceding diagram suggests that this comment is correct in one respect, but potentially incorrect in another. The right half of the diagram is not scaled byobligation, whereas the left half is. In this

respect, Feinberg's comment is correct. However, the full horizontal line is connected by a single scale of moral value in which the right is continuous with the left. For example, obligatory acts of beneficence and supererogatory acts of beneficence are on the same scale because they are morally of the same kind. The domain of supererogatory ideals is continuous with the domain of norms of obligation by *exceeding* those obligations in accordance with the several defining conditions of supererogation listed previously.

<2>**The Place of Ideals in Biomedical Ethics**</2>

Many beneficent actions by health care professionals straddle the territory marked in the preceding diagram between *Obligation* and *Beyond Obligation* (in particular, the territory between [2] and [3]). Matters become more complicated when we introduce the distinction discussed in Chapter 1 between professional obligations and obligations incumbent on everyone. Many moral duties established by roles in health care are not moral obligations for persons not in these roles. These duties in medicine and nursing are profession-relative, and some are role obligations even when not formally stated in professional codes. For example, the expectation that physicians and nurses will encourage and cheer

despondent patients is a profession-imposed obligation, though not one typically incorporated in a professional code of ethics.

Some customs in the medical community are not well established as obligations, such as the belief that physicians and nurses should efface self-interest and take risks in attending to patients. The nature of "obligations" when caring for patients with SARS (severe acute respiratory syndrome), Ebola, and other diseases with a significant risk of transmission and a significant mortality rate has been controversial, and professional codes and medical association pronouncements have varied.[51] One of the strongest statements of physician duty appeared in the previously mentioned original 1847 Code of Medical Ethics of the American Medical Association (AMA): "when pestilence prevails, it is their [physicians'] duty to face the danger, and to continue their labours for the alleviation of the suffering, even at the jeopardy of their own lives."[52] This statement was retained in subsequent versions of the AMA code until the 1950s, when the statement was eliminated, perhaps in part because of a false sense of the permanent conquest of dangerous contagious diseases.

We usually cannot resolve controversies about duty in face of risk without determining the level of risk—in terms of both the probability and the seriousness of harm—that professionals are expected to assume and setting a threshold

beyond which the level of risk is so high that it renders action optional rather than obligatory. The profound difficulty of drawing this line should help us appreciate why some medical associations have urged their members to be courageous and treat patients with potentially lethal infectious diseases, while other associations have advised their members that treatment is optional in many circumstances.[53] Still others have taken the view that both virtue and obligation converge to the conclusion that health care professionals should set aside self-interest, within limits, and that the health care professions should take actions to ensure appropriate care.[54]

Confusion occasionally arises about such matters because of the indeterminate boundaries of what is required in the common morality, what is or should be required in professional communities, and what is a matter of moral character beyond the requirements of moral obligations. In many cases it is doubtful that health care professionals fail to discharge *moral obligations* when they fall short of the highest standards in the profession.

<1>Moral Excellence</1>

Aristotelian ethical theory closely connects moral excellence to moral character, moral virtues, and moral ideals. Aristotle succinctly presents this idea: "A truly

good and intelligent person . . . from his resources at any time will do the finest actions he can, just as a good general will make the best use of his forces in war, and a good shoemaker will produce the finest shoe he can from the hides given him, and similarly for all other craftsmen."[55] This passage captures the demanding nature of Aristotle's theory by contrast to ethical theories that focus largely or entirely on the moral minimum of obligations.

The value of this vision of excellence is highlighted by John Rawls, in conjunction with what he calls the "Aristotelian principle":

> <EXT>The excellences are a condition of human flourishing; they are goods from everyone's point of view. These facts relate them to the conditions of self-respect, and account for their connection with our confidence in our own value. . . . [T]he virtues are [moral] excellences. . . . The lack of them will tend to undermine both our self-esteem and the esteem that our associates have for us.[56]</EXT>

We now draw on this general background in Aristotelian theory and on our prior analysis of moral ideals and supererogation for an account of moral excellence.

<2>**The Idea of Moral Excellence** </2>

We begin with four considerations that motivate us to treat this subject. First, we hope to overcome an undue imbalance in contemporary ethical theory and bioethics that results from focusing narrowly on the moral minimum of

obligations while ignoring supererogation and moral ideals.[57] This concentration dilutes the moral life, including our expectations for ourselves, our close associates, and health professionals. If we expect only the moral minimum of obligation, we may lose an ennobling sense of moral excellence. A second and related motivation is our hope to overcome a suppressed skepticism in contemporary ethical theory concerning high ideals in the moral life. Some influential writers note that high moral ideals must compete with other goals and responsibilities in life, and consequently that these ideals can lead persons to neglect other matters worthy of attention, including personal projects, family relationships, friendships, and experiences that broaden outlooks.[58] A third motivation concerns what we call in Chapter 9 the *criterion of comprehensiveness* in an ethical theory. Recognizing the value of moral excellence allows us to incorporate a broad range of moral virtues and forms of supererogation beyond the obligations, rights, and virtues that comprise ordinary morality. Fourth, a model of moral excellence merits pursuit because it indicates what is worthy of aspiration. Morally exemplary lives provide ideals that help guide and inspire us to higher goals and morally better lives.

<2>**Aristotelian Ideals of Moral Character**</2>

Aristotle maintained that we acquire virtues much as we do skills such as carpentry, playing a musical instrument, and cooking.[59] Both moral and nonmoral skills require training and practice. Obligations play a less central role in his account. Consider, for example, a person who undertakes to expose scientific fraud in an academic institution. It is easy to frame this objective as a matter of obligation, especially if the institution has a policy on fraud. However, suppose this person's correct reports of fraud to superiors are ignored, and eventually her job is in jeopardy and her family receives threats. At some point, she has fulfilled her obligations and is not morally required to pursue the matter further. However, if she does persist, her continued pursuit would be praiseworthy, and her efforts to bring about institutional reform could even reach heroic dimensions. Aristotelian theory could and should frame this situation in terms of the person's level of commitment, the perseverance and endurance shown, the resourcefulness and discernment in marshalling evidence, and the courage, as well as the decency and diplomacy displayed in confronting superiors.

An analogy to education illustrates why setting goals beyond the moral minimum is important, especially when discussing moral character. Most of us are trained to aspire to an ideal of education. We are taught to prepare ourselves as best we can. No educational aspirations are too high unless they exceed our

abilities and cannot be attained. If we perform at a level below our educational potential, we may consider our achievement a matter of disappointment and regret even if we obtain a university degree. As we fulfill our aspirations, we sometimes expand our goals beyond what we had originally planned. We think of getting another degree, learning another language, or reading widely beyond our specialized training. However, we do not say at this point that we have an *obligation* to achieve at the highest possible level we can achieve.

The Aristotelian model suggests that moral character and moral achievement are functions of self-cultivation and aspiration. Goals of moral excellence can and should enlarge as moral development progresses. Each individual should seek to reach a level as elevated as his or her ability permits, not as a matter of *obligation* but of *aspiration*. Just as persons vary in the quality of their performances in athletics and medical practice, so too in the moral life some persons are more capable than others and deserve more acknowledgment, praise, and admiration. Some persons are sufficiently advanced morally that they exceed what persons less well developed are able to achieve.

Wherever a person is on the continuum of moral development, there will be a goal of excellence that exceeds what he or she has already achieved. This potential to revise our aspirations is centrally important in the moral life. Consider

a clinical investigator who uses human subjects in research but who asks only, "What am I obligated to do to protect human subjects?" This investigator's presumption is that once this question has been addressed by reference to a checklist of obligations (for example, government regulations), he or she can ethically proceed with the research. By contrast, in the model we are proposing, this approach is only the starting point. The most important question is, "How could I conduct this research to maximally protect and minimally inconvenience subjects, commensurate with achieving the objectives of the research?" Evading this question indicates that one is morally less committed than one could and probably should be.

The Aristotelian model we have sketched does not expect perfection, only that persons strive toward perfection. This goal might seem impractical, but moral ideals truly can function as practical instruments. As *our* ideals, they motivate us and set out a path that we can climb in stages, with a renewable sense of progress and achievement.

<2>**Exceptional Moral Excellence: Saints, Heroes, and Others**</2>

Extraordinary persons often function as models of excellence whose examples we aspire to follow. Among the many models, the moral hero and the moral saint are the most celebrated.

The term *saint* has a long history in religious traditions where a person is recognized for exceptional holiness, but, like *hero*, the term *saint* has a secular moral use where a person is recognized for exceptional action or virtue. Excellence in other-directedness, altruism, and benevolence are prominent features of the moral saint.[60] Saints do their duty and realize moral ideals where most people would fail to do so, and saintliness requires regular fulfillment of duty and realization of ideals over time. It also demands consistency and constancy. We likely cannot make an adequate or final judgment about a person's moral saintliness until the record is complete. By contrast, a person may become a moral hero through a single exceptional action, such as accepting extraordinary risk while discharging duty or realizing ideals. The hero resists fear and the desire for self-preservation in undertaking risky actions that most people would avoid, but the hero also may lack the constancy over a lifetime that distinguishes the saint.

Many who serve as moral models or as persons from whom we draw moral inspiration are not so advanced morally that they qualify as saints or heroes. We

learn about good moral character from persons with a limited repertoire of exceptional virtues, such as conscientious health professionals. Consider, for example, John Berger's biography of English physician John Sassall (the pseudonym Berger used for physician John Eskell), who chose to practice medicine in a poverty-ridden, culturally deprived country village in a remote region of northern England. Under the influence of works by Joseph Conrad, Sassall chose this village from an "ideal of service" that reached beyond "the average petty life of self-seeking advancement." Sassall was aware that he would have almost no social life and that the villagers had few resources to pay him, to develop their community, and to attract better medicine, but he focused on their needs rather than his. Progressively, Sassall grew morally as he interacted with members of the community. He developed a deep understanding of, and profound respect for, the villagers. He became a person of exceptional caring, devotion, discernment, conscientiousness, and patience when taking care of the villagers. His moral character deepened year after year. People in the community, in turn, trusted him under adverse and personally difficult circumstances.[61]

From exemplary lives such as that of John Sassall and from our previous analysis, we can extract four criteria of moral excellence.[62] First, Sassall is faithful to a *worthy moral ideal* that he keeps constantly before him in making judgments

and performing actions. The ideal is deeply devoted service to a poor and needy community. Second, he has a *motivational structure* that conforms closely to our earlier description of the motivational patterns of virtuous persons who are prepared to forgo certain advantages for themselves in the service of a moral ideal. Third, he has an *exceptional moral character;* that is, he possesses moral virtues that dispose him to perform supererogatory actions of a high order and quality.[63] Fourth, he is a *person of integrity*—both moral integrity and personal integrity—and thus is not overwhelmed by distracting conflicts, self-interest, or personal projects in making judgments and performing actions.

These four conditions are jointly sufficient conditions of *moral excellence.* They are also relevant, but not sufficient, conditions of both moral saintliness and moral heroism. John Sassall does not face extremely difficult tasks, a high level of risk, or deep adversity (although he faces some adversity including his bi-polar condition), and these are typically the sorts of conditions that contribute to making a person a saint or a hero. Exceptional as he is, Sassall is neither a saint nor a hero. To achieve this elevated status, he would have to satisfy additional conditions.

Much admired (though sometimes controversial) examples of moral saints acting from a diverse array of religious commitments are Mahatma Gandhi, Florence Nightingale, Mother Teresa, the 14th Dalai Lama (religious name:

Tenzin Gyatso), and Albert Schweitzer. Many examples of moral saints are also found in secular contexts where persons are dedicated to lives of service to the poor and downtrodden. Clear examples are persons motivated to take exceptional risks to rescue strangers.[64] Examples of prominent moral heroes include soldiers, political prisoners, and ambassadors who take substantial risks to save endangered persons by acts such as falling on hand grenades to spare comrades and resisting political tyrants.

Scientists and physicians who experiment on themselves to generate knowledge that may benefit others may be heroes. There are many examples: Daniel Carrion injected blood into his arm from a patient with verruga peruana (an unusual disease marked by many vascular eruptions of the skin and mucous membranes as well as fever and severe rheumatic pains), only to discover that it had given him a fatal disease (Oroya fever). Werner Forssman performed the first heart catheterization on himself, walking to the radiological room with the catheter sticking into his heart.[65] Daniel Zagury injected himself with an experimental AIDS vaccine, maintaining that his act was "the only ethical line of conduct."[66]

A person can qualify as a moral hero or a moral saint only if he or she meets some combination of the previously listed four conditions of moral

excellence. It is too demanding to say that a person must satisfy all four conditions to qualify as a moral hero, but a person must satisfy all four to qualify as a moral saint. This appraisal does not imply that moral saints are more valued or more admirable than moral heroes. We are merely proposing conditions of moral excellence that are more stringent for moral saints than for moral heroes.[67]

To pursue and test this analysis, consider two additional cases.[68] First, reflect on physician David Hilfiker's *Not All of Us Are Saints,* which offers an instructive model of very exceptional but not quite saintly or heroic conduct in his efforts to practice "poverty medicine" in Washington, DC.[69] His decision to leave a rural medical practice in the Midwest to provide medical care to the very poor, including the homeless, reflected both an ambition and a felt obligation. Many health problems he encountered stemmed from an unjust social system, in which his patients had limited access to health care and to other basic social goods that contribute to health. He experienced severe frustration as he encountered major social and institutional barriers to providing poverty medicine, and his patients were often difficult and uncooperative. His frustrations generated stress, depression, and hopelessness, along with vacillating feelings and attitudes including anger, pain, impatience, and guilt. Exhausted by his sense of endless needs and personal limitations, his wellspring of compassion failed to respond one

day as he thought it should: "Like those whom on another day I would criticize harshly, I harden myself to the plight of a homeless man and leave him to the inconsistent mercies of the city police and ambulance system. Numbness and cynicism, I suspect, are more often the products of frustrated compassion than of evil intentions."

Hilfiker declared that he is "anything but a saint." He considered the label "saint" to be inappropriate for people, like himself, who have a safety net to protect them. Blaming himself for "selfishness," he redoubled his efforts, but recognized a "gap between who I am and who I would like to be," and he considered that gap "too great to overcome." He abandoned "in frustration the attempt to be Mother Teresa," observing that "there are few Mother Teresas, few Dorothy Days who can give everything to the poor with a radiant joy." Hilfiker did consider many of the people with whom he worked day after day as heroes, in the sense that they "struggle against all odds and survive; people who have been given less than nothing, yet find ways to give."

Second, in *What Really Matters: Living a Moral Life Amidst Uncertainty and Danger,* psychiatrist and anthropologist Arthur Kleinman presents half-a-dozen real-life stories about people who, as the book's subtitle suggests, attempt to live morally in the context of unpredictability and hazard.[70] A story that

provided the impetus for his book portrays a woman he names Idi Bosquet-Remarque, a French-American who for more than fifteen years was a field representative for several different international aid agencies and foundations, mainly in sub-Saharan Africa. Her humanitarian assistance, carried out almost anonymously, involved working with vulnerable refugees and displaced women and children as well as with the various professionals, public officials, and others who interacted with them. Kleinman presents her as a "moral exemplar," who expressed "our finest impulse to acknowledge the suffering of others and to devote our lives and careers to making a difference (practically and ethically) in their lives, even if that difference must be limited and transient."

At times Bosquet-Remarque was dismayed by various failures, including her own mistakes. She despaired about the value of her work given the overwhelming odds against the people she sought to help, and she recognized some truth in several criticisms of her humanitarian assistance. Faced with daunting obstacles, she persisted because of her deep commitment but eventually experienced physical and emotional burnout, numbness, and demoralization. Nevertheless, she returned to the field because of her deep commitment to her work. Bosquet-Remarque recognized that her motives might be mixed. In addition to her altruism and compassion, she also could have been working out

family guilt or seeking to liberate her soul. Despite the ever-present risk of serious injury and even death from violence, she was uncomfortable with the image of the humanitarian worker as "hero."

After Bosquet-Remarque's death in an automobile accident, Kleinman informed her family that he wanted to tell her story. Her mother requested that her daughter not be identified by name: "That way, you will honor what she believed in. Not saints or heroes, but ordinary nameless people doing what they feel they must do, even in extraordinary situations. As a family, we believe in this too."

These observations about ordinary persons who act in extraordinary ways are also relevant to what has been called moral heroism in living organ and tissue donation—a topic to which we now turn.

<2>**Living Organ Donation**</2>

In light of our moral account thus far, how should we assess a person's offer to donate a kidney to a friend or a stranger?

Health care professionals frequently function as moral gatekeepers to determine who may undertake living donation of organs and tissues for transplantation. Blood donation raises few questions, but in cases of bone marrow donation and the donation of kidneys or portions of livers or lungs, health care

professionals must consider whether, when, and from whom to invite, encourage, accept, and effectuate donation. Living organ donation raises challenging ethical issues because the transplant team subjects a healthy person to a variably risky surgical procedure, with no medical benefit to him or her. It is therefore appropriate for transplant teams to probe prospective donors' competence to make such decisions and their understanding, voluntariness, and motives.

Historically, transplant teams were suspicious of living, genetically unrelated donors—particularly of strangers and mere acquaintances but, for a long time, even of emotionally related donors such as spouses and friends. This suspicion had several sources, including concerns about donors' motives and worries about their competence to decide, understanding of the risks, and voluntariness in reaching their decisions. This suspicion increased in cases of nondirected donation, that is, donation not to a particular known individual, but to anyone in need. Such putatively altruistic decisions to donate seemed to require heightened scrutiny. However, in contrast to some professionals' attitudes,[71] a majority of the public in the United States believes that the gift of a kidney to a stranger is reasonable and proper and that, in general, the transplant team should accept it.[72] A key reason is that the offer to donate a kidney whether by a friend, an acquaintance, or a stranger typically does not involve such high risks that

serious questions should be triggered about the donor's competence, understanding, voluntariness, or motivation.[73]

Transplant teams can and should decline some heroic offers of organs for moral reasons, even when the donors are competent, their decisions informed and voluntary, and their moral excellence beyond question. For instance, transplant teams have good grounds to decline a mother's offer to donate her heart to save her dying child, because the donation would involve others in directly causing her death. A troublesome case arose when an imprisoned, 38-year-old father who had already lost one of his kidneys wanted to donate his remaining kidney to his 16-year-old daughter whose body had already rejected one kidney transplant.[74] The family insisted that medical professionals and ethics committees had no right to evaluate, let alone reject, the father's act of donation. However, questions arose about the voluntariness of the father's offer (in part because he was in prison), about the risks to him (many patients without kidneys do not thrive on dialysis), about the probable success of the transplant (because of his daughter's problems with her first transplant), and about the costs to the prison system (approximately $40,000 to $50,000 a year for dialysis for the father if he donated the remaining kidney).

We propose that society and health care professionals start with the presumption that living organ donation is praiseworthy but optional. Transplant teams need to subject their criteria for selecting and accepting living donors to public scrutiny to ensure that the teams do not inappropriately use their own values about sacrifice, risk, and the like, as the basis for their judgments.[75] Policies and practices of encouraging prospective living donors are ethically acceptable as long as they do not turn into undue influence or coercion. For instance, it is ethically acceptable to remove financial disincentives for potential donors, such as the costs of post-operative care, expenses associated with travel and accommodations, and the loss of wages while recovering from donation. It is also ethically acceptable to provide a life-insurance policy to reduce risks to the family of the living donor.[76] In the final analysis, live organ donors may not rise to the level of heroes, depending on the risks involved, but many embody a moral excellence that merits society's praise, as well as acceptance by transplant teams in accord with defensible criteria. (In Chapter 9, in each major section, we analyze from several perspectives the case of a father who is reluctant, at least partly because of a lack of courage, to donate a kidney to his dying daughter.)

<1>CONCLUSION</1>

In this chapter we have moved to a moral territory distinct from the principles, rules, obligations, and rights treated in Chapter 1. We have sought to render the two domains consistent without assigning priority to one over the other. We have discussed how standards of virtue and character are closely connected to other moral norms, in particular to moral ideals and aspirations of moral excellence that enrich the rights, principles, and rules discussed in Chapter 1. There is no reason to consider one domain inferior to or derivative from the other, and there is reason to believe that these categories all have a significant place in the common morality.

Still other domains of the moral life of great importance in biomedical ethics remain unaddressed. In Chapter 3 we turn to the chief domain not yet analyzed: moral status.

<N-1>**NOTES**</N-1>

<N>[1] For relevant literature on the subjects discussed in Chapter 2 and in the last section of Chapter 9, see Stephen Darwall, ed., *Virtue Ethics* (Oxford: Blackwell Publishing, 2003); Roger Crisp and Michael Slote, eds., *Virtue Ethics* (Oxford: Oxford University Press, 1997); Roger Crisp, ed., *How Should One Live? Essays on the Virtues* (Oxford: Oxford University

Press, Clarendon, 1996); and Daniel Statman, ed., *Virtue Ethics: A Critical Reader* (Washington, DC: Georgetown University Press, 1997). Many constructive discussions of virtue theory are indebted to Aristotle. For a range of treatments, see Julia Annas, *Intelligent Virtue* (New York: Oxford University Press, 2011) and Annas, "Applying Virtue to Ethics," *Journal of Applied Philosophy* 32 (2015): 1–14; Christine Swanton, *Virtue Ethics: A Pluralistic View* (New York: Oxford University Press, 2003); Nancy Sherman, *The Fabric of Character: Aristotle's Theory of Virtue* (Oxford: Clarendon, 1989); Alasdair MacIntyre, *After Virtue: A Study in Moral Theory,* 3rd ed. (Notre Dame, IN: University of Notre Dame Press, 2007) and *Dependent Rational Animals: Why Human Beings Need the Virtues* (Chicago: Open Court, 1999); Timothy Chappell, ed., *Values and Virtues: Aristotelianism in Contemporary Ethics* (Oxford: Clarendon, 2006); and Robert Merrihew Adams, *A Theory of Virtue: Excellence in Being for the Good* (Oxford: Clarendon, 2006), and Adams, "A Theory of Virtue: Response to Critics," *Philosophical Studies* 148 (2010): 159–65.

[2] Bentham, *Deontology or the Science of Morality* (Chestnut Hill, MA: Adamant Media Corporation, 2005; reprinted in the Elibron Classics Series of the 1834 edition, originally published in London by Longman et al., 1834), p. 196.

[3] This sense of "virtue" is intentionally broad. We do not require, as did Aristotle, that virtue involve habituation rather than a natural character trait. See *Nicomachean Ethics,* trans. Terence Irwin (Indianapolis, IN: Hackett Publishing, 1985), 1103ª18–19. Nor do we follow St. Thomas Aquinas (relying on a formulation by Peter Lombard), who additionally held that virtue is a good quality of mind by which we live rightly and therefore cannot be put to bad use. See *Treatise on the Virtues* (from *Summa Theologiae,* I–II), Question 55, Arts. 3–4. We treat problems of the definition of "virtue" in more detail in Chapter 9.

[4] This definition is the primary use reported in the *Oxford English Dictionary* (*OED*). It is defended philosophically by Alan Gewirth, "Rights and Virtues," *Review of Metaphysics* 38 (1985): 751; and Richard B. Brandt, "The Structure of Virtue," *Midwest Studies in Philosophy* 13 (1988): 76. See also the consequentialist account in Julia Driver, *Uneasy Virtue* (Cambridge: Cambridge University Press, 2001), esp. chap. 4, and Driver, "Response to my Critics," *Utilitas* 16 (2004): 33–41. Edmund Pincoffs presents a definition of virtue in terms of desirable dispositional qualities of persons, in *Quandaries and Virtues: Against Reductivism in Ethics* (Lawrence, KS: University Press of Kansas, 1986), pp. 9, 73–100. See also MacIntyre, *After Virtue,* chaps. 10–18; and Raanan Gillon, "Ethics Needs Principles," *Journal of Medical Ethics* 29 (2003): 307–12, esp. 309.

[5] See the pursuit of this Aristotelian theme in Annas, *Intelligent Virtue,* chap. 5. Elizabeth Anscombe's "Modern Moral Philosophy" (*Philosophy* 33 (1958): 1-19) is the classic mid-twentieth-century paper on the importance for ethics of categories such as character, virtue, the emotions, and Aristotelian ethics, by contrast to moral theories based on moral law, duty, and principles of obligation.

[6] This analysis of practices is influenced by Alasdair MacIntyre, *After Virtue,* esp. chap. 14; and Dorothy Emmet, *Rules, Roles, and Relations* (New York: St. Martin's, 1966). See also Justin Oakley and Dean Cocking, *Virtue Ethics and Professional Roles* (Cambridge: Cambridge University Press, 2001); Oakley, "Virtue Ethics and Bioethics," in *The Cambridge Companion to Virtue Ethics*, ed. Daniel C. Russell (Cambridge: Cambridge University Press, 2013), pp. 197–220; and Tom L. Beauchamp, "Virtue Ethics and Conflict of Interest," in *The Future of Bioethics: International Dialogues*, ed. Akira Akabayashi (Oxford: Oxford University Press, 2014), pp. 688-92.

[7] A somewhat similar thesis is defended, in dissimilar ways, in Edmund D. Pellegrino, "Toward a Virtue-Based Normative Ethics for the Health Professions," *Kennedy Institute Ethics Journal* 5 (1995): 253–77. See also John Cottingham, "Medicine, Virtues and Consequences," in *Human Lives: Critical Essays on Consequentialist Bioethics,* ed. David S. Oderberg (New York: Macmillan, 1997); Alan E. Armstrong, *Nursing Ethics: A Virtue-Based Approach* (Houndmills, Eng. and New York: Palgrave Macmillan, 2007); and Jennifer Radden and John Z. Sadler, *The Virtuous Psychiatrist: Character Ethics in Psychiatric Practice* (New York: Oxford University Press, 2010).

[8] Charles L. Bosk, *Forgive and Remember: Managing Medical Failure*, 2nd edition (Chicago: University of Chicago Press, 2003). In addition to the three types of error we mention, Bosk recognizes a fourth type of error: "quasi-normative errors," based on the attending's special protocols. In the Preface to the 2nd edition, he notes that his original book did not stress as much as it should have the problems that were created when normative and quasi-normative breaches were treated in a unitary fashion (p. xxi).

[9] Thomas Percival, *Medical Ethics; or a Code of Institutes and Precepts, Adapted to the Professional Conduct of Physicians and Surgeons* (Manchester, England: S. Russell, 1803), pp. 165–66. This book formed the substantive basis of the first American Medical Association code in 1847.

[10] For this shift, see Gerald R. Winslow, "From Loyalty to Advocacy: A New Metaphor for Nursing," *Hastings Center Rep*ort 14 (June 1984): 32-40; and Helga Kuhse, *Caring: Nurses, Women and Ethics* (Oxford, UK, and Maldon, MA: Blackwell Publishers, 1997), esp. chaps. 1, 2, & 9.

[11] See the virtue-based approach to nursing ethics in Armstrong, *Nursing Ethics: A Virtue-Based Approach.*

[12] Contrast Virginia Held's argument for a sharp distinction between the ethics of care and virtue ethics on the grounds that the former focuses on relationships and the latter on individuals' dispositions: *The Ethics of Care: Personal, Political, and Global* (New York: Oxford University Press, 2006). We are skeptical of her argument, and of the similar view developed by Nel Noddings in "Care Ethics and Virtue Ethics," in *The Routledge Companion to*

Virtue Ethics, ed., Lorraine Besser-Jones and Michael Slote (London and New York: Routledge, 2015), pp. 401-414. Drawing on related themes, Ruth Groenhout challenges the standard taxonomies that lump a feminist ethic of care together with virtue ethics (developed from a non-feminist history); see her "Virtue and a Feminist Ethic of Care," in *Virtues and Their Vices*, ed., Kevin Timpe and Craig A. Boyd (Oxford and New York: Oxford University Press, 2014), pp. 481-501. For an argument closer to ours, see Raja Halwani, "Care Ethics and Virtue Ethics," *Hypatia* 18 (2003): 161-92.

[13] Carol Gilligan, *In a Different Voice* (Cambridge, MA: Harvard University Press, 1982), esp. p. 21. See also her "Mapping the Moral Domain: New Images of Self in Relationship," *Cross Currents* 39 (Spring 1989): 50–63.

[14] Gilligan and others deny that the two distinct voices correlate strictly with gender. See Gilligan and Susan Pollak, "The Vulnerable and Invulnerable Physician," in *Mapping the Moral Domain,* ed. C. Gilligan, J. Ward, and J. Taylor (Cambridge, MA: Harvard University Press, 1988), pp. 245–62.

[15] See Gilligan and G. Wiggins, "The Origins of Morality in Early Childhood Relationships," in *The Emergence of Morality in Young Children,* ed. J. Kagan and S. Lamm (Chicago: University of Chicago Press, 1988). See also Margaret Olivia Little, "Care: From Theory to Orientation and Back," *Journal of Medicine and Philosophy* 23 (1998): 190–209.

[16] Our formulations of these criticisms is influenced by Alisa L. Carse, "The 'Voice of Care': Implications for Bioethical Education," *Journal of Medicine and Philosophy* 16 (1991): 5–28, esp. 8–17. For assessment of such criticisms, see Abraham Rudnick, "A Meta-Ethical Critique of Care Ethics," *Theoretical Medicine* 22 (2001): 505–17.

[17] Alisa L. Carse, "Impartial Principle and Moral Context: Securing a Place for the Particular in Ethical Theory," *Journal of Medicine and Philosophy* 23 (1998): 153–69.

[18] See See Christine Grady and Anthony S. Fauci, "The Role of the Virtuous Investigator in Protecting Human Research Subjects," *Perspectives in Biology and Medicine* 59 (2016): 122-131; Nel Noddings, *Caring: A Feminine Approach to Ethics and Moral Education,* 2nd ed. (Berkeley, CA: University of California Press, 2003), and the evaluation of Noddings' work in Halwani, "Care Ethics and Virtue Ethics," esp. pp. 162ff.

[19] See Nancy Sherman, *The Fabric of Character* (Oxford: Oxford University Press, 1989), pp. 13–55; and Martha Nussbaum, *Love's Knowledge* (Oxford: Oxford University Press, 1990). On "attention" in medical care, see Margaret E. Mohrmann, *Attending Children: A Doctor's Education* (Washington, DC: Georgetown University Press, 2005).

[20] Carse, "The 'Voice of Care,'" p. 17.

[21] Other virtues are similarly important. We treat several later in this chapter and in Chapter 9. On the historical role of a somewhat different collection of central virtues in medical ethics and their connection to vices, especially since the eighteenth century, see Frank A. Chervenak and Laurence B. McCullough, "The Moral Foundation of Medical Leadership: The Professional Virtues of the Physician as Fiduciary of the Patient," *American Journal of Obstetrics and Gynecology* 184 (2001): 875–80.

[22] Edmund D. Pellegrino, "Toward a Virtue-Based Normative Ethics," p. 269. Compassion is often regarded as one of the major marks of an exemplary health care professional. See Helen Meldrum, *Characteristics of Compassion: Portraits of Exemplary Physicians* (Sudbury, MA; Jones and Bartlett, 2010).

[23] See Lawrence Blum, "Compassion," in *Explaining Emotions,* ed. Amélie Oksenberg Rorty (Berkeley, CA: University of California Press, 1980); and David Hume, *A Dissertation on the Passions,* ed. Tom L. Beauchamp (Oxford: Clarendon Press, 2007), Sect. 3, §§ 4–5.

[24] Martha Nussbaum, *Upheavals of Thought: The Intelligence of Emotions* (Cambridge: Cambridge University Press, 2001), p. 302. Part II of this book is devoted to compassion.

[25] See Jodi Halpern, *From Detached Concern to Empathy: Humanizing Medical Practice* (New York: Oxford University Press, 2001). For a variety of largely positive essays on empathy, see Howard Spiro, et al., eds., *Empathy and the Practice of Medicine* (New Haven, CT: Yale University Press, 1993); and Ellen Singer More and Maureen A. Milligan, eds., *The Empathic Practitioner: Empathy, Gender, and Medicine* (New Brunswick, NJ: Rutgers University Press, 1994). A valuable set of philosophical and psychological perspectives on empathy appears in Amy Coplan and Peter Goldie, eds., *Empathy: Philosophical and Psychological Perspectives* (Oxford: Oxford University Press, 2011). Jean Decety, ed., *Empathy: From Bench to Bedside* (Cambridge: MIT Press, 2012) includes several essays in Part VI on "Empathy in Clinical Practice." For dangers of an overemphasis on empathy in medicine, see Jane Mcnaughton, "The Art of Medicine: The Dangerous Practice of Empathy," *The Lancet* 373(2009): 1940-1941. Paul Bloom offers a sustained psychological argument against empathy in favor of "rational compassion" in health care, and many other areas, in his *Against Empathy: The Case for Rational Compassion* (New York: Ecco Press of HarperCollins, 2016). Some commentators on his thesis recognize the legitimacy of his concerns, for instance, about empathy in health care, but call for a more nuanced perspective and greater appreciation of the value of empathy. See the discussion in response to his essay entitled "Against Empathy" in a Forum in the *Boston Review*, September 10, 2014, available at http://bostonreview.net/forum/paul-bloom-against-empathy (accessed July 22, 2018). Much in this debate hinges on different interpretations of the concept, criteria, and descriptions of empathy.

[26] David Hume, *A Treatise of Human Nature,* ed. David Fate Norton and Mary Norton

(Oxford: Clarendon Press, 2007), 3.3.1.7.

[27] Baruch Brody, "Case No. 25. 'Who Is the Patient, Anyway': The Difficulties of Compassion," in *Life and Death Decision Making* (New York: Oxford University Press, 1988), pp. 185–88.

[28] Aristotle, *Nicomachean Ethics,* trans. Terence Irwin, second edition (Indianapolis: Hackett, 2000), $1106^{b}15$–29, $1141^{a}15$–$1144^{b}17$.

[29] Annette Baier, "Trust, Suffering, and the Aesculapian Virtues," in *Working Virtue: Virtue Ethics and Contemporary Moral Problems,* ed. Rebecca L. Walker and Philip J. Ivanhoe (Oxford: Clarendon, 2007), p. 137.

[30] See Annette Baier's "Trust and Antitrust" and two later essays on trust in her *Moral Prejudices* (Cambridge, MA: Harvard University Press, 1994); Nancy N. Potter, *How Can I Be Trusted: A Virtue Theory of Trustworthiness* (Lanham, MD: Rowman & Littlefield, 2002); Philip Pettit, "The Cunning of Trust," *Philosophy & Public Affairs* 24 (1995): 202–25; and Pellegrino and Thomasma, *The Virtues in Medical Practice,* chap. 5.

[31] Aristotle, *Eudemian Ethics,* $1242^{b}23$–$1243^{a}13$, in *The Complete Works of Aristotle,* ed. Jonathan Barnes (Princeton, NJ: Princeton University Press, 1984).

[32] For discussions of the erosion of trust in medicine, see Robert J. Blendon, John M. Benson, and Joachim O. Hero, "Public Trust in Physicians—U.S. Medicine in International Perspective" (a project studying 29 industrialized countries sponsored by the Robert Wood Johnson Foundation), *New England Journal of Medicine* 371 (2014): 1570-1572; David A. Axelrod and Susan Dorr Goold, "Maintaining Trust in the Surgeon-Patient Relationship: Challenges for the New Millennium," *JAMA Surgery* (Archives Surgery) 135 (January 2000), available at https://jamanetwork.com/journals/jamasurgery/fullarticle/390488 (accessed March 17, 2018); David Mechanic, "Public Trust and Initiatives for New Health Care Partnerships," *Milbank Quarterly* 76 (1998): 281–302; Pellegrino and Thomasma in *The Virtues in Medical Practice,* pp. 71–77; and Mark A. Hall, "The Ethics and Empirics of Trust," in *The Ethics of Managed Care: Professional Integrity and Patient Rights,* ed. W. B. Bondeson and J. W. Jones (Dordrecht, Netherlands: Kluwer, 2002), pp. 109–26. Broader explorations of trustworthiness, trust, and distrust appear in Russell Hardin's *Trust and Trustworthiness,* The Russell Sage Foundation Series on Trust, vol. 4 (New York: Russell Sage Foundation Publications, 2004). See further Onora O'Neill's proposals to restore trust in medical and other contexts where mistrust results from factors such as bureaucratic structures of accountability, excessive transparency, and public culture: *A Question of Trust* (Cambridge: Cambridge University Press, 2002) and *Autonomy and Trust in Bioethics* (Cambridge: Cambridge University Press, 2003).

[33] Brody, *Life and Death Decision Making,* p. 35. On the interpretation of integrity as a virtue, see Damian Cox, Marguerite La Caze, and Michael Levine, "Integrity," *The Stanford*

Encyclopedia of Philosophy (Spring 2017 Edition), ed. Edward N. Zalta, available at https://plato.stanford.edu/archives/spr2017/entries/integrity/ (accessed March 27, 2018).

[34] On the connection of, and the distinction between, autonomy and integrity, see Carolyn McLeod, "How to Distinguish Autonomy from Integrity," *Canadian Journal of Philosophy* 35 (2005): 107–133.

[35] On integrity as a virtue in the medical professions, see Edmund D. Pellegrino, "Codes, Virtue, and Professionalism," in *Methods of Medical Ethics,* ed. Jeremy Sugarman and Daniel P. Sulmasy, revised 2nd edition (Washington, DC: Georgetown University Press, 2010), pp. 91–107, esp. 94; and Michael Wreen, "Medical Futility and Physician Discretion," *Journal of Medical Ethics* 30 (2004): 275–78.

[36] For useful discussions of this question in nursing, see Martin Benjamin and Joy Curtis, *Ethics in Nursing: Cases, Principles, and Reasoning,* 4th ed. (New York: Oxford University Press, 2010), pp. 122–26; and Betty J. Winslow and Gerald Winslow, "Integrity and Compromise in Nursing Ethics," *Journal of Medicine and Philosophy* 16 (1991): 307–23. A wide-ranging discussion is found in Martin Benjamin, *Splitting the Difference: Compromise and Integrity in Ethics and Politics* (Lawrence, KS: University Press of Kansas, 1990).

[37] For a historically grounded critique of such conceptions and a defense of conscience as a virtue, see Douglas C. Langston, *Conscience and Other Virtues: From Bonaventure to MacIntyre* (University Park, PA: Pennsylvania State University Press, 2001). For another historical perspective, see Richard Sorabji, *Moral Conscience Through the Ages: Fifth Century BCE to the Present* (Chicago: University of Chicago Press, 2014).

[38] Bernard Williams, "A Critique of Utilitarianism," in J. J. C. Smart and Williams, *Utilitarianism: For and Against* (Cambridge: Cambridge University Press, 1973), pp. 97–98.

[39] We here draw from two sources: Hannah Arendt, *Crises of the Republic* (New York: Harcourt, Brace, Jovanovich, 1972), p. 62; and John Stuart Mill, *Utilitarianism,* chap. 3, pp. 228–29, and *On Liberty,* chap. 3, p. 263, in *Collected Works of John Stuart Mill,* vols. 10, 18 (Toronto, Canada: University of Toronto Press, 1969, 1977).

[40] Carl H. Fellner, "Organ Donation: For Whose Sake?" *Annals of Internal Medicine* 79 (October 1973): 591.

[41] Carson Strong, "Specified Principlism," *Journal of Medicine and Philosophy* 25 (2000): 285–307; John H. Evans, "A Sociological Account of the Growth of Principlism," *Hastings Center Report* 30 (September–October 2000): 31–38; Evans, *Playing God: Human Genetic Engineering and the Rationalization of Public Bioethical Debate* (Chicago: University of Chicago Press, 2002); and Evans, *The History and Future of Bioethics: A Sociological View* (New York: Oxford University Press, 2011). For a critical analysis of Evans' arguments,

particularly in *Playing God*, see James F. Childress, "Comments," *Journal of the Society of Christian Ethics* 24, no. 1 (2004): 195-204. See also Daniel P. Sulmasy, "What Is Conscience and Why Is Respect for It So Important?" *Theoretical Medicine and Bioethics* 29 (2008): 135–149; Damian Cox, Marguerite La Caze, and Michael Levine, "Integrity," *The Stanford Encyclopedia of Philosophy* (Spring 2017 Edition), ed. Edward N. Zalta, available at https://plato.stanford.edu/archives/spr2017/entries/integrity/ (accessed February 25, 2018); Larry May, "On Conscience," *American Philosophical Quarterly* 20 (1983): 57–67; C. D. Broad, "Conscience and Conscientious Action," in *Moral Concepts,* ed. Joel Feinberg (Oxford: Oxford University Press, 1970), pp. 74–79; James F. Childress, "Appeals to Conscience," *Ethics* 89 (1979): 315–35;.

[42] Douglas B. White and Baruch Brody, "Would Accommodating Some Conscientious Objections by Physicians Promote Quality in Medical Care?" *JAMA* 305 (May 4, 2011): 1804-1805.

[43] For several models, see Rebecca Dresser, "Professionals, Conformity, and Conscience," *Hastings Center Report* 35 (November–December 2005): 9–10; Mark R. Wicclair, *Conscientious Objection in Health Care: An Ethical Analysis* (Cambridge: Cambridge University Press, 2011); Alta R. Charo, "The Celestial Fire of Conscience—Refusing to Deliver Medical Care," *New England Journal of Medicine* 352 (2005): 2471–73; and Elizabeth Fenton and Loren Lomasky, "Dispensing with Liberty: Conscientious Refusal and the 'Morning-After Pill,'" *Journal of Medicine and Philosophy* 30 (2005): 579–92.

[44] See Holly Fernandez Lynch, *Conflicts of Conscience: An Institutional Compromise* (Cambridge, MA: MIT Press, 2008).

[45] The rest of the physicians are opposed or undecided. Farr A. Curlin et al., "Religion, Conscience, and Controversial Clinical Practices," *New England Journal of Medicine* 356 (February 8, 2007): 593–600.

[46] Dan W. Brock offers a similar framework for ethical analysis in what he calls the "conventional compromise" in "Conscientious Refusal by Physicians and Pharmacists: Who is Obligated to Do What, and Why?" *Theoretical Medicine and Bioethics* 29 (2008): 187-200. For the legal framework in the U.S., see Elizabeth Sepper, "Conscientious Refusals of Care," in *The Oxford Handbook of U.S. Health Law*, ed. I. Glenn Cohen, Allison Hoffman, and William M. Sage (New York: Oxford University Press, 2017), Chapter 16.

[47] Our analysis is indebted to David Heyd, *Supererogation: Its Status in Ethical Theory* (Cambridge: Cambridge University Press, 1982); Heyd, "Tact: Sense, Sensitivity, and Virtue," *Inquiry* 38 (1995): 217–31; Heyd, "Obligation and Supererogation," *Encyclopedia of Bioethics,* 3rd ed. (New York: Thomson Gale, 2004), vol. 4, pp. 1915–20; and Heyd, "Supererogation," *The Stanford Encyclopedia of Philosophy* (Spring 2016 Edition), ed. Edward N. Zalta, available

at https://plato.stanford.edu/archives/spr2016/entries/supererogation (accessed March 27, 2018). We are also indebted to J. O. Urmson, "Saints and Heroes," *Essays in Moral Philosophy,* ed. A. I. Melden (Seattle, WA: University of Washington Press, 1958), pp. 198–216; John Rawls, *A Theory of Justice* (Cambridge, MA: Harvard University Press, 1971; rev. ed. 1999), pp. 116–17, 438–39, 479–85 (1999: 100–01, 385–86, 420–25); Joel Feinberg, "Supererogation and Rules," *Ethics* 71 (1961); and Gregory Mellema, *Beyond the Call of Duty: Supererogation, Obligation, and Offence* (Albany, NY: State University of New York Press, 1991). For central connections between virtue and supererogation, see Roger Crisp, "Supererogation and Virtue," in *Oxford Studies in Normative Ethics* (vol. 3), ed. Mark Timmons (Oxford and New York: Oxford University Press, 2013), article 1.

[48] Albert Camus, *The Plague,* trans. Stuart Gilbert (New York: Knopf, 1988), p. 278.

[49] The formulation in this sentence relies in part on Rawls, *A Theory of Justice,* p. 117 (1999 edition, p. 100).

[50] Feinberg, "Supererogation and Rules," 397.

[51] See Dena Hsin-Chen and Darryl Macer, "Heroes of SARS: Professional Roles and Ethics of Health Care Workers," *Journal of Infection* 49 (2004): 210–15; Joseph J. Fins, "Distinguishing Professionalism and Heroism When Disaster Strikes: Reflections on 9/11, Ebola, and Other Emergencies," *Cambridge Quarterly of Healthcare Ethics* 24 (October 2015): 373-84; Angus Dawson, "Professional, Civic, and Personal Obligations in Public Health Emergency Planning and Response," in *Emergency Ethics: Public Health Preparedness and Response*, ed. Bruce Jennings, John D. Arras, Drue H. Barrett, and Barbara A. Ellis (New York: Oxford University Press, 2016), pp. 186-219. Early discussions of HIV/AIDS, when there were major concerns about transmission in the clinical setting, frequently addressed the clinician's responsibility to treat. Examples include Bernard Lo, "Obligations to Care for Persons with Human Immunodeficiency Virus," *Issues in Law & Medicine* 4 (1988): 367–81; Doran Smolkin, "HIV Infection, Risk Taking, and the Duty to Treat," *Journal of Medicine and Philosophy* 22 (1997): 55–74; and John Arras, "The Fragile Web of Responsibility: AIDS and the Duty to Treat," *Hastings Center Report* 18 (April–May 1988): S10–20.

[52] American Medical Association (AMA), *Code of Medical Ethics of the American Medical Association*, adopted May 1847 (Philadelphia: T.K. and P.G. Collins, 1848), available at http://ethics.iit.edu/ecodes/sites/default/files/Americaan%20Medical%20Association%20Code%20of%20Medical%20Ethics%20%281847%29.pdf (accessed March 17, 2018).

[53] See American Medical Association, Council on Ethical and Judicial Affairs, "Ethical Issues Involved in the Growing AIDS Crisis," *Journal of the American Medical Association* 259 (March 4, 1988): 1360–61.

[54] Health and Public Policy Committee, American College of Physicians and Infectious Diseases Society of America, "The Acquired Immunodeficiency Syndrome (AIDS) and Infection with the Human Immunodeficiency Virus (HIV)," *Annals of Internal Medicine* 108 (1988): 460–61. See further Edmund D. Pellegrino, "Character, Virtue, and Self-Interest in the Ethics of the Professions," *Journal of Contemporary Health Law and Policy* 5 (1989): 53–73, esp. 70–71.

[55] Aristotle, *Nicomachean Ethics,* trans. Irwin, 1101^{a}1–7.

[56] Rawls, *A Theory of Justice,* pp. 443–45 (1999 edition: 389–91). On the Aristotelian principle, see pp. 424–33 (1999 edition: 372–80).

[57] Urmson recognized this problem in "Saints and Heroes," pp. 206, 214. Imbalance is found in forms of utilitarianism that make strong demands of obligation. However, see the attempt to revise consequentialism to bring it in line with common moral intuitions in Douglas W. Portman, "Position-Relative Consequentialism, Agent-Centered Options, and Supererogation," *Ethics* 113 (2003): 303–32.

[58] A reasonable skepticism is evident in some influential philosophical works such as those of Susan Wolf (in the article cited below), Philippa Foot, Bernard Williams, and Thomas Nagel.

[59] Aristotle, *Nicomachean Ethics,* trans. Irwin, 1103^{a}32–1103^{b}1.

[60] Edith Wyschogrod offers a definition of a "saintly life" as "one in which compassion for the other, irrespective of cost to the saint, is the primary trait." Wyschogrod, *Saints and Postmodernism: Revisioning Moral Philosophy* (Chicago: University of Chicago Press, 1990), pp. xiii, xxii, et passim.

[61] John Berger (and Jean Mohr, photographer), *A Fortunate Man: The Story of a Country Doctor* (London: Allen Lane, the Penguin Press, 1967), esp. pp. 48, 74, 82ff, 93ff, 123–25, 135. Lawrence Blum pointed us to this book and influenced our perspective on it. Sassall's wife played a critical role in running his medical practice and helping him deal with his manic-depressive illness; she receives little attention in the book, which is, however, dedicated to her. She died in 1981, and he committed suicide the next year. See Roger Jones, "Review: *A Fortunate Man*," *British Journal of General Practice,* February 9, 2015, available at http://bjgplife.com/2015/02/09/review-a-fortunate-man/ (accessed July 20, 2018). See also Gavin Francis, "John Berger's *A Fortunate Man*: A Masterpiece of Witness," *The Guardian*, February 7, 2015, available at https://www.theguardian.com/books/2015/feb/07/john-sassall-country-doctor-a-fortunate-man-john-berger-jean-mohr (accessed, July 20, 2018).

[62] Our conditions of moral excellence are indebted to Lawrence Blum, "Moral Exemplars," *Midwest Studies in Philosophy* 13 (1988): 204. See also Blum's "Community and

Virtue," in *How Should One Live?: Essays on the Virtues,* ed. Crisp.

[63] Our second and third conditions are influenced by the characterization of a saint in Susan Wolf's "Moral Saints," *Journal of Philosophy* 79 (1982): 419–39. For a pertinent critique of Wolf's interpretation, see Robert Merrihew Adams, "Saints," *Journal of Philosophy* 81 (1984), reprinted in Adams, *The Virtue of Faith and Other Essays in Philosophical Theology* (New York: Oxford University Press, 1987), pp. 164–73.

[64] For an examination of some 21st-century figures who lived under extreme conditions with exceptional moral commitment, see Larissa MacFarquhar, *Strangers Drowning: Impossible Idealism, Drastic Choices, and the Urge to Help* (New York: Penguin Books, 2016).

[65] Jay Katz, ed., *Experimentation with Human Beings* (New York: Russell Sage Foundation, 1972), pp. 136–40; Lawrence K. Altman, *Who Goes First?: The Story of Self-Experimentation in Medicine,* 2nd edition, with a new preface (Berkeley, CA: University of California Press, 1998), pp. 1-5, 39-50, et passim.

[66] Philip J. Hilts, "French Doctor Testing AIDS Vaccine on Self," *Washington Post,* March 10, 1987, p. A7; Altman, *Who Goes First?,* pp. 26-28.

[67] We will not consider whether these conditions point to a still higher form of moral excellence: the combination of saint and hero in one person. There have been such extraordinary persons, and we could make a case that some of these extraordinary figures are more excellent than others. But at this level of moral exemplariness, such fine distinctions serve no purpose.

[68] These cases can be read as suggesting that many people who are commonly called heroes or saints are not very different from good and decent but morally ordinary people. This theory is not explored here (except implicitly in our account of the continuum from ordinary morality to supererogation), but it is examined in Andrew Michael Flescher, *Heroes, Saints, and Ordinary Morality* (Washington: Georgetown University Press, 2003). Flescher provides historical examples of people commonly regarded as saints or heroes.

[69] David Hilfiker, *Not All of Us Are Saints: A Doctor's Journey with the Poor* (New York: Hill & Wang, 1994). The summaries and quotations that follow come from this book. His earlier book, *Healing the Wounds: A Physician Looks at His Work* (New York: Pantheon, 1985) focuses on his previous experiences as a family physician in rural Minnesota. The personal problems he (and some others we discuss) faced underline a critical point in this chapter: Difficulties that can arise in balancing a commitment to a moral ideal or moral excellence with personal needs.

[70] Arthur Kleinman, *What Really Matters: Living a Moral Life Amidst*

Uncertainty and Danger (New York: Oxford University Press, 2006), chap. 3. The quotations are from this work.

[71] For the attitudes of nephrologists, transplant nephrologists, transplant surgeons, and the like, see Carol L. Beasley, Alan R. Hull, and J. Thomas Rosenthal, "Living Kidney Donation: A Survey of Professional Attitudes and Practices," *American Journal of Kidney Diseases* 30 (October 1997): 549–57; and Reginald Y. Gohh, Paul E. Morrissey, Peter N. Madras, et al., "Controversies in Organ Donation: The Altruistic Living Donor," *Nephrology Dialysis Transplantation* 16 (2001): 619-21, available at https://academic.oup.com/ndt/article/16/3/619/1823109 (accessed Feb. 26, 2018). Even though strong support now exists for living kidney donation, actual medical practice is not uniformly in agreement.

[72] See Aaron Spital and Max Spital, "Living Kidney Donation: Attitudes Outside the Transplant Center," *Archives of Internal Medicine* 148 (May 1988): 1077–80; Aaron Spital, "Public Attitudes toward Kidney Donation by Friends and Altruistic Strangers in the United States," *Transplantation* 71 (2001): 1061-64.

[73] From 1996 to 2005, as living kidney donation overall doubled in the United States, the annual percentage of genetically unrelated kidney donors (excluding spouses) rose from 5.9% to 22%. *2006 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1996–2005* (Rockville, MD: Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, 2006). During the years 2001–03, acts of living organ donation outnumbered acts of deceased organ donation, but living organ donation, which had increased for the preceding five years, declined steadily after 2004 for both kidneys and livers. See A. S. Klein, E. E. Messersmith, L. E. Ratner, et al., "Organ Donation and Utilization in the United States, 1999–2008," *American Journal of Transplantation* 10 (Part 2) (2010): 973–86. This slide has continued. See James R. Rodrigue, Jesse D. Schold, and Didier A. Mandelbrot, "The Decline in Living Kidney Donation in the United States: Random Variation or Cause for Concern?" *Transplantation Journal* 96 (2013): 767-773.

[74] Evelyn Nieves, "Girl Awaits Father's 2nd Kidney, and Decision by Medical Ethicists," *New York Times,* December 5, 1999, pp. A1, A11.

[75] See Linda Wright, Karen Faith, Robert Richardson, and David Grant, "Ethical Guidelines for the Evaluation of Living Organ Donors," *Canadian Journal of Surgery* 47 (December 2004): 408–12. See also A. Tong, J. R. Chapman, G. Wong, et al., "Living Kidney Donor Assessment: Challenges, Uncertainties and Controversies Among Transplant Nephrologists and Surgeons," *American Journal of Transplantation* 13 (2013): 2912-23. For further examination of ethical issues in living organ donation, see James F. Childress and Cathryn T. Liverman, eds., *Organ Donation: Opportunities for Action* (Washington, DC: National Academies Press, 2006), chap. 9.

[76] A vigorous debate continues about whether it would be ethically acceptable to add financial incentives for living organ donation, beyond removing financial disincentives. Such incentives would change some donors' motivations for donation, which already may include factors in addition to their altruism. </N>

bioethics

Bioethics ISSN 0269-9702 (print); 1467-8519 (online)
Volume 25 Number 6 2011 pp 293–300

doi:10.1111/j.1467-8519.2009.01757.x

ARTICLE

APPLYING THE FOUR-PRINCIPLE APPROACH

JOHN-STEWART GORDON, OLIVER RAUPRICH AND JOCHEN VOLLMANN

Keywords
principlism,
four principles,
specification,
balancing,
common morality,
applying principlism

ABSTRACT
The four-principle approach to biomedical ethics is used worldwide by practitioners and researchers alike but it is rather unclear what exactly people do when they apply this approach. Ranking, specification, and balancing vary greatly among different people regarding a particular case. Thus, a sound and coherent applicability of principlism seems somewhat mysterious. What are principlists doing? The article examines the methodological strengths and weaknesses of the applicability of this approach. The most important result is that a sound and comprehensible application of the four principles is additionally ensured by making use of the organizing meta-principle of common morality, which is the starting point and constraining framework of moral reasoning.

INTRODUCTION

The *Journal of Medical Ethics* 2003, a festschrift edition in honour of Raanan Gillon, includes articles on the question of how to apply the four principles – autonomy, nonmaleficence, beneficence, and justice – to different cases in biomedical ethics. Although the essays are interesting, they seem too perfunctory with regard to a thorough application of the principles to different cases. It is striking that there is hardly any literature that is thorough on the question of how to apply the four-principles approach to a special case. This might be for two different reasons: first, the authors pay, in general, rather little attention to presenting a detailed case study, or secondly, there is a systematic weakness in this approach.

Beauchamp and Childress hold a common morality approach, which can be roughly described as follows:

> The common morality is the set of norms shared by all persons committed to morality. The common morality is not merely *a* morality, in contrast to other moralities. The common morality is applicable to all persons in all places, and we rightly judge all human conduct by its standards.[1]

Furthermore, the justification of the four universal prima facie principles rests on the shared considered judgements of persons who are serious about morality. Common morality is the starting point and the constraining framework of moral reasoning. Particular moralities contain non-universal moral norms, which are due to cultural, religious, or institutional sources. These norms are concrete and rich in substance, unlike the universal principles, which are abstract and content-thin. The method of specification and the method of balancing are the main tools for enriching the abstract and content-thin universal principles with empirical data that come from the particular moralities. That is, people from different particular moralities may specify and balance the principles differently by virtue of differing empirical data and sources. Some particular moralities, such as the *Pirates'*

[1] T. Beauchamp & J. Childress. 2009. *Principles of Biomedical Ethics*. Oxford: Oxford University Press: 3.

Address for correspondence: John-Stewart Gordon, Queen's University Kingston, Department of Philosophy, Kingston, Ontario K7L 3N6, Canada.
jsgordon@queensu.ca

Creed of Ethics, lie outside the boundaries of the common morality and, hence, are deficient. Beauchamp and Childress seem to claim that the other particular moralities strive for perfection and try to come as close as possible to the common morality. The most developed particular morality is closest to the common morality.

In this article we present a case study using the method of principlism in order to analyze methodological strengths and weaknesses with regard to the applicability of this particular approach. The first part of the article contains the case description, which will be the starting point for the present case study. The second part offers a systematic application of the four-principles approach by presenting different specifications in order to grasp the moral conflict. The third part deals with the issue of how a principlist can deal with a given moral problem after discovering that it cannot be solved by a simple application of the four principles. The fourth part examines the methodological question of whether principlists (can) make use of an organizing or guiding principle in order to decide between conflicting principles. The last part contains some closing remarks.

1. THE CASE OF MARIA[2]

Maria was a woman from Athens who died at the age of 82. She was seriously incapacitated by arthritis for over two years prior to her death and was also virtually blind following unsuccessful cataract and glaucoma treatment. Maria had been cared for at home by her family, who never complained. Maria's condition deteriorated drastically when she suffered a severe stroke and was admitted to hospital where she fell into a 'semi-coma'. There, Maria was provided with artificial nutrition and hydration by means of a nasogastric tube. According to the physician, no other treatment was appropriate as Maria was very unlikely to recover.

Maria's family visited her at the hospital regularly but they found these visits very upsetting. Maria found it extremely difficult to speak and was very distressed. Right from the beginning, Maria found her situation intolerable and during the first six weeks of her hospitalization she repeatedly expressed her wish to be allowed to die. She did this through the use of signs and hard-fought words, even though this was itself extremely difficult and distressing for her. Maria became increasingly frustrated and made several repeated attempts to remove her feeding tube.

Maria's family knew that their mother had a lifelong aversion to hospitals and medicine. They also felt a duty to respect her wish to die. After discussing this among themselves, Maria's children decided to approach her physician about the possibility of withdrawing treatment and allowing her to die. The physician made it very clear that he would not consider acceding to such a request. He emphasized that the request would contravene his responsibilities as a physician. Further, he argued that Maria's request should not be taken at face value since Maria had a recent history of mild depression. Maria's family were unhappy with this decision and with the physician's reasoning; they thought that they had no other choice but to accept it.

One week later, Maria fell into a full and irreversible coma. After further discussion with the family, the physician agreed to withdraw nutrition but refused to withdraw hydration. Maria had no complications during the next two weeks; she then died suddenly when she suffered a second stroke.

After Maria's death, her son complained bitterly to the physician about the way his mother had been dealt with. He argued that his mother would have died sooner and would have suffered a great deal less if the physician had agreed with the family's request to withdraw all kinds of treatment when this was originally requested. He claimed that when it is clear that a patient will die soon, the physician's duty is to alleviate the patient's suffering; this means that it can sometimes be wrong to keep a patient alive for as long as possible and at all costs.

The physician responded that hydration was not simply another 'form of treatment' but, in fact, the most fundamental form of care. It was his duty as a physician to provide this fundamental care to any patient. Although he would not unnecessarily prolong a dying patient's life, he strongly believed that allowing a patient to die from lack of hydration could not be considered a dignified and peaceful death. This would, in fact, contravene his duty of care as a physician. Additionally, he argued that such action would be against any Greek medical or religious tradition and against his personal beliefs.

2. APPLYING THE FOUR-PRINCIPLE APPROACH

The following analysis is an attempt to apply the four-principle approach thoroughly to a particular case and may be helpful for the examination of other cases as well. In the case of Maria, we detected two main differing views: (i) the principle of nonmaleficence (as interpreted from Maria's and her relatives' view) and the principle of beneficence (as interpreted from the physician's view) are conflicting, and (ii) the persons concerned interpret the principle of autonomy differently. Both points are addressed in order.

[2] M. Parker & D. Dickenson. 2005. *The Cambridge Medical Ethics Workbook: Case Studies, Commentaries and Activities*. Cambridge: Cambridge University Press (abridged version): 4–5.

(i) Nonmaleficence and beneficence

Both Maria and the physician agree that there is no chance Maria will recover and that she will die soon; hence the goal is not to prolong life but to provide appropriate care at the end of her life. However, according to Maria, nutrition/hydration is harmful because it prolongs suffering, and therefore a dignified and peaceful death means – with regard to her present situation –allowing her to die by withdrawing treatment. According to the physician, artificial nutrition and hydration is not just another form of medical treatment but the most fundamental form of care which a terminally ill patient should receive by any means. It is a necessary condition for a dignified and peaceful death. To withdraw hydration and nutrition would undermine the patient's dignity. This conflict can be specified as follows:

Maria

1. Do respect the principle of nonmaleficence.
2. Do respect the principle of nonmaleficence by not harming another person.
3. Do not harm another person by violating another person's dignity.
4. Do not violate another person's dignity by preventing a patient who will die soon from dying in a dignified and peaceful manner.
5. Do not prevent a patient who will die soon from dying in a dignified and peaceful manner by providing life-sustaining treatments which prolong suffering.
6. Do not sustain the life of a suffering patient who will die soon by providing artificial nutrition and hydration.

Physician

1. Do respect the principle of beneficence.
2. Do respect the principle of beneficence by promoting good.
3. Do promote good by promoting/enabling dignity.
4. Do promote/enable dignity by letting a patient die in a dignified and peaceful manner.
5. Do let a patient die in a dignified and peaceful manner by (still) providing fundamental care.
6. Do provide fundamental care for a patient by providing artificial nutrition and hydration.

(ii) The principle of autonomy

As we saw, the principle of nonmaleficence (as specified from Maria's viewpoint) and the principle of beneficence (as specified by the physician's viewpoint) are in conflict with one another. The core of the conflict seems to be that artificial nutrition and hydration is a precondition for a dignified death, according to the physician, while Maria believes that it is incompatible with a dignified death. How can we decide this issue? Whose view should prevail? Could the principle of autonomy solve the case? The following analysis concerns the principle of autonomy and presents in detail the differing readings of the persons concerned. Maria wants to die through the withdrawal of treatment and she wants her wish to be respected. The physician, however, denies her request, in part because he thinks that Maria's recent diagnosis of mild depression calls her competence into question. Further, and more important, he stresses the traditional duties and commitments of his profession, that is, his professional autonomy.

Maria

1. Do respect the principle of autonomy.
2. Do respect the principle of autonomy by respecting the concept of informed consent.
3. Do respect the concept of informed consent by respecting individual informed consent.
4. Do respect individual informed consent by giving the patient the right to decide what is in his or her best interest.
5. Do respect the patient's right to decide what is in his or her best interest by respecting his or her refusal of artificial nutrition and hydration.

Physician

1. Do respect the principle of autonomy.
2. Do respect the principle of autonomy by respecting the physician's right to self-determination.
3. Do respect the physician's right to self-determination by respecting his or her personal and professional belief that nutrition and hydration is the most fundamental form of care all terminally ill patients should receive.
4. Do respect the physician's personal and professional belief that nutrition and hydration is the most fundamental form of care all terminally ill patients should receive by respecting his decision to refuse Maria's wish to withdraw artificial nutrition and hydration.

EVALUATION 1: WHERE IS THE MORAL CONFLICT?

The first step of principlism (and any other ethical theory) is to detect and determine the moral conflict of a given case by using the power of judgement. In the case of

Maria, two vital conflicts have been examined: (i) the conflict between the principle of nonmaleficence (Maria) and the principle of beneficence (physician), and (ii) the different specifications of the principle of autonomy, i.e. autonomy as respect for informed refusal (Maria) and as respect for conscious objection (physician). At first sight, the analysis of the moral conflict above seems successful, although we should say something more about this below. One should always keep in mind, however, that there is no absolute certainty that one is able to determine all the issues of a given case by one single method; good work is done when the core problems of a case are identified and a solution presented.

It is obvious that the physician does not need to deny that nutrition or hydration prolong Maria's suffering but he can still argue that dying through the withdrawal of treatment is even worse because it undermines Maria's dignity. Hence, it is better to suffer physically and psychologically at the end of one's life than to die without dignity. Whether it is possible that Maria acknowledges the physician's point of view but nevertheless adheres to her wish to die is questionable for logical reasons if the manner of her death undermines her concept of dignity. The deep conflict between the principle of nonmaleficence (Maria) and the principle of beneficence (physician) in the present case is challenging and should be further examined. There is no (absolute) certainty that all central aspects of a given case are always properly reconstructed. Case analysis rests for large parts on experience and the ethical power of judgement irrespective of the particular method applied, although different methods, of course, generally determine the outcome. We hold the view that the central issues have been discovered, but it seems to us that we need more information in order to make a sound principlist decision. This can be done by adding missing facts and by examining the assumptions of the conflicting views.

Deepening the analysis

First, from what does Maria suffer? Maria suffers from severe pain which is both physical (problems with swallowing) and psychological (total dependency on others);[3] she has made it clear, by signs, hard-fought words, and repeated attempts to remove her feeding tube, that she wants to die. She is distressed and frustrated, has great difficulty in speaking, is handicapped and solely dependent on other people, and has had a lifelong aversion to hospitals and medicine. In addition, she will die soon and wants no further nutrition or hydration because she supposes that this will quicken her death, which in turn will end her suffering.

[3] Unfortunately, the case description offers no other details about Maria's pain, which could help us to determine issues with important consequences for the evaluation of the case.

Secondly, given that Maria has mild depression, as the physician diagnosed, which affects her capacity for decision-making, what follows from this? The decisive question is whether the depression rests on her increasing frustration because of the physician's refusal to let her die by withdrawing nutrition and hydration, or whether it rests on her initial ill-health so that she was already incompetent when she first expressed her wish to die after being admitted to hospital. According to us, it seems more likely, with regard to the case description, that her mild depression rests on the physician's refusal to let her die; and thus her initial wish to die should be respected. To put it in a nutshell, it may be, of course, that Maria's condition is getting worse during her illness but it seems somewhat inappropriate to question her initial decision to be allowed to die by virtue of her later, deteriorated condition; this would be putting the cart before the horse.

Thirdly, is artificial hydration just another 'form of treatment' or is it the 'most fundamental form of care that [. . .] a physician feels is his duty to provide to any patient'? This point seems somewhat controversial: On the one hand, it is certainly true that artificial hydration is, of course, a form of medical treatment. On the other hand, we acknowledge the fact that the physician wants to make a distinction between other forms of treatment and providing a patient with hydration, which he claims to be 'the most fundamental form of care'. Losing a patient because he or she dies of thirst seems to be like having to bite the bullet against the background of probably the most important medical credo, *primum nil nocere*. According to other people, however, providing hydration is seen in some cases as a futile treatment, which only prolongs the patient's suffering, and hence patients should be allowed to die through the withdrawal of treatment. We think that there is no ultimate solution to this issue; one has to examine each case in order to find its suitable solution.

Fourthly, should the medical tradition of a given country always prevail over the patient's personal beliefs? To justify his decision to refuse Maria's demand to die, the physician claims that acceding to this request would contravene the medical tradition of his country. Maria is also Greek but she may not be absolutely devoted to the rules of the predominant medical tradition of her country. The decisive question is whether this should play any vital role in the process of ethical decision-making. Who decides which tradition is the predominant one and how many people should support it? Should it be 51%, 75%, or over 90% of the people in the country, or just the highest number of supporters in comparison to other groups (30%, 28%, 22%, 10% etc.)? Should the predominant tradition be allowed to influence the lives of other people who live according to different standards? There seems to be no one tradition or culture; there are always different ways of being devoted to a country's tradition and culture.

Fifthly, should the religious beliefs of the physician play any decisive role? According to principlism, the country's religious traditions are part of the particular morality. The particular morality provides the empirical data for the specification and balancing of the four principles of the common morality. Regarding the religious tradition and the physician's religious beliefs, one may question whether either should play any vital part in the decision-making process. It is difficult to assess whether the specific religious beliefs of a given country or idiosyncratic convictions (ever) lead to valid specifications of universal principles. Religious beliefs may well explain why one holds a special view but they seem less good at justifying particular specifications or forming a reasonable and reliable guide for solving conflicts by meeting universal demands.

The main result is that the abovementioned facts[4] are additional determinants in the process of decision-making. They provide us with additional information on issues related to the main conflicts of the case in question and are meant to broaden our minds to be more case-sensitive.

3. HOW CAN A PRINCIPLIST DEAL WITH THE PRESENT MORAL PROBLEM?

There are two different ways, at least, to enrich the moral analysis of a particular case with regard to the principlist strategy: (i) to make additional specifications, and (ii) to make use of the method of balancing.

(i) Additional specifications

By making additional specifications, the principlist tries to solve the conflicts between (a) differing principles (e.g. nonmaleficence and beneficence) or (b) different interpretations of one principle (e.g. autonomy). Conflicting principles and interpretations should be reconciled against the background of new facts and assumptions in order to solve the moral conflict.

(a) Beneficence

The following specification of the principle of beneficence (physician) can solve the conflict between the differing principles of Maria and the physician. The line of argumentation is as follows: Dying through the withdrawal of treatment (nutrition/hydration) is an undignified death if and only if it expresses disrespect for the person in question (Maria). However, withdrawing treatment and, at the same time, providing high-quality palliative care and personal attention to Maria would certainly not express disrespect, and hence it should not be seen as an undignified death.

(b) Autonomy

The principle of autonomy was initially directed against the more paternalistic reasoning of physicians who cared little about patients' wishes. In the present case, however, the line of argumentation concerning Maria's mild depression can be specified as follows: Maria has the right to decide what is in her best interest if and only if her decision is based on her informed consent. At the time of her decision, she must be competent and her decision voluntary; her initial decision must not be conditioned by a state of depression (or maybe mild depression), in order to be sure that she is able to make sound decisions. It seems plausible to us, then, that Maria's initial wish can be seen as an oral advance directive, assuming that she was competent, which functions as her present living will in cases of incompetence. Thus, the physician should acknowledge and accept this as legally binding. This means that he is committed to her initial wish that artificial nutrition and hydration should be withdrawn.

The additional specifications support the general line of argumentation that Maria should be allowed to have her treatment withdrawn. High-quality palliative care and her initial will, which can be seen as an oral advance directive, seem to be appropriate reasons for her justified decision. It is hard to see how the physician can argue in another well-justified way with regard to principlism, given the prior examination of the principles concerning the case in question. Therefore, it seems that no sound alternative specifications are available for the physician that could justify his view. The analysis is determined in form and content by the method of principlism.

(ii) Balancing: personal autonomy trumps professional autonomy

The principle of autonomy can be specified in different ways; in Maria's case two rival but valid specifications (personal autonomy and professional autonomy) conflict with each other. One systematic way for the four-principle approach to deal with such conflicts is to balance the conflicting specifications[5] We hold the view

[4] (i) The kind of harm Maria suffers, (ii) the assessment of Maria's competence with respect to her capacity to make informed decisions, (iii) whether artificial nutrition is a form of treatment or the most fundamental form of care, (iv) the issue of whether the medical tradition of the country should play a vital role in the process of decision making, and (v) whether the personal and religious beliefs of the physician should be acknowledged.

[5] Balancing is, according to Beauchamp and Childress, 'especially important for reaching judgments in individual cases' (T. Beauchamp & J. Childress. 2001. *Principles of Biomedical Ethics*. Oxford: Oxford

that personal autonomy trumps professional autonomy in the present case because the six conditions given by Beauchamp and Childress seem to justify the former in a more appropriate way. Professional duties and traditions, that is, professional autonomy, should play an important role in daily medical practice but they are improper when they undermine the personal autonomy of a patient who prefers treatment to be withdrawn because he or she will not recover, is suffering greatly, and will die soon.

In order to show why we think that personal autonomy trumps professional autonomy with regard to this particular case we would like to focus on the third condition, 'the infringement is morally preferable', in more detail. We have seen that the physician's position of preferring to provide fundamental care causes severe physical and mental harm to Maria. Given that she is an old woman who has lived her life and will die soon it seems somewhat inappropriate to refuse her initial wish (i.e. her oral advance directive) for treatment to be withdrawn against the background that high-quality palliative care could be provided. Professional autonomy is certainly very important in health care, but there are cases where the personal autonomy of the patient should prevail. It seems morally preferable to us that personal autonomy prevails in the present case and, therefore, to treat Maria according to her initial will, which will give her dignity, at least in her view.

EVALUATION 2: SOLVING THE MORAL PROBLEM

The opponents of principlism such as Gert and Clouser claim that principlists do not use a guiding principle and hence are unable to make a justified decision with regard to opposing specifications in a particular case. The reason is that Beauchamp and Childress' conception of principlism, in their view, does not contain an organizing meta-principle such as Kant's Categorical Imperative or the Utilitarian principle that decides which of the four principles or particular specifications should prevail when people are faced with a deep moral conflict, such as in the case of Maria. This also holds against the background of the method of balancing, which is helpful, as we saw above, but still not sufficient.[6] At first sight, this (standard) objection seems to have some plausibility if people only consider the differing specifications without making any attempt to reconcile them in a second step. At second glance, however, one acknowledges that the common morality itself is a principle that organises the specifications, at least, to some extent. The next section examines this promising way of principled reasoning.

4. COMMON MORALITY AS AN ORGANIZING PRINCIPLE

First, we would like to begin with a clarification with regard to ethical theories that apply a single organizing or guiding principle, such as is provided by classical Kantianism (the Categorical Imperative) or Utilitarianism (the greatest good for the greatest number). Proponents of these classical theories usually argue that their theories are superior to other theories that have no single organizing principle but several independent principles. This is so, according to their view, because the other theories are simply unable to solve moral problems in a clear and comprehensible way (e.g. principlism). This can be called the standard objection. It remains unclear, however, whether this is really the case; Kantianism and Utilitarianism usually have greater problems when they are applied to complex cases in applied ethics because of their lack of case sensitivity. These ethical theories adhere to the deductive model of justification (theory–principle–rules–judgement), which seems to be less sufficient in the area of applied ethics, in particular, bioethics.

Even one of the most vehement opponents of principlism, Bernard Gert, acknowledges in his work, *Common Morality. Deciding What to Do*:

> But the claim that morality is based solely on human nature does not mean that common morality provides a unique correct answer to every moral question. It is impossible to provide a description of morality that will both resolve every moral disagreement and also be endorsed by all rational persons. Common morality is a framework or system that can help individuals decide

University Press: 18), i.e. balancing is 'the process of finding reasons to support beliefs about which moral norms should prevail' (Beauchamp & Childress, *op. cit.* note 1, p. 20). This means that balancing has something to do with providing good reasons for justified acts. The following six conditions meet the important objection that balancing seems too intuitive and open-ended: (1) the overriding norm is more reasonable, (2) the infringement's justifying objective must be achievable, (3) the infringement is morally preferable, (4) the infringement must be in accord with the primary goal of action, (5) the infringement's possible negative effects must be minimized, and (6) there must be impartiality in action (Ibid: 23). That is why Beauchamp and Childress make the conciliatory claim that 'in some circumstances we will not be able to determine which moral norm to follow' (Ibid: 24).

[6] One may gain the impression that there is still no really sufficient solution to the case in question; but this is somewhat misleading. One has to distinguish two levels in this issue: the practical level and the theoretical level. Practically speaking, the results at stake seem sufficient for solving the problem but still lack the theoretical constraining framework. That is, the theoretical level should be examined in more detail in order to help us see how it can enrich the practical level by providing more methodological certainty.

what to do when faced with a moral problem, but within limits, it allows for divergent answers to most controversial questions.[7]

His considerations are certainly true, but what is most interesting concerning his criticism of principlism is that he seems to accept plausible divergent answers to controversial issues for his own theory, but denies the same right to Beauchamp and Childress. In the following, however, we would like to show how one could conceive of common morality as an organizing or guiding principle. Common morality not only concerns certain particular moralities by being their starting point and constraining framework, but also applies to concrete situations, in which, for example, one knows not to lie, not to steal property, to keep promises, to respect the rights of others, not to kill or cause harm to innocent persons, and the like.[8] This is important because common morality can, then, function as a guiding principle in situations where diverse principles and rules may conflict. Of course, we do not hold the view that common morality is able to provide a unique correct answer,[9] but it can be seen as a constraining framework that, first, separates ethical from unethical answers, and secondly, indicates which ethical answer seems more appropriate with regard to the ideal of common morality without saying that this is the only correct available answer. However, if the regulative idea of common morality can be seen as the proposed meta-principle of principlism, then we should be able to apply this meta-principle to the present case in order to provide a well-justified solution for the moral conflict.

What then are the particular weighting considerations that can be derived from the common morality in order to solve the particular conflict? An appropriate response to this important question concerns the notion of common morality itself and how the common morality is justified. In recent years, Beauchamp and Childress have offered three main ways to determine the common morality: (i) by appealing to morally serious persons,[10] (ii) by appealing to persons committed to the objectives of morality,[11] or (iii) by appealing to persons committed to morality.[12]

In the first approach, common morality is defined as a set of norms shared by all morally serious persons. In the second approach, common morality is defined as a set of norms shared by all persons committed to the objectives of morality, which are those 'of promoting human flourishing by counteracting conditions that cause the quality of people's lives to worsen'.[13] In the third approach the notion of common morality is based neither on morally serious persons nor on the objectives of morality but on the idea that common morality – as a set of norms shared by all persons committed to morality – is applicable to all persons in all places and judges all human conduct.

We believe that the first approach (morally serious persons) is the best one to use in applying common morality to particular cases. Although considered judgements are moral convictions of the highest grade of confidence and the lowest level of bias, Rawls[14] claims that considered judgements should be accepted 'provisionally as fixed points' but that they are 'liable to revision'. For Beauchamp and Childress the aim of reflective equilibrium is to match, prune, and adjust considered judgements in order to make them coherent with the premises of the most general moral commitments concerning human conduct. Furthermore, the powerful methods of specification and balancing provide further 'weighting considerations' in order to solve the moral conflict, as we have thoroughly demonstrated by our detailed analysis of how to apply principlism in the present case of Maria.

To put it in a nutshell, the appeal to common morality suggests the following main line of argumentation: Morally serious persons agree that the wishes of competent adult persons with regard to medical treatments should be respected unless they are not in their best interest. Maria experiences suffering from a serious health condition and will die soon, hence she should be allowed to die by the withdrawal of nutrition and hydration. To prolong the process of dying by acting against her expressed wish seems not to be in her best interest. Given the many details of this case, her request to be allowed to die seems reasonable and in accord with common morality. To act otherwise, that is, to continue the medical treatment, would be unjustified and would undermine her initial autonomous decision.

EVALUATION 3: DOES THE ORGANIZING PRINCIPLE DO ANY GOOD?

By applying the meta-principle of common morality in the above-mentioned way as a constraining framework, it seems that Maria's wish should be respected and that high-quality palliative care and personal attention must

[7] B. Gert. 2007. *Common Morality. Deciding What to Do.* Oxford: Oxford University Press: 4.

[8] Beauchamp & Childress. *op.cit.* note 1.

[9] The view that there is only 'one' best solution to a moral problem has been held by various well-known philosophers such as Aristotle (virtue ethics), Kant (deontology), and Bentham (Utilitarianism). Other philosophers, however, e.g. Beauchamp and Childress (principlism) or Gert (common morality approach), believe instead that there can be different and equally good solutions to moral problems. To 'solve a moral problem', then, means to provide a well-justified solution for a particular moral conflict without necessarily claiming that this is the only acceptable answer.

[10] Beauchamp & Childress, *op. cit.* note 5.

[11] T. Beauchamp. Defense of Common Morality. *Kennedy Inst Ethics J* 2003: 13(3): 259–274.

[12] Beauchamp & Childress, *op. cit.* note 1.

[13] Beauchamp, *op. cit.* note 11, p. 260.

[14] J. Rawls. 1971. *A Theory of Justice*. Cambridge MA: Harvard University Press.

be provided to her. To act otherwise would harm Maria and deprive her of her initial autonomous decision to arrange the way in which her life should end. Maria's deliberations should be respected even if it means that the physician in charge has serious doubts; and if he is not willing to comply with her wishes, he should refer the case to another colleague. The latter point is of great importance because not to offer Maria the opportunity to see another physician would severely undermine her autonomy and right to self-determination. This would harm Maria in addition to her current situation.

Elderly people who suffer from a severe illness and will die soon are not living puppets in the medical theatre of end-of-life decisions; their wishes should be respected as a form of showing final respect toward them. Human well-being can fall victim to wrong paternalistic and idiosyncratic reasoning when we do not act in the patient's best interest. End-of-life decisions should be made by mutual consent; that is, both parties – the patient and the physician – should act in concert. In complex cases, however, this does not always happen and the important question is, what should then be done. Although the physician, by virtue of his understanding of his medical profession, is no simple handmaid who fulfils all patients' wishes without question, he nevertheless has a duty not to give the patient feelings of helplessness and loneliness by simply acting against the patient's wishes. It seems that, depending on the particular situation, but particularly in hopeless end-of-life cases, physicians should simply accept that their patients might be permitted to do what they want to do.

5. CONCLUSIONS

We have seen that applying the method of principlism is not an easy task. Our analysis showed that principlism is not a mere 'checklist' method when it is done properly. The application of principlism is a challenging way to solve moral conflicts in biomedical ethics; it follows certain procedures to achieve the best solution it can. The analysis has shown, however, that the most important feature, in addition to the methods of specification and balancing, is the guiding meta-principle of common morality, which functions as a regulative idea to solve deep conflicts between rival principles. The four-principles approach, properly used, is a powerful tool for bioethical decision-making.

Acknowledgements

We are very thankful to the two anonymous reviewers for their helpful comments. This work is funded by the German Research Foundation (DFG, RA 1372/1).

John-Stewart Gordon is Visiting Professor in philosophy at Queen's University in Kingston, Canada. He is a member of the board of *Bioethics* and area-editor of The Internet Encylopedia of Philosophy (IEP). He is the author of *Aristoteles über Gerechtigkeit. Das V. Buch der Nikomachischen Ethik* (Alber Press, 2007) and *Bemerkungen zum Begründungstrilemma* (Lit Press, 2007), editor of *Morality and Justice* (Rowman & Littlefield, 2009) and co-editor of *Bioethics and Culture* (Cambridge University Press, 2010).

Oliver Rauprich is Senior Research Scholar in medical ethics and Head of Junior Research Group 'Justice in Modern Medicine' at the Institute for Medical Ethics and History of Medicine at Ruhr-University, in Bochum, Germany. His research focuses on four areas: Allocation and Justice in Health Care, Theoretical Foundations of Biomedical Ethics, Public Health Ethics and Evolutionary Ethics.

Jochen Vollmann is Professor and Director of the Institute for Medical Ethics and History of Medicine and Chair of the Centre for Medical Ethics, Ruhr-University Bochum, Germany. He received a prize for Brain Research in Geriatrics from the University of Witten/Herdecke in 1999 and the Stehr-Boldt Prize for Medical Ethics from the University of Zürich in 2001. His research interests include informed consent and capacity assessment, ethics and psychiatry, end-of-life decision-making, advance directives, medical professionalism, clinical ethics committees and clinical ethics consultation.

Journal of medical ethics, 1995; **21: 332–338**

Not just autonomy – the principles of American biomedical ethics

Søren Holm *University of Copenhagen*

Abstract

The Principles of Biomedical Ethics *by Tom L Beauchamp and James F Childress which is now in its fourth edition has had a great influence on the development of bioethics through its exposition of a theory based on the four principles: respect for autonomy; non-maleficence; beneficence, and justice (1).*

The theory is developed as a common-morality theory, and the present paper attempts to show how this approach, starting from American common-morality, leads to an underdevelopment of beneficence and justice, and that the methods offered for specification and balancing of principles are inadequate.

Introduction

It is obviously an impossible project to diagnose the state of the whole of the field of bioethics in the USA in anything less than a book-length treatment. The aim of this paper is therefore somewhat more modest, and it will only look at one specific influential school of thought within American bioethics.

The paper will proceed by offering close readings and analyses of important sections in the latest edition of the most read bioethics textbook in the USA (and probably in the world) *Principles of Biomedical Ethics,* in its fourth edition (PBE4) by Tom Beauchamp and James Childress (1).

Through this process it will become evident that the ethical system propounded by Beauchamp and Childress lacks the necessary resources satisfactorily to handle the ethically complex situations created in the interface between medicine and social justice.

Just looking at one specific approach in American bioethics could be seen as setting up a straw man, but this method is justified by the widespread use of the four principles framework in medical and nursing ethics, both academically and in practice: PBE4 is not just a small and insignificant part of American bioethics.

Key words

Principlism; beneficence; justice; specification; balancing.

Another problem is that the book contains 526 pages of densely printed text, and any extract of this is liable to be accused of selection bias. In the present case this is in one sense true. I only cite material which is relevant for the critique I want to put forward, but to avoid bias I have tried to provide fairly extensive quotes, and summaries of pertinent parts of the discussion which cannot be quoted at length.

In PBE4 the authors give a much longer and more in-depth account of their views on ethical theory than in the previous editions of The *Principles of Biomedical Ethics*, and this makes it possible to trace the basis of their theory in more detail than was previously possible.

The *Principles of Biomedical Ethics*, 4th ed, is a very rich book, and does reward careful study. It may well be that the widespread resistance to the four principles in the bioethics community would not have occurred if every student and end-user of the principles had been required to read the whole book. But, on the other hand, if this had been a requirement, the principles would probably never have gained the same degree of popularity among health care professionals.

Not just autonomy?

The ethical system put forward in PBE4 is usually known as principlism. This specific version of principlism is often referred to as the 'Georgetown mantra' or 'The four principles', and its most vigorous European proponent is Raanan Gillon (2,3). The present paper is primarily concerned with the version of the four principles found in PBE4. The version put forward by Gillon is, for instance, somewhat different from the PBE4 version, and some of the argument presented here may not affect this or other non-PBE4 versions of the four principles approach.

The PBE4 version of principlism incorporates four principles as the basis for bioethical thought: respect for autonomy; non-maleficence; beneficence; and justice.

The authors go to great lengths to emphasize that this listing of the principles does not imply a ranking,

thereby trying to answer a common criticism that whereas PBE4 mentions four principles, only one or two (ie, autonomy and non-maleficence) are really important, when it comes to analysing bioethical problems.

The authors of PBE4 reject foundationalism in bioethics, and instead develop their theory as a common-morality theory: 'A common-morality theory takes its basic premises directly from the morality shared in common by the members of *a* society – that is, unphilosophical common sense and tradition' [(4), my emphasis].

The fact that common-morality theory necessarily uses the shared morality in *a specific society* as its basic premise, is often overlooked by both proponents and opponents of the four principles.

These basic premises derived from common morality are further analysed and re-arranged in order to reach a coherent moral theory, but it should come as no surprise that the content of this theory will be influenced by its basic premises, and therefore by the morality and culture of the society from which it originates.

Because the theory of PBE4 is developed from American common morality (and in reality only from a subset of that morality) it will mirror certain aspects of American society, and may, for this reason alone, be untransferable to other contexts and other societies.

Beauchamp and Childress do not explicitly limit the scope of application of their principles to the USA, or indicate that the approach should only be used by persons working in American health care institutions. It seems fair to assume that the authors must know that their book is widely read outside the USA, given that it is now in its fourth edition. If they themselves believed that the application of their principles should be restricted to the culture from which they are derived, or that transfer to other cultural contexts requires changes in form or content, then they could have written a few lines about how such a transfer might be accomplished.

One way to accomplish a relatively un-problematic transfer would be to build on the premise that the form of the ethical system is constant, ie, the four principles point to important parts of morality in all cultures, but that the exact content and strength of the individual principles may vary between cultures. This seems to be the approach advocated by Gillon (3), but it does not seem to be available to Beauchamp and Childress. First of all, they use more than 60 pages to specify the contents of each of the four principles, without any disclaimers that this content is only valid for the USA. Secondly, they explicitly reject the criticism put forward by Clouser and Gert that the principles are 'little more than names, checklists, or headings for values worth remembering, leaving principles without deep moral substance or capacity to guide actions' (5) by claiming that they agree that the principles need additional content and specificity before they are of use, and that this content is supplied in the four long chapters describing the principles.

A more general problem with an account which construes the four principles as relatively contentless pointers or labels is that it can obscure important differences in moral outlook. Let us imagine that I read a paper which states: 'Based on the principle of beneficence x, y, and z follow'. If the four principles are just pointers or labels, then I would have to know what version of the principle of beneficence the author is talking about (ie, beneficence (USA), beneficence (Denmark), or beneficence (India), etc) before I could assess the reasoning and engage in discussion. If I just assume that the author's principle of beneficence has the same content as my own, I may be seriously misled.

The American influence on the content of the principles as they are explicated in PBE4 is, for instance, exemplified in an analysis of the duties of a physician who happens to pass by the scene of an accident where people are injured. The authors wonder whether the physician has any special duty of beneficence in this situation, just because he is a physician, and reach the following conclusion: 'The physician at the scene of an accident is obligated to do more than the lawyer or student to aid the injured, in accordance with the need for the skills of the medical profession; yet a physician-stranger is not morally required to assume the same level of commitment and risk that is legally and morally required in a prior contractual relationship with a patient or hospital' (6).

It may well be true in the context of American and British common morality and law that the physician is only obligated to a limited extent, but this analysis does not travel well to many countries in continental Europe, where Good Samaritan laws have been on the statute books for at least one hundred years, and physicians have been held answerable to the full extent of their professional duties even if no prior contract was established.

Beneficence and justice the American way!

The greatest influence of American common morality can be detected in the analysis of the principles of beneficence and justice. This is of the greatest importance in the present context. The cost of optimal (or even good) treatment and care for diseases like cancer or HIV/AIDS, from the time of diagnosis to the time of death, is so large that it is outside the economic possibilities of most private persons. In the end people with these diseases will therefore have to rely on the beneficence and sense of justice of their fellow citizens.

The fourth edition of The *Principles of Biomedical Ethics* defines the scope of the duty of beneficence in the following way: 'Apart from special moral

relationships such as contracts, a person X has a determinate obligation of beneficence toward a person Y if and only if each of the following conditions is satisfied (assuming X is aware of the relevant facts):

1. Y is at risk of significant loss of or damage to life or health or some other major interest.
2. X's action is needed (singly or in concert with others) to prevent this loss or damage.
3. X's action (singly or in concert with others) has a high probability of preventing it.
4. X's action would not present significant risks, costs, or burdens to X.
5. The benefit that Y can be expected to gain outweighs any harms, costs, or burdens that X is likely to incur' (7).

The crucial clause in this analysis, and the one which most clearly reflects American common morality, is clause 4, which states that a duty of beneficence only exists if it can be discharged without incurring significant risks, costs, or burdens. We probably all agree that there is some limit to the burdens a moral agent can be expected to incur in order to help others, but it seems strange to state that the *moral duty* of beneficence is only operative if it can be discharged without significant risk. On the previous pages of PBE4 the authors discuss the suggestion by Peter Singer that: 'If it is in our power to prevent something bad from happening, without thereby sacrificing anything of comparable moral importance, we ought, morally, to do it' (8,9).

This claim is immediately rejected, and it is suggested that if we require sacrifice of people in the discharge of their duty of beneficence, we may require something which is beyond the capability of most moral agents. This seems to me to be an extremely bleak view to take of human nature. We may all agree that beneficence must be restricted both in degree and in scope, there cannot be a duty to devote all our time and resources to acting beneficently. However, if a duty of beneficence is to have any meaning, it must at least contain the notion of the possibility of sacrifice of personal interests in the discharge of the duty.

The authors then continue with a discussion of Singer's later proposal that 10 per cent of one's income given to good causes is the minimum that any reasonable ethical standard requires, and they seem to accept this, but as a maximum instead of a minimum.

In light of this, clause 4 above must therefore be interpreted as stating that a duty of beneficence only exists if it can be discharged within the yearly allocation of 10 per cent of one's income, where risks and non-monetary burdens are represented by their comparable money value. An interpretation taking this limit at face value must therefore lead to the conclusion that a society can only legitimately collect taxes amounting to 10 per cent of the income of individual citizens in order to pay for those parts of the public social and health care programmes that cannot be legitimated by reference to their prudential value for the individual (for example, by reference to their function as an insurance substitute). And even this 10 per cent tax must be reduced if citizens are simultaneously obligated to perform other acts of beneficence.

It is also interesting to note that a strict interpretation of clause 5 would entail that it would never be morally required to put one's life at risk to save *one* other person, except within the special moral relationships mentioned in the initial *ceteris paribus* clause.

Even earlier in their exposition the authors of PBE4 distinguishes rules of beneficence from rules of non-maleficence, and present two strong claims: 'But, with rare exceptions, obligations of non-maleficence must be discharged impartially and obligations of beneficence need not be discharged impartially (10).

'Advocates of a principle of general beneficence, however, argue the far more demanding thesis that we are obligated to act impartially to promote the interests of persons beyond our limited sphere of relationships and influence' (10).

The reason for these assertions/conclusions is given in the following way: 'It is possible to act non-maleficently toward all persons, but it would be impossible to act beneficently toward all persons' (11).

Simply wrong

But this is simply wrong. It is possible to act beneficently toward all persons (for example, if I made a will dividing my property into six billion equal shares, given that my property was of a sufficient size, and I had no natural heirs); and, as marxist and feminist analyses have shown, it may very well be impossible to act non-maleficently towards all because of necessarily oppressive societal structures. It may simply be impossible to live as a citizen in a modern, first-world country without harming somebody through one's action. On one, not totally ludicrous, interpretation it is, for instance, the case that every time I buy coffee in my local supermarket I act maleficently towards a large number of people in the third world. I may not be aware that that is what I am doing, but I am inflicting harm. I might claim that this harmdoing is not intentional, but this seems a rather disingenuous excuse, given that it would only require minimal effort to make myself aware of the consequences of my act.

It could be argued that I cannot in reality act beneficently towards all, because I cannot act beneficently towards future persons. If we accept that future persons fall within the scope of the principle of beneficence that may well be true. Even if I benefit

every living person, I cannot be certain that this will also benefit future persons, and I cannot benefit future persons directly; but the same argument goes for non-maleficence. The future consequences of my present acts of non-maleficence are equally uncertain, and acting non-maleficently may in the long run create more harm than is prevented.

If future persons fall within the scope of the principle of beneficence, then they must also fall within the scope of the principle of non-maleficence, since both principles are of the same person-affecting kind. But, in that case the impossibility of acting beneficently towards all, caused by the problem of future persons, implies a similar impossibility of acting non-maleficently towards all.

The content of the principle of beneficence which emerges in PBE4 is, as we have seen, very limited, and it is not strange that critics of the PBE4 framework have claimed that beneficence disappears when compared to respect for autonomy and non-maleficence.

The principle of justice fares equally badly. Very early on in the book we read: 'For example, if the theory proposed such high requirements for personal autonomy ... or such lofty standards of social justice ... that, realistically, no person could be autonomous and no society be just, the proposed theory would be deeply defective' (12).

A just society

It is interesting to note in this context that on most accounts of justice it is actually the case that it will be very difficult or realistically impossible to create and maintain a just society. It seems impossible to claim that any presently existing society is just in a strict sense, and no realistic plans have been put forward to rectify this lamentable state of affairs. But on the PBE4 account we can probably instead simply choose to abandon our ideas about justice, since they are obviously too strict and stringent.

Whether this conclusion follows in a way which is damaging to the PBE4 account of justice depends on the meaning of the clause 'realistically could'. The fourth edition of the *Principles of Biomedical Ethics* uses a notion of 'realistic possibility' or 'practicality' to distinguish between obligatory and supererogatory acts, and in the assessment of ethical theories. The exact meaning of this notion is never made explicit, but it is, for instance, used to cast doubt on utilitarianism as a viable moral theory because of its stringent moral demands, and it is claimed that utilitarians cannot maintain the crucial distinction between the obligatory and the supererogatory. This is a fairly commonplace objection, and could be made even if the PBE4 notion of practicality put the dividing line between the obligatory and the supererogatory so that the area of obligation became very large. The PBE4 discussion of supererogation at the end of the book does, however, support a reading which points towards the area of obligation as being rather restricted. The closest possible approximation to the PBE4 idea of 'realistically could' one can get to is therefore something like 'within the reach of the average person'.

According to this conception of realistic possibility, it seems that the authors of PBE4 must place the quest for a just society within the realm of the supererogatory, and outside of the obligatory, because the chance of reaching a just society is small (or non-existent), and the effort required great. But it is difficult to see how the fulfilment of a putative obligation to work towards a just society could ever be supererogatory. If I know that the society in which I live is unjust, then I must have an obligation to try to rectify this state of affairs, even though that obligation might well be unfulfillable.

In their chapter on the principle of justice the authors discuss Michael Walzer's contention that within the sphere of health care there is a distinctive logic that 'Care should be proportionate to illness and not to wealth' (13,14), and that this distinctive logic forms part of common morality. The fourth edition of the *Principles of Biomedical Ethics* rejects this contention: 'It is doubtful that equal access to health care finds stronger support throughout the American tradition than free-market principles or beliefs in the right to a decent basic minimum of health care' (15).

From this, probably correct, interpretation of the American moral tradition PBE4 can only draw the conclusion that an egalitarian health care system is not morally mandated, but only some form of two-tier or multi-tier system with a decent minimum of health care for everybody: 'The first tier would *presumably* cover *at least* public health measures and preventive care, primary care, acute care, and special social services for those with disabilities' (16) [my emphasis].

'... , the decent-minimum proposal has proved difficult to explicate and implement. It raises problems of whether society can fairly, consistently, and unambiguously devise a public policy that recognizes a right to care for primary needs without creating a right to exotic and expensive forms of treatment, such as liver transplants costing over $200,000 for what many deem to be marginal benefits in quality-adjusted life-years' (17).

It is only with great hesitancy that I invite the reader to ponder how many people would evaluate the costs and benefits in using $50,000 each year for a number of years on the care and treatment of a drug-addict with HIV-infection and multi-resistant tuberculosis.

If the content of common morality is to any extent dependent on the number of members of the community who hold a certain point of view, I will safely predict that this treatment scenario falls outside what American (and European) common morality countenances.

And even if we reject clearly prejudicial components in common morality, it seems that the present

cost-benefit ratio of AIDS care or care for persons with untreatable cancers may put it beyond the decent-minimum commitment in the communal first tier.

A common theme which emerges in the treatment of beneficence and justice in PBE4 is a reluctance to endow these principles with much substantive content. There are many rejections of other authors who put forward too demanding and stringent conceptions of either principle, and through the gradual grinding down by removing the demanding components of the duty of beneficence and the principle of justice we end up with a totally watered-down conception without any substance or moral bite.

Specification and balancing

Another serious problem with the moral framework put forward in PBE4 is its lack of explicit decision rules. According to PBE4 good moral theories and principles should have 'output power', they should give 'creative and practical solutions', and be 'adaptive to novelty' (18). The principlism in PBE4 fulfils all these criteria, but unfortunately at the expense of any clear guidance as to how we are to reach answers to moral questions. The theory may have a lot of output power, but what is produced is produced via, but not by, the theory.

What do I mean by this?

According to PBE4 moral judgment can be aided by reflecting on the four principles, and by applying them to the case at hand through the processes of specification and balancing. Specification and balancing are not parts of the generic four principles approach (which would then be a six principles approach), but they are integral parts of the model for justification in morality which is developed in PBE4, and the total PBE4 model cannot be assessed just by looking at the four principles. Without specification and balancing the four principles are morally inert.

Specification takes place when we explicate the exact content of a given principle, norm, or rule. When we, for instance, specify the rule, 'Doctors should put their patients' interests first' we see that it does not imply that they should falsify information on insurance forms (19). Specification involves one principle and can resolve some moral conflicts, whereas moral problems involving more than one principle also requires balancing between these principles (see below). Unfortunately no procedural rules are put forward to guide the process of specification, apart from the rules of justification and coherence regulative for all rational discourse.

When it comes to balancing we get some more specific guidance. The fourth edition of the *Principles of Biomedical Ethics* accepts the distinction between *prima facie* and actual obligations as proposed by W D Ross, but the authors further argue for a set of conditions that must be met to justify infringing one *prima facie* norm in order to adhere to another:

'1. Better reasons can be offered to act on the overriding norm than on the infringed norm. ...
2. The moral objective justifying the infringement has a realistic prospect of achievement.
3. No morally preferable alternative actions can be substituted.
4. The form of infringement selected is the least possible, commensurate with achieving the primary goal of the action.
5. The agent seeks to minimize the negative effects of the infringement' (20).

The authors note that some of these conditions appear to be tautological, and it is difficult not to agree with them. If one applies the 'not test' by trying to assert the opposite of the five conditions it is obvious that they are not only nearly tautological but also totally uncontroversial. It would indeed be strange to override a *prima facie* obligation if 'Only worse reasons can be offered to act on the overriding norm than on the infringed norm'!

But can the five conditions help us, if we don't have any further conditions delimiting the field of considerations that can validly be introduced in the balancing?

Not very much, because they are almost purely formal. We are given no criteria with which we can decide whether something is a relevant *moral* consideration.

Strangely enough the authors of PBE4 seem to see this as a strength in their theory: 'As with specification, the process of balancing cannot be rigidly dictated by some formulaic "method" in ethical theory. The model of balancing will satisfy neither those who seek clear-cut, specific guidance about what one ought to do in particular cases nor those who believe in a lexical or serial ranking of principles with automatic overriding conditions' (21).

I will leave aside the question of lexical ranking, but a balancing model, which is a central component in a moral theory put forward for use in the health care context, must be able to give 'clear-cut, specific guidance about what one ought to do in particular cases' in a reasonably large number of cases, otherwise it is at greater risk of becoming a rhetorical justification of intuitions or prejudices.

It is evident that a lack of definitive moral decidability will greatly expand the output power of a moral theory, at least in terms of the number of answers produced, and that this lack will also enhance the ability to give 'creative and practical solutions' (although they will not be definitive), and the ability to be 'adaptive to novelty'. Unfortunately the answers produced will be underdetermined by the content of the theory, and the final choice between available answers will have to be made on the basis of considerations outside of the PBE4

framework. We can only hope that these decisive considerations will be moral considerations.

The theory in PBE4 therefore, not surprisingly, fulfils all the PBE4 criteria for a good moral theory, but the cost which has been paid is very high.

Conclusion

The problem with the principlism of PBE4 is thus not only the explicitly American nature of the model, with its subsequent underdevelopment of the positive obligations incorporated in beneficence and justice, but also that we are presented with a structure for moral reasoning which cannot give any definite answers to moral problems, or perhaps more accurately can produce almost any answer we want.

This problem is freely acknowledged by the authors, but they fail to see that it shifts the ground beneath their elaborate theoretical structure. They write: 'The attempt to work out the implications of general theories for specific forms of conduct and moral judgment will be called *practical ethics* here... . The term *practical* refers to the use of ethical theory and methods of analysis to examine moral problems, practices, and policies in several areas, including the professions and public policy. Often no straightforward movement from theory or principles to particular principles is possible in these contexts, although general reasons, principles, and even ideals can play some role in evaluating conduct and establishing policies' (22) [italics in original].

'We have not attempted a general ethical theory and do not claim that our principles mimic, are analogous to, or substitute for the foundational principles in leading classical theories such as utilitarianism (with its principle of utility) and Kantianism (with its categorical imperative) ... . As we have acknowledged, even the core principles of our account are so scant that they cannot provide an adequate basis for deducing most of what we can justifiably claim to know in the moral life' (23).

But what use do we have in the practical health care setting for an account where even the proponents claim that '... even the core principles of our account are so scant that they cannot provide an adequate basis for deducing most of what we can *justifiably claim to know in the moral life*' (23) [my emphasis]?

One answer could be, that even if the four principles approach cannot provide definitive answers it can provide an initial mapping of the moral domain in individual problem cases, it can facilitate the identification of the morally relevant facts, and it can thereby create the basis for an adequate discussion of such cases.

This suggestion raises two questions: a. does the PBE4 framework map the whole moral domain, and b. does the PBE4 framework contain sufficient guidance about the moral relevance of specific considerations?

There is no doubt that large parts of the moral domain can be accommodated within the four principles approach, but the inclusion in PBE4 of a chapter on 'Virtues and ideals in professional life' enumerating four(!) focal virtues, suggests that even the inventors of the four principles approach believe that there is more to morality than principles. Using only the four principles as an analytic tool, may therefore leave out other important moral considerations.

Within the PBE4 framework, the only guidance about the moral relevance of specific considerations is found in the chapters explicating the content of the four principles. I have argued above that much of this content is only applicable within an American context, and that it cannot be transferred in any straightforward manner to other cultural contexts. Even if this is only partly true it leaves the non-American user of the PBE4 approach with limited or no guidance as to the moral relevance of specific considerations falling within one of the four broad principles. Any use of the PBE4 approach as an analytic tool outside America can therefore only proceed, if the content of the four principles is worked out for the specific cultural context in which the framework is applied.

The two considerations mentioned here indicate that although the PBE4 approach may have value as a tool for elucidating specific moral problems, this value is predicated on a re-working of the content of the four principles for each new cultural context, and on an explicit recognition that the four principles must be supplemented by further moral considerations.

Acknowledgements

This paper was written in pursuance of the project for the European Commission Biomedical and Health Research Programme: *AIDS: Ethics, Justice and European Policy*. The author gratefully acknowledges the stimulus and support provided by the commission. A preliminary version of this paper was read at a seminar at Ersta Institute of Health Care Ethics, Stockholm. I thank all the participants for their comments. I also thank the editor and two anonymous referees for their helpful comments and suggestions.

Søren Holm, MA, MD, is Senior Research Fellow in the Department of Medical Philosophy and Clinical Theory at the University of Copenhagen, Denmark.

References

(1) Beauchamp T L, Childress J F. *Principles of biomedical ethics* [4th ed]. New York: Oxford University Press, 1994.

(2) Gillon R. *Philosophical medical ethics*. Chichester: John Wiley and Sons, 1986.

(3) Gillon R, ed. *Principles of health care ethics.* Chichester: John Wiley and Sons, 1994.
(4) See reference (1): 100.
(5) See reference (1): 106.
(6) See reference (1): 271.
(7) See reference (1): 266.
(8) See reference (1): 264.
(9) Singer P. Famine, affluence and morality. *Philosophy and public affairs* 1972; 1: 229–243.
(10) See reference (1): 263.
(11) See reference (1): 262.
(12) See reference (1): 47.
(13) See reference (1): 339.
(14) Walzer M. *Spheres of justice: a defense of pluralism and equality.* New York: Basic Books, 1983.
(15) See reference (1): 339.
(16) See reference (1): 356.
(17) See reference (1): 357.
(18) See reference (1): 26.
(19) See reference (1): 29.
(20) See reference (1): 34.
(21) See reference (1): 36.
(22) See reference (1): 4.
(23) See reference (1): 106–107.

News and notes

Endowed chair in medical ethics

The Department of Medicine of the SUNY Health Science Center at Syracuse is seeking an outstanding individual to assume a newly endowed alumni chair in Bio-Ethics. We seek an established academician with clinical expertise in international medicine or one of its specialties and an established academic record in Bio-Ethics to further promote scholarship and teaching in Bio-Ethics in a clinical setting, and augment an ongoing and substantial programme in the Department of Humanities. Time will be split between clinical care and the programme, and programmatic needs will be supported from the endowment.

Reply to Dr David Duggan, Chair of the Search Committee for Endowed Professor of Bio-Ethics, Department of Medicine, SUNY Health Center at Syracuse, 750 East Adams Street, Syracuse, New York 13210, USA.

Ethics of Research with Human Subjects

Ruth Faden

Required Reading

Ruth Faden, Tom Beauchamp, Nancy Kass, "Informed Consent, Comparative Effectiveness, and Learning Health Care," New England Journal of Medicine 370(8) (2014): 766-768

EJ Emanuel, D. Wendler, C. Grady, "What makes clinical research ethical?," JAMA 283(20): 2701-11. (2000).

Suggested Further Reading

Ruth Faden and Tom Beauchamp, "The development of Consent Requirements in Research Ethics," The History and Theory of Informed Consent, (Oxford University Press 1986): 150-199.

Tom L. Beauchamp, "Autonomy and Consent," in Franklin G. Miller and Alan Wertheimer, eds., The Ethics of Consent: Theory and Practice (New York: Oxford University Press, 2010), chap. 3.

Franklin G. Miller and Alan Wertheimer, "The Fair Transaction Model of Informed Consent: An Alternative to Autonomous Authorization," Kennedy Institute of Ethics Journal 21 (2011): 201–18.

Health Law, Ethics, and Human Rights

Mary Beth Hamel, M.D., M.P.H., *Editor*

Informed Consent, Comparative Effectiveness, and Learning Health Care

Ruth R. Faden, Ph.D., M.P.H., Tom L. Beauchamp, Ph.D., and Nancy E. Kass, Sc.D.

Interest in learning health care systems and in comparative-effectiveness research (CER) is exploding. One major question is whether informed consent should always be required for randomized comparative-effectiveness studies, particularly studies conducted in a learning health care system. Our answer to this question is no. It will often be unethical to go forward with CER in which patients are randomly assigned to different interventions without their written, prospective, informed consent. However, in a mature learning health care system with ethically robust oversight policies and practices, some randomized CER studies may justifiably proceed with a streamlined consent process and others may not require patient consent at all.

The current oversight system, requiring informed consent for most clinical research, grew out of a scandal-ridden period in which people were included in research and exposed to considerable risk without their knowledge or consent. In intervening decades, the clinical-research enterprise has changed. Some research, including some CER, may pose only minimal risks, yet the potential effect on patients' welfare of answering the core question of CER — which standard interventions work best for whom — is immense.

Elsewhere we have presented an ethical justification for the transition to a learning health care system and for the streamlining of both consent requirements and oversight practices within the system.[1,2] A key premise in our justification is that current consent and oversight practices too often overprotect patients from research that has little effect on what matters to patients, whereas in other cases oversight practices underprotect patients from medical errors and inappropriate medical management because they make research to reduce these problems unduly burdensome to conduct.

We also have put forward an ethics framework for learning health care to serve as the moral foundation for a learning health care system.[2] Our Common Purpose Framework builds on traditional principles of clinical and research ethics, including the Belmont Report, but is designed to provide guidance for activities in which research and practice are integrated to enable rapid, systematic learning. The Framework comprises seven moral obligations: first, respect the rights and dignity of patients; second, respect the clinical judgments of clinicians; third, provide optimal care to each patient; fourth, avoid imposing nonclinical risks and burdens on patients; fifth, reduce health inequalities among populations; sixth, conduct activities that foster learning from clinical care and clinical information; and seventh, contribute to the common purpose of improving the quality and value of clinical care and health care systems. The first six obligations fall on researchers, clinicians, health care administrators, institutions, payers, and insurers. The seventh falls on patients to participate in certain types of learning activities that will be integrated with their clinical care.

Extensive consultation with patients and other stakeholders is necessary for appropriate specification of the institutional implications of the Framework. All involved must appreciate that they are receiving care or working in an institution committed to the shared mission of continuous learning that feeds directly into improving patient care. An ethical learning health care system must have core commitments to engagement, transparency, and accountability in ways that are keenly sensitive to the rights and interests of patients. Patients will be engaged in two respects: by helping to set the CER priorities of the system and by serving on ethics-oversight panels that will review proposed CER studies in light of the obligations of the Common Purpose

n engl j med 370;8 nejm.org february 20, 2014

Framework and other ethical requirements and determine the appropriate forms of consent and authorization.

In this system, all patients will be told that patients serve on ethics-oversight panels and how they operate. The panels will determine whether particular CER (and quality-improvement) activities fall above or below a threshold of negative effect on expected clinical outcomes or other outcomes or values that matter morally to patients. Research that falls below the threshold will be integrated into clinical care without specific notification to or consent from individual patients; however, public notification will be provided to the community of the system, including patients. Other CER studies, determined by panels to have minor but still meaningful effects on patients' interests, will proceed with specific notification to affected patients, who will have an option to decline participation. Still other studies, determined to be clearly above the threshold, will require prospective, written, informed consent before proceeding. The system will thus aim to counteract problems of both underprotection and overprotection.

Transparent mechanisms will ensure that patients and other stakeholders can easily learn which CER studies are ongoing. In addition, and critically, a learning health care system will be accountable for rapid modifications of clinical practice that are supported by CER findings and for providing public reasons when modifications are not made.

In learning health care systems with these ethically robust practices, it will be ethically acceptable for some randomized CER studies, having no or only minor effects on important patient interests, to proceed without informed consent from or specific notification to individual patients. Consider, for example, randomized studies that compare the effectiveness of sending medication reminders by text or e-mail to patients who have previously given permission to be contacted by either mechanism or the usefulness of repeating a routine laboratory test once or twice during a patient hospitalization when both are standard practice. In a mature learning health care system, an ethics-oversight panel might justifiably approve the integration of these studies into clinical care routines with only public notification to the community of the system that the research is being conducted.

Consider also a pragmatic, randomized clinical trial that compares two widely used hypertension medications, perhaps two diuretics, and in which there are no delineated clinical characteristics that would favor one drug over another for many patients. Although an algorithm identifies eligible patients, treating physicians make the final enrollment determination. Physicians and patients can override the randomized choice. Physicians may change drugs, adjust dosages, or add therapies for any patient at any time. This study is unlikely to negatively affect expected clinical outcomes for patients, and respect for physician judgment is maintained. The drugs are similar in administration and side-effect profiles, both drugs have acceptable side-effect profiles, and adverse events are rare. It is unlikely that patients would have personal preferences for one drug over the other. This trial therefore accords well with the obligations in the Common Purpose Framework requirements.[3] In a mature learning health care system of the sort that we envision, simply telling patients about the study through a streamlined process and giving them an opportunity to decline participation would be an ethically acceptable, warranted mechanism of authorization. It may even be acceptable for an ethics-oversight panel to permit the study to proceed with broad notification to the community of the system, without requiring that individual patients be told about the randomization.

However, some randomized CER studies in learning health care systems cannot be ethically authorized by either of these mechanisms. Explicit informed consent will be required if risk, uncertainty, or informational need is higher. Included would be studies in which the prospect of differential clinical outcomes or considerable risk looms large as well as studies in which interventions are different in terms of other considerations that matter to patients. Consider a study that randomly assigns patients with back pain to acupuncture or to a home exercise regimen or that randomly assigns patients with scoliosis to surgery or to bracing. Even if the alternative treatments were considered standard practice and even if clinicians were uncertain and evidence was lacking about which is more effective, the two options have such different implications for patients' lives that informed consent is essential. Among the critical functions of hav-

ing substantial patient engagement in ethics oversight of CER (and other research) in learning health care is to ensure that patients' values, beyond their interest in securing the best possible clinical outcomes, are respected.

Our position that informed consent is not a morally necessary condition for the conduct of all randomized CER assumes a learning health care system grounded in a set of moral commitments against which specific studies have been vetted and found to satisfy the conditions that permit authorization through processes other than informed consent. The transformation to a learning health care system is still in its infancy, and no system on the path to this important goal has yet to adopt an ethical framework with accompanying policies and practices of the sort we are proposing. However, the Common Purpose Framework can provide helpful guidance in current health care settings. Some randomized CER studies that would assess favorably against the first four obligations of the Framework could proceed ethically with a streamlined consent process. These include studies that, in comparison with what patients would otherwise encounter in their care, have no expected negative effects on clinical outcomes or on other considerations that matter to patients.

Consider now the previously mentioned randomized clinical trial comparing two similar hypertension drugs to see what authorization approaches might be justified in the current environment. We suggested that in an ethically robust learning health care system, characterized by extensive patient engagement, transparency, and accountability, it would be ethically acceptable for the study to proceed with a streamlined consent process and potentially even without specific notification to affected patients. In the present context, in which morally relevant features of a mature learning health care system are not in place, proceeding without specific notification to patients would not be ethically acceptable. However, it may still be ethically justifiable to use a streamlined consent process, similar to that suggested by others,[4,5] because the study has no apparent effects on the risks or burdens that patients otherwise face in clinical care (the third and fourth obligations), clinician judgment is respected (the second obligation), and the interventions do not differ on matters of importance to patients (the first obligation). In the streamlined process, physicians would inform their patients about the study and the use of randomization. Their explanations would be brief, akin to the conversation that physicians typically have with patients about a new prescription, and accompanied by a short, written description. Patients would be given an opportunity to opt out of the research and to learn more if they wish, but patients would not be asked for written informed consent. This approach could be designed to be respectful of patients and less burdensome for them and for clinicians than the lengthier process entailed by current informed-consent requirements, thereby increasing the numbers ofclinicians willing to take part and increasing the numbers of important clinical questions that can be addressed.

Clinical research varies widely in the risks to which patients are exposed and the degree to which research alters the care that patients receive in ways that matter to them. The importance of streamlining oversight and consent requirements, so that higher-risk research gets the focused attention it deserves and less consequential research can proceed more rapidly, is increasingly being acknowledged. As more low-risk CER is planned, it will be essential to identify additional, valid authorization mechanisms, rather than using a one-size-fits-all approach to informed consent. The transformation to ethically robust learning health care systems is critical to this goal.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Berman Institute of Bioethics, Johns Hopkins University, Baltimore (R.R.F., N.E.K.); and the Kennedy Institute of Ethics, Georgetown University, Washington, DC (T.L.B.).

1. Kass NE, Faden RR, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight. Hastings Cent Rep 2013;43:S4-S15.
2. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning healthcare system: a departure from traditional research ethics and clinical ethics. Hastings Cent Rep 2013;Spec No:S16-S27.
3. Faden R, Kass N, Whicher D, Stewart W, Tunis S. Ethics and informed consent for comparative effectiveness research with prospective electronic clinical data. Med Care 2013;51:Suppl 3: S53-S57.
4. Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized, controlled trials? N Engl J Med 1999;340:804-7.
5. Morris MC, Nelson RM. Randomized, controlled trials as minimal risk: an ethical analysis. Crit Care Med 2007;35:940-4.

DOI: 10.1056/NEJMhle1313674

What Makes Clinical Research Ethical?

Ezekiel J. Emanuel, MD, PhD
David Wendler, PhD
Christine Grady, PhD

Many believe that informed consent makes clinical research ethical. However, informed consent is neither necessary nor sufficient for ethical clinical research. Drawing on the basic philosophies underlying major codes, declarations, and other documents relevant to research with human subjects, we propose 7 requirements that systematically elucidate a coherent framework for evaluating the ethics of clinical research studies: (1) value—enhancements of health or knowledge must be derived from the research; (2) scientific validity—the research must be methodologically rigorous; (3) fair subject selection—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects; (4) favorable risk-benefit ratio—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks; (5) independent review—unaffiliated individuals must review the research and approve, amend, or terminate it; (6) informed consent—individuals should be informed about the research and provide their voluntary consent; and (7) respect for enrolled subjects—subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored. Fulfilling all 7 requirements is necessary and sufficient to make clinical research ethical. These requirements are universal, although they must be adapted to the health, economic, cultural, and technological conditions in which clinical research is conducted.

JAMA. 2000;283:2701-2711 www.jama.com

WHAT MAKES RESEARCH involving human subjects ethical? Informed consent is the answer most US researchers, bioethicists, and institutional review board (IRB) members would probably offer. This response reflects the preponderance of existing guidance on the ethical conduct of research and the near obsession with autonomy in US bioethics.[1-4] While informed consent is necessary in most but not all cases, in no case is it sufficient for ethical clinical research.[5-8] Indeed, some of the most contentious contemporary ethical controversies in clinical research, such as clinical research in developing countries,[9-13] the use of placebos,[14-16] phase 1 research,[17-19] protection for communities,[20-24] and involvement of children,[25-29] raise questions not of informed consent, but of the ethics of subject selection, appropriate risk-benefit ratios, and the value of research to society. Since obtaining informed consent does not ensure ethical research, it is imperative to have a systematic and coherent framework for evaluating clinical studies that incorporates all relevant ethical considerations.

In this article, we delineate 7 requirements that provide such a framework by synthesizing traditional codes, declarations, and relevant literature on the ethics of research with human subjects. This framework should help guide the ethical development and evaluation of clinical studies by investigators, IRB members, funders, and others.

THE 7 ETHICAL REQUIREMENTS

The overarching objective of clinical research is to develop generalizable knowledge to improve health and/or increase understanding of human biology[30,31]; subjects who participate are the means to securing such knowledge.[32] By placing some people at risk of harm for the good of others, clinical research has the potential for exploitation of human subjects.[33,34] Ethical requirements for clinical research aim to minimize the possibility of exploitation by ensuring that research subjects are not merely used but are treated with respect while they contribute to the social good.[30]

For the past 50 years, the main sources of guidance on the ethical conduct of clinical research have been the Nuremberg Code,[35] Declaration of Helsinki,[36] Belmont Report,[37] International Ethical Guidelines for Biomedical Research Involving Human Subjects,[38] and similar documents (**TABLE 1**). However, many of these documents were written in response to specific events and to avoid future scandals.[50,51] By focusing on the instigating issues, these guidelines tend to

Author Affiliations: Department of Clinical Bioethics, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, Md.
Corresponding Author and Reprints: Christine Grady, PhD, Warren G. Magnuson Clinical Center, Bldg 10, Room 1C118, National Institutes of Health, Bethesda, MD 20892-1156 (e-mail: cgrady@nih.gov).

emphasize certain ethical requirements while eliding others. For instance, the Nuremberg Code[35] was part of the judicial decision condemning the atrocities of the Nazi physicians and so focused on the need for consent and a favorable risk-benefit ratio but makes no mention of fair subject selection or independent review. The Declaration of Helsinki[36] was developed to remedy perceived lacunae in the Nuremberg Code, especially as related to physicians conducting research with patients, and so focuses on favorable risk-benefit ratio and independent review; the Declaration of Helsinki also emphasizes a distinction between therapeutic and nontherapeutic research that is rejected or not noted by other documents.[30,52] The Belmont Report[37] was meant to provide broad principles that could be used to generate specific rules and regulations in response to US research scandals such as Tuskegee[53] and Willowbrook.[54,55] It focuses on informed consent, favorable risk-benefit ratio, and the need to ensure that vulnerable populations are not targeted for risky research. The Council for International Organizations of Medical Sciences (CIOMS) guidelines[38] were intended to apply the Declaration of Helsinki "in developing countries... [particularly for] large-scale trials of vaccines and drugs." The CIOMS guidelines lack a separate section devoted to risk-benefit ratios, although the council considers this issue in commentary on other guidelines. It also includes a section on compensation for research injuries not found in other documents. Because the Advisory Committee on Human Radiation Experiments was responding to covert radiation experiments, avoiding deception was among its 6 ethical standards and rules; most other major documents do not highlight this.[56] This advisory committee claims that its ethical standards are general, but acknowledges that its choices were related to the specific circumstances that occasioned the report.[56] Finally some tensions, if not outright contradictions, exist among the provisions of the various guidelines.[5,19,30,51,52,57,58] Absent a universally applicable ethical framework, investigators, IRB members, funders, and others lack coherent guidance on determining whether specific clinical research protocols are ethical.

Table 1. Selected Guidelines on the Ethics of Biomedical Research With Human Subjects*

Guideline	Source	Year and Revisions
	Fundamental	
Nuremberg Code[35]	Nuremberg Military Tribunal decision in *United States v Brandt*	1947
Declaration of Helsinki[36]	World Medical Association	1964, 1975, 1983, 1989, 1996
Belmont Report[37]	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research	1979
International Ethical Guidelines for Biomedical Research Involving Human Subjects[38]	Council for International Organizations of Medical Sciences in collaboration with World Health Organization	Proposed in 1982; revised, 1993
	Other	
45 CFR 46, Common Rule[8]	US Department of Health and Human Services (DHHS) and other US federal agencies	DHHS guidelines in 1981; Common Rule, 1991
Guidelines for Good Clinical Practice for Trials on Pharmaceutical Products[42]	World Health Organization	1995
Good Clinical Practice: Consolidated Guidance[44]	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use	1996
Convention on Human Rights and Biomedicine[43]	Council of Europe	1997
Guidelines and Recommendations for European Ethics Committees[45]	European Forum for Good Clinical Practice	1997
Medical Research Council Guidelines for Good Clinical Practice in Clinical Trials[46]	Medical Research Council, United Kingdom	1998
Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda[47]	Uganda National Council for Science and Technology	1998
Ethical Conduct for Research Involving Humans[48]	Tri-Council Working Group, Canada	1998
National Statement on Ethical Conduct in Research Involving Humans[49]	National Health and Medical Research Council, Australia	1999

*CFR indicates Code of Federal Regulations. More extensive lists of international guidelines on human subjects research can be found in Brody[39] and Fluss.[40] An extensive summary of US guidelines can be found in Sugarman et al.[41]

There are 7 requirements that provide a systematic and coherent framework for determining whether clinical research is ethical (**TABLE 2**). These requirements are listed in chronological order from the conception of the research to its formulation and implementation. They are meant to guide the ethical development, implementation, and review of individual clinical protocols. These 7 requirements are intended to elucidate the ethical standards specific for clinical research and assume general ethical obligations, such as intellectual honesty and responsibility. While none of the traditional ethical guidelines on clinical research explicitly includes all 7 requirements, these requirements systematically elucidate the fundamental protections embedded in the basic philosophy of all these documents.[30] These requirements are not limited to a specific tragedy or scandal or to the practices of researchers in 1 country; they are meant to be universal, although their application will require adaptation to particular cultures, health conditions, and economic settings. These

7 requirements can be implemented well or ineffectively. However, their systematic delineation is important and conceptually prior to the operation of an enforcement mechanism. We need to know what to enforce.

Value

To be ethical, clinical research must be valuable,[4,35] meaning that it evaluates a diagnostic or therapeutic intervention that could lead to improvements in health or well-being; is a preliminary etiological, pathophysiological, or epidemiological study to develop such an intervention; or tests a hypothesis that can generate important knowledge about structure or function of human biological systems, even if that knowledge does not have immediate practical ramifications.[4,30] Examples of research that would not be socially or scientifically valuable include clinical research with nongeneralizable results, a trifling hypothesis, or substantial or total overlap with proven results.[4] In addition, research with results unlikely to be disseminated or in which the intervention could never be practically implemented even if effective is not valuable.[12,13,38,59] Only if society will gain knowledge, which requires sharing results, whether positive or negative, can exposing human subjects to risk in clinical research be justified. Thus, evaluation of clinical research should ensure that the results will be disseminated, although publication in peer-reviewed journals need not be the primary or only mechanism.

There are 2 fundamental reasons why social, scientific, or clinical value should be an ethical requirement: responsible use of finite resources and avoidance of exploitation.[4] Research resources are limited. Even if major funding agencies could fund all applications for clinical research, doing so would divert resources from other worthy social pursuits. Beyond not wasting resources, researchers should not expose human beings to potential harms without some possible social or scientific benefit.[4,30,35,38]

It is possible to compare the relative value of different clinical research studies; clinical research that is likely to generate greater improvements in health or well-being given the condition being investigated, the state of scientific understanding, and the feasibility of implementing the intervention is of higher value. Comparing relative value is integral to determinations of funding priorities when allocating limited funds among alternative research proposals.[60] Similarly, a comparative evalu-

Table 2. Seven Requirements for Determining Whether a Research Trial Is Ethical*

Requirement	Explanation	Justifying Ethical Values	Expertise for Evaluation
Social or scientific value	Evaluation of a treatment, intervention, or theory that will improve health and well-being or increase knowledge	Scarce resources and nonexploitation	Scientific knowledge; citizen's understanding of social priorities
Scientific validity	Use of accepted scientific principles and methods, including statistical techniques, to produce reliable and valid data	Scarce resources and nonexploitation	Scientific and statistical knowledge; knowledge of condition and population to assess feasibility
Fair subject selection	Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favored for potentially beneficial research	Justice	Scientific knowledge; ethical and legal knowledge
Favorable risk-benefit ratio	Minimization of risks; enhancement of potential benefits; risks to the subject are proportionate to the benefits to the subject and society	Nonmaleficence, beneficence, and nonexploitation	Scientific knowledge; citizen's understanding of social values
Independent review	Review of the design of the research trial, its proposed subject population, and risk-benefit ratio by individuals unaffiliated with the research	Public accountability; minimizing influence of potential conflicts of interest	Intellectual, financial, and otherwise independent researchers; scientific and ethical knowledge
Informed consent	Provision of information to subjects about purpose of the research, its procedures, potential risks, benefits, and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Respect for potential and enrolled subjects	Respect for subjects by (1) permitting withdrawal from the research; (2) protecting privacy through confidentiality; (3) informing subjects of newly discovered risks or benefits; (4) informing subjects of results of clinical research; (5) maintaining welfare of subjects	Respect for subject autonomy and welfare	Scientific knowledge; ethical and legal knowledge; knowledge of particular subject population

*Ethical requirements are listed in chronological order from conception of research to its formulation and implementation.

ation of value may be necessary in considering studies involving finite scientific resources such as limited biological material or the small pool of long-term human immunodeficiency virus nonprogressors.

Scientific Validity

To be ethical, valuable research must be conducted in a methodologically rigorous manner.[4] Even research asking socially valuable questions can be designed or conducted poorly and produce scientifically unreliable or invalid results.[61] As the CIOMS guidelines succinctly state: "Scientifically unsound research on human subjects is ipso facto unethical in that it may expose subjects to risks or inconvenience to no purpose."[38]

For a clinical research protocol to be ethical, the methods must be valid and practically feasible: the research must have a clear scientific objective; be designed using accepted principles, methods, and reliable practices; have sufficient power to definitively test the objective; and offer a plausible data analysis plan.[4] In addition, it must be possible to execute the proposed study. Research that uses biased samples, questions, or statistical evaluations, that is underpowered, that neglects critical end points, or that could not possibly enroll sufficient subjects cannot generate valid scientific knowledge and is thus unethical.[4,30,62] For example, research with too few subjects is not valid because it might be combined in a meaningful meta-analysis with other, as yet unplanned and unperformed clinical research; the ethics of a clinical research study cannot depend on the research that others might but have not yet done. Of course the development and approval of a valid method is of little use if the research is conducted in a sloppy or inaccurate manner; careless research that produces uninterpretable data is not just a waste of time and resources, it is unethical.

Clinical research that compares therapies must have "an honest null hypothesis" or what Freedman called clinical equipoise.[30,63] That is, there must be controversy within the scientific community about whether the new intervention is better than standard therapy, including placebo, either because most clinicians and researchers are uncertain about whether the new treatment is better, or because some believe the standard therapy is better while others believe the investigational intervention superior.[63] If there exists a consensus about what is the better treatment, there is no null hypothesis, and the research is invalid. In addition, without clinical equipoise, research that compares therapies is unlikely to be of value because the research will not contribute to increasing knowledge about the best therapy, and the risk-benefit ratio is unlikely to be favorable because some of the subjects will receive inferior treatment.

Importantly, a "good question" can be approached by good or bad research techniques; bad research methods do not render the question valueless. Thus, the significance of a hypothesis can and should be assessed prior to and independent of the specific research methods. Reviewers should not dismiss a proposal that uses inadequate methods without first considering whether adjustments could make the proposal scientifically valid.

The justification of validity as an ethical requirement relies on the same 2 principles that apply to value—limited resources and the avoidance of exploitation.[4,30] "Invalid research is unethical because it is a waste of resources as well: of the investigator, the funding agency, and anyone who attends to the research."[4] Without validity the research cannot generate the intended knowledge, cannot produce any benefit, and cannot justify exposing subjects to burdens or risks.[50]

Fair Subject Selection

The selection of subjects must be fair.[30,37,56] Subject selection encompasses decisions about who will be included both through the development of specific inclusion and exclusion criteria and the strategy adopted for recruiting subjects, such as which communities will be study sites and which potential groups will be approached. There are several facets to this requirement.

First, fair subject selection requires that the scientific goals of the study, not vulnerability, privilege, or other factors unrelated to the purposes of the research, be the primary basis for determining the groups and individuals that will be recruited and enrolled.[3,30,37] In the past, groups sometimes were enrolled, especially for research that entailed risks or offered no potential benefits, because they were "convenient" or compromised in their ability to protect themselves, even though people from less vulnerable groups could have met the scientific requirements of the study.[30,37,53,54]

Similarly, groups or individuals should not be excluded from the opportunity to participate in research without a good scientific reason or susceptibility to risk that justifies their exclusion.[64] It is important that the results of research be generalizable to the populations that will use the intervention. Efficiency cannot override fairness in recruiting subjects.[37] Fairness requires that women be included in the research, unless there is good reason, such as excessive risks, to exclude them.[65-69] This does not mean that every woman must be offered the opportunity to participate in research, but it does mean that women as a class cannot be peremptorily excluded.

Second, it is important to recognize that subject selection can affect the risks and benefits of the study.[70] Consistent with the scientific goals, subjects should be selected to minimize risks and enhance benefits to individual subjects and society. Subjects who are eligible based on the scientific objectives of a study, but are at substantially higher risk of being harmed or experiencing more severe harm, should be excluded from participation.[71] Selecting subjects to enhance benefits entails consideration of which subjects will maximize the benefit or value of the information obtained. If a potential drug or procedure is likely to be prescribed for women or children if proven safe and effective, then these groups should be

included in the study to learn how the drug affects them.[63,66,67] Indeed, part of the rationale for recent initiatives to include more women, minorities, and children in clinical research is to maximize the benefits and value of the study by ensuring that these groups are enrolled.[65-67,72,73] It is not necessary to include children in all phases of research. Instead, it may be appropriate to include them only after the safety of the drug has been assessed in adults.

Additionally, fair subject selection requires that, as far as possible, groups and individuals who bear the risks and burdens of research should be in a position to enjoy its benefits,[12,13,38,59,74] and those who may benefit should share some of the risks and burdens.[75] Groups recruited to participate in clinical research that involves a condition to which they are susceptible or from which they suffer are usually in a position to benefit if the research provides a positive result, such as a new treatment. For instance, selection of subjects for a study to test the efficacy of an antimalarial vaccine should consider not only who will best answer the scientific question, but also whether the selected groups will receive the benefits of the vaccine, if proven effective.[12,13,37,59,74,76] Groups of subjects who will predictably be excluded as beneficiaries of research results that are relevant to them typically should not assume the burdens so that others can benefit. However, this does not preclude the inclusion of subjects who are scientifically important for a study but for whom the potential products of the research may not be relevant, such as healthy control subjects.

Fair subject selection should be guided by the scientific aims of the research and is justified by the principles that equals should be treated similarly and that both the benefits and burdens generated by social cooperation and activities such as clinical research should be distributed fairly.[3,30,37,38,66,67] This does not mean that individual subjects and members of groups from which they are selected must directly benefit from each clinical research project or that people who are marginalized, stigmatized, powerless, or poor should never be included. Instead, the essence of fairness in human subjects research is that scientific goals, considered in dynamic interaction with the potential for and distribution of risks and benefits, should guide the selection of subjects.

Favorable Risk-Benefit Ratio

Clinical research involves drugs, devices, and procedures about which there is limited knowledge. As a result, research inherently entails uncertainty about the degree of risk and benefits, with earlier phase research having greater uncertainty. Clinical research can be justified only if, consistent with the scientific aims of the study and the relevant standards of clinical practice, 3 conditions are fulfilled: the potential risks to individual subjects are minimized, the potential benefits to individual subjects are enhanced, and the potential benefits to individual subjects and society are proportionate to or outweigh the risks.[30,36,37]

Assessment of the potential risks and benefits of clinical research by researchers and review bodies typically involves multiple steps. First, risks are identified and, within the context of good clinical practice, minimized "by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes."[8]

Second, potential benefits to individual subjects from the research are delineated and enhanced. Potential benefits focus on the benefits to individual subjects, such as health improvements, because the benefits to society through the generation of knowledge are assumed if the research is deemed to be of value and valid. The specification and enhancement of potential benefits to individual subjects should consider only health-related potential benefits derived from the research.[77] Assessment of the research plan should determine if changes could enhance the potential benefits for individual subjects. For example, consistent with the scientific objectives, tests and interventions should be arranged to increase benefit to subjects. However, extraneous benefits, such as payment, or adjunctive medical services, such as the possibility of receiving a hepatitis vaccine not related to the research, cannot be considered in delineating the benefits compared with the risks, otherwise simply increasing payment or adding more unrelated services could make the benefits outweigh even the riskiest research. Furthermore, while participants in clinical research may receive some health services and benefits, the purpose of clinical research is not the provision of health services. Services directly related to clinical research are necessary to ensure scientific validity and to protect the well-being of the individual subjects.

In the final step, risks and potential benefits of the clinical research interventions to individual subjects are compared. In general, the more likely and/or severe the potential risks the greater in likelihood and/or magnitude the prospective benefits must be; conversely, research entailing potential risks that are less likely and/or of lower severity can have more uncertain and/or circumscribed potential benefits. If the potential benefits to subjects are proportional to the risks they face, as generally found when evaluating phase 2 and 3 research, then the additional social benefits of the research, assured by the fulfillment of the value and validity requirements, imply that the cumulative benefits of the research outweigh its risks.[30]

Obviously, the notions of "proportionality" and potential benefits "outweighing" risks are nonquantifiable.[37] However, the absence of a formula to determine when the balance of risks and potential benefits is proportionate does not connote that such judgments are inherently haphazard or subjective. Instead, assessments of risks and potential benefits to the same individuals can appeal to explicit standards, informed by existing data on the potential types

of harms and benefits, their likelihood of occurring, and their long-term consequences.[37] People routinely make discursively justifiable intrapersonal comparisons of risks and benefits for themselves and even for others, such as children, friends, and employees, without the aid of mathematical formulae.[78]

An additional evaluation is necessary for any clinical research that presents no potential benefits to individual subjects, such as phase 1 safety, pharmacokinetic, and even some epidemiology research, or when the risks outweigh the potential benefits to individual subjects.[72] This determination, which Weijer[79] calls a "risk-knowledge calculus," assesses whether the societal benefits in terms of knowledge justify the excess risks to individual subjects. Determination of when potential social benefits outweigh risks to individual subjects requires interpersonal comparisons that are conceptually and practically more difficult.[78] However, policymakers often are required to make these kind of comparisons, for example when considering whether pollution and its attendant harms to some people are worth the potential benefits of higher employment and tax revenues to others. There is no settled framework for how potential social benefits should be balanced against individual risks. Indeed, the appeal to a utilitarian approach of maximization, as in cost-benefit analysis, is quite controversial both morally and because many risks and benefits of research are not readily quantifiable on commensurable scales.[78-82] Nevertheless, these comparisons are made,[83] and regulations mandate that investigators and IRBs make them with respect to clinical research. When research risks exceed potential medical benefits to individuals and the benefit of useful knowledge to society, the clinical research is not justifiable.

The requirement for a favorable risk-benefit ratio embodies the principles of nonmaleficence and beneficence, long recognized as fundamental values of clinical research.[3,30,36,37] The principle of nonmaleficence states that one ought not to inflict harm on a person.[3] This justifies the need to reasonably reduce the risks associated with research. The principle of beneficence "refers to a moral obligation to act for the benefit of others."[3] In clinical research, this translates into the need to enhance the potential benefits of the research for both individual subjects and society.[3,30,37] Ensuring that the benefits outweigh the risks is required by the need to avoid the exploitation of subjects.[30,37]

Independent Review

Investigators inherently have multiple, legitimate interests—interests to conduct high-quality research, complete the research expeditiously, protect research subjects, obtain funding, and advance their careers. These diverse interests can generate conflicts that may unwittingly distort the judgment of even well-intentioned investigators regarding the design, conduct, and analysis of research.[84-87] Wanting to complete a study quickly may lead to the use of questionable scientific methods or readily available rather than the most appropriate subjects. Independent review by individuals unaffiliated with the clinical research helps minimize the potential impact of such conflicts of interest.[86,88] For some research with few or no risks, independent review may be expedited, but for much of clinical research, review should be done by a full committee of individuals with a range of expertise who have the authority to approve, amend, or terminate a study.

Independent review of clinical research is also important for social accountability. Clinical research imposes risks on subjects for the benefit of society. Independent review of a study's compliance with ethical requirements assures members of society that people who enroll in trials will be treated ethically and that some segments of society will not benefit from the misuse of other human beings. Review also assures people that if they enroll in clinical research, the trial is ethically designed and the risk-benefit ratio is favorable.

In the United States, independent evaluation of research projects occurs through multiple groups including granting agencies, local IRBs, and data and safety monitoring boards.[89-91] In other countries, independent review of clinical research is conducted in other ways.

Informed Consent

Of all requirements, none has received as much explication as informed consent.[2-4,6,7,19,30-32,35-38] The purpose of informed consent is 2-fold: to ensure that individuals control whether or not they enroll in clinical research and participate only when the research is consistent with their values, interests, and preferences.[2,3,30-32,35,37,92-96] To provide informed consent, individuals must be accurately informed of the purpose, methods, risks, benefits, and alternatives to the research; understand this information and its bearing on their own clinical situation; and make a voluntary and uncoerced decision whether to participate.[97-99] Each of these elements is necessary to ensure that individuals make rational and free determinations of whether the research trial is consonant with their interests.

Informed consent embodies the need to respect persons and their autonomous decisions.[2,3,97,98] To enroll individuals in clinical research without their authorization is to treat them merely as a means to purposes and ends they may not endorse and deny them the opportunity to choose what projects they will pursue.

Children and adults with diminished mental capacity who are unable to make their own decisions about participating in research nonetheless have interests and values.[2,3] For instance, individuals rendered unconscious due to head trauma or a stroke typically retain the interests and values they had just before the accident. Even individuals with severe Alzheimer disease retain some interests, if only those related to personal dignity and physical comfort. Showing respect for these nonautonomous persons means ensuring that research participation is consistent with their interests and values; this

usually entails empowering a proxy decision maker to determine whether to enroll the person in clinical research. In making this decision, the proxy uses the substituted judgment standard: what research decision would the subject make if he or she could.[2,3,100]

However, an individual's preferences and values related to clinical research may be unknown or unknowable, or, in the case of children, the individual may not have developed mature preferences related to research. In such cases, research proxies should choose the option that is in the individual's best medical interests. There is controversy about how much discretion proxies should have in such circumstances, especially given the inherent uncertainty of the risks and potential benefits of research participation.[101-105] The National Bioethics Advisory Commission has urged that proxies should exercise "great caution" in making judgments about a subject's best interest regarding research.[103] Other groups believe that proxies should have more discretion.

In emergency settings that preclude time for identifying and eliciting the consent of a proxy decision maker, research can proceed without either informed consent or permission of proxy decision makers when conducted under strict guidelines.[6] Most importantly, there should be clinical equipoise—the absence of a consensus regarding the comparative merits of the interventions to be tested.[63] In such a case, the subject is not worse off by enrolling.

Respect for Potential and Enrolled Subjects

Ethical requirements for clinical research do not end when individuals either sign the consent form and are enrolled or refuse enrollment.[106] Individuals must continue to be treated with respect from the time they are approached—even if they refuse enrollment—throughout their participation and even after their participation ends. Respecting potential and enrolled subjects entails at least 5 different activities. First, since substantial information will be collected about potential as well as enrolled subjects, their privacy must be respected by managing the information in accordance with confidentiality rules. Second, respect includes permitting subjects to change their mind, to decide that the research does not match their interests, and to withdraw without penalty. Third, in the course of clinical research new information about the effect of the intervention or the subject's clinical condition may be gained. Respect requires that enrolled subjects be provided with this new information. For instance, when informed consent documents are modified to include additional risks or benefits discovered in the course of research, subjects already enrolled should be informed. Fourth, the welfare of subjects should be carefully monitored throughout their research participation. If subjects experience adverse reactions, untoward events, or changes in clinical status, they should be provided with appropriate treatment and, when necessary, removed from the study. Finally, to recognize subjects' contribution to clinical research, there should be some mechanism to inform them of what was learned from the research.

For commentators used to thinking about respect in terms of privacy and confidentiality alone, these different activities may seem a haphazard agglomeration of informed consent, confidentiality, and other protections. In fact, this requirement integrates into a coherent framework actions the commonality of which often goes unrecognized. As such, it reminds investigators, subjects, IRB members, and others that respect for subjects requires the respectful treatment of individuals who choose not to enroll and the careful ongoing monitoring of those who do, in addition to ensuring the privacy and confidentiality of enrolled subjects. This requirement emphasizes that the ethics of clinical research do not end with the signing of a consent document but encompass the actual implementation, analysis, and dissemination of research. Indeed, it suggests that although "human subjects" is the prevailing designation, the term *subject* may not fully reflect appropriate respect: human research participant or partner may be more appropriate terminology.

Respect for potential and enrolled subjects is justified by multiple principles including beneficence, nonmaleficence, and respect for persons.[3] Permitting subjects to withdraw and providing them additional information learned from the research are key aspects of respecting subject autonomy.[3,37] Protecting confidentiality and monitoring well-being are motivated by respect for persons, beneficence, and nonmaleficence.[3]

ARE THESE ETHICAL REQUIREMENTS NECESSARY AND SUFFICIENT?

Value, validity, fair subject selection, favorable risk-benefit ratio, and respect for subjects embody substantive ethical values. As such, they are all necessary: clinical research that neglected or violated any of these requirements would be unethical. Conversely, independent review and informed consent are procedural requirements intended to minimize the possibility of conflict of interest, maximize the coincidence of the research with subjects' interests, and respect their autonomy.[30] However, other procedures may also achieve these results. For instance, evidence of an individual's preferences regarding research may be obtained from a research advance directive rather than the individual's concurrent informed consent.[103] Given the existence of alternative procedures, informed consent requirements can be minimized, and, in some circumstances, consent can even be waived.[7,101,103] Research on emergency life-saving interventions for subjects who are unconscious or otherwise not mentally capable of consent and for whom family or proxy consent is not immediately available may be conducted without informed consent.[6,107-109] Thus, all requirements need to be satisfied, but they may have to be adjusted and balanced given the circumstances of different types of research.

As interpreted and elaborated for specific research protocols, the fulfillment of each of these 7 requirements ensures that research is socially valuable and subjects are not exploited, that subjects are treated fairly and with respect, and that their interests are protected. As a result, these requirements should be sufficient to ensure that the vast majority of clinical research is ethical.[30] While it may be impossible to exclude the possibility that additional requirements are needed in rare cases, these 7 requirements are the essential ones.

UNIVERSALITY OF THE REQUIREMENTS

These 7 requirements for ethical clinical research are also universal.[35-49,110] They are justified by ethical values that are widely recognized and accepted and in accordance with how reasonable people would want to be treated.[110-112] Indeed, these requirements are precisely the types of considerations that would be invoked to justify clinical research if it were challenged.

Like constitutional provisions and amendments, these ethical requirements are general statements of value that must be elaborated by traditions of interpretation and that require practical interpretation and specification that will inherently be context and culture dependent.[110-113] For instance, while informed consent is meant to ensure that research subjects are treated with respect, what constitutes respect varies from culture to culture.[110,114] In some places, it will be necessary to elicit the consent of elders before individual subjects can be approached for informed consent.[115] Similarly, who is considered vulnerable for the purposes of fair subject selection criteria will vary by locale. While in the United States special efforts are necessary to ensure that racial minorities are not just targeted for research with high potential for risks,[53,73] in other places fair subject selection may require special focus on religious groups. Similarly, local traditions and economic conditions will influence when financial payments may constitute undue inducements. Also, whether research has a favorable risk-benefit ratio will depend on the underlying health risks in a society. Research that is unacceptable in one society because its risks outweigh the risks posed by the disease may have a favorable risk-benefit ratio in another society where the risks posed by the disease are significantly greater. Adapting these requirements to the identities, attachments, and cultural traditions embedded in distinct circumstances neither constitutes moral relativism nor undermines their universality[110-112]; doing so recognizes that while ethical requirements embody universal values, the manner of specifying these values inherently depends on the particular context.[110-112]

NECESSARY EXPERTISE

These ethical requirements emphasize the type of training and skills necessary for clinical investigators and those conducting independent review (Table 2). Not only must clinical investigators be skilled in the appropriate methods, statistical tests, outcome measures, and other scientific aspects of clinical trials, they must have the training to appreciate, affirm, and implement these ethical requirements, such as the capacity and sensitivity to determine appropriate subject selection criteria, evaluate risk-benefit ratios, provide information in an appropriate manner, and implement confidentiality procedures. Similarly, because independent review of clinical research must assess its value, validity, selection criteria, risk-benefit ratios, informed consent process, and procedures for monitoring enrolled subjects, the necessary skills must range from scientific to ethical to lay knowledge. Consequently, the independent ethical review of research trials should involve individuals with training in science, statistics, ethics, and law, as well as reflective citizens who understand social values, priorities, and the vulnerability and concerns of potential subjects (Table 2).

ACTUAL CASES

Considering actual cases illuminates how the requirements can guide ethical evaluation of clinical research. One persistently controversial issue is the use of placebo controls.[14-16] A new class of antiemetics, serotonin antagonists, such as ondansetron hydrochloride and granistron hydrochloride, were developed about 10 years ago. To evaluate these drugs, investigators conducted placebo-controlled trials randomizing cancer patients receiving emetogenic chemotherapy to either placebo or the serotonin antagonists.[116-118]

In evaluating the ethics of this clinical research, all requirements need to be fulfilled, but 3 requirements seem particularly relevant: value, scientific validity, and risk-benefit ratio. There is no doubt that the dominant antiemetic therapies of the time, such as prochlorperazine, metoclopramide hydrochloride, and high-dose corticosteroids are effective. However, they are not completely effective, especially for strongly emetogenic chemotherapy such as platinum, and they have significant adverse effects, especially dystonic reactions. Alternative antiemetic therapies that would be more effective and have fewer adverse effects were viewed as desirable and of value. However, there was no value in knowing whether the serotonin antagonists were better than placebo in controlling emesis, since placebo was not the standard of care at the time of the research.[14,63] Even if the serotonin antagonists were shown to be more effective than placebo, it would be a further issue to evaluate their effectiveness and adverse-event profile compared with the extant interventions. Thus, a placebo-controlled trial of the serotonin antagonists for chemotherapy-induced emesis does not fulfill the value requirement.

Comparative studies evaluating the difference between 2 active treatments are common in cancer therapy and valid as a study design.[14-16] Some argue that active-controlled studies are scientifically more difficult to conduct than placebo-controlled trials.[119] However, any ethically and scientifically valid randomized trial requires that there be an honest null hypothesis.[30,63] The null hypothesis that the serotonin antagonists are equivalent to

placebo was not reasonable at the time of the clinical research.[14,63] Indeed, coeval with the placebo-controlled studies were randomized controlled trials with serotonin antagonists vs active antiemetic therapy.[120,121] Thus, a placebo-controlled trial was not the only scientifically valid method.

Those who supported the notion of a randomized, placebo-controlled trial of serotonin antagonists argued that there was no serious risk from using a placebo because emesis is a transitory discomfort that results in no permanent disability.[119,122] However, emesis is not pleasant. Indeed, the entire rationale for developing serotonin antagonists is that chemotherapy-induced emesis is a sufficiently serious health problem that development and use of effective interventions in clinical practice are justifiable and desirable.[123] As one published report of a randomized placebo-controlled trial of ondansetron stated to justify the research: "Uncontrolled nausea and vomiting [from chemotherapy] frequently results in poor nutritional intake, metabolic derangements, deterioration of physical and mental condition, as well as the possible rejection of potentially beneficial treatment. Many patients are more afraid of uncontrolled nausea and vomiting than of alopecia."[118]

Furthermore, the placebo-controlled trials for antiemetics included "'rescue' medication if patients had persistent nausea or vomiting."[118] This indicates both that there was an alternative standard treatment for chemotherapy-induced emesis and that emesis was sufficiently harmful to require intervention.[14,15,123,124] Permitting patients to vomit while being administered placebo causes them unnecessary harm.[14,123,124] Thus, a placebo-controlled trial of antiemetics for chemotherapy-induced emesis does not minimize harm in the context of good clinical practices and so fails the favorable risk-benefit ratio when an available clinical intervention can partially ameliorate some of the harm.[123]

Importantly, the evaluation of these placebo-controlled trials of antiemetics did not need to address informed consent to determine whether they were ethical.[122] Indeed, even if patients had signed an informed consent document that indicated they could be randomized to placebo and that there were alternative effective treatments, the placebo-controlled research on serotonin antagonists would still be unethical.

Another controversial issue involves research in developing countries.[9-13,57,59] Recently, a rhesus rotavirus tetravalent (RRV-TV) vaccine was licensed in the United States after randomized trials in developed countries demonstrated a 49% to 68% efficacy in preventing diarrhea and up to 90% efficacy in preventing severe cases of diarrhea.[125-127] However, shortly after approval, the vaccine was withdrawn from the US market because of a cluster of cases of intussusception, representing an approximately 1 in 10000 added risk of this complication.[128] Should randomized controlled trials of RRV-TV vaccine proceed as planned in developing countries or wait for a new vaccine candidate to be developed? (C. Weijer, MD, PhD, written communication, March 24, 2000) In evaluating the ethics of these proposed trials, the requirements of value, scientific validity, fair subject selection, and risk-benefit ratio are particularly relevant.

Despite oral rehydration therapy, more than 600000 children in developing countries die annually from rotavirus diarrhea.[129] In some countries, the death rate from rotavirus is nearly 1 in 200. Clearly, a rotavirus vaccine with even 80% efficacy that prevented more than half a million deaths would be of great value. But is research using the RRV-TV vaccine ethical when the risk of intussusception stopped its use in the United States? The RRV-TV vaccine was the first and only licensed rotavirus vaccine and has already been administered to nearly 1 million children; potential alternative rotavirus vaccines are still years away from phase 3 research. Thus, given the potential benefit of preventing deaths from rotavirus in developing countries, a trial of RRV-TV vaccine now—even if a better vaccine becomes evaluable in a few years—is worthwhile. There is value to the research on the vaccine for developing countries only if there is reasonable assurance children in the country would be able to obtain it if it proved effective.[12,13,59]

Vaccines effective in developed countries may or may not be as effective or safe in developing countries. Host, viral, and environmental factors and seasonality of the disease can alter the efficacy and safety profiles of a vaccine.[130] Thus, there is good scientific rationale for determining whether the RRV-TV vaccine can achieve sufficient levels of protection against diarrhea with an acceptably low incidence of complications in children in developing countries. In this case, given the lack of an established method of preventing rotavirus infections in these countries, a placebo-controlled trial would be valid.

Two factors suggest that, in the RRV-TV vaccine study, subjects in developing countries are being selected for reasons of science and not being exploited. First, the most appropriate subjects for a rotavirus vaccine trial are infants and children who have a high incidence of rotavirus infection and who experience significant morbidity and mortality from the infection. In such a population the efficacy of the vaccine would be most apparent. Second, since the RRV-TV vaccine has been withdrawn from the US market, children in developing countries are not being selected to assume risks to evaluate a vaccine that will ultimately benefit children in developed countries (Weijer, written communication). As long as the RRV-TV vaccine would be made available to the population recruited for the study if proven safe and effective, children in the developing countries are being selected appropriately.[12,13,59]

The final element is evaluation of the risk-benefit ratio. In the United States, the RRV-TV vaccine posed a risk of intussusception of about 1 in 10000, while rotavirus causes about 20 deaths annually or in fewer than 5 in 1 million children. Thus, in developed countries the risk-benefit ratio is not favorable—1 death from rotavirus diarrhea pre-

vented at the risk of 20 to 40 cases of intussusception. Because of underlying disease burden, the risk-benefit ratio in developing countries is much different. If rotavirus causes the death of 1 in 200 children while the RRV-TV vaccine causes intussusception in 1 in 10 000 children, about 50 deaths from rotavirus diarrhea are prevented for each case of intussusception. Consequently, the risk-benefit ratio of the RRV-TV vaccine is favorable for individual subjects in developing countries while it is unfavorable for subjects in developed countries. This difference in risk-benefit ratios is a fundamental part of the justification for conducting the research on an RRV-TV vaccine in a developing country when it could not be ethically conducted in a developed country (Weijer, written communication). Obviously, to be ethical, randomized controlled trials of an RRV-TV vaccine would also have to adhere to the other requirements—independent review, informed consent, and respect for enrolled subjects.

CONCLUSION

These 7 requirements for considering the ethics of clinical research provide a systematic framework to guide researchers and IRBs in their assessments of individual clinical research protocols. Just as constitutional rulings are rarely unanimous, this framework will not necessarily engender unanimous agreement on the ethics of every clinical research study. Reasonable disagreement results from 3 sources: differences of interpretations of the requirements, of views about the need for additional requirements, and of application to specific studies. Nevertheless, this framework does provide the necessary context for review bodies to generate traditions of interpretation, understand disagreements, and highlight the kinds of considerations that must be invoked to resolve them. Like a constitution, these requirements can be reinterpreted, refined, and revised with changes in science and experience. Yet these requirements must all be considered and met to ensure that clinical research—wherever it is practiced—is ethical.

Disclaimer: The views herein are those of the authors and do not represent the views or policies of the Department of Health and Human Services or the National Institutes of Health.

Acknowledgment: We thank Robert J. Levine, MD, Steven Joffe, MD, Franklin Miller, PhD, Robert Truog, MD, James Childress, PhD, Francis Crawley, PhD, and Albert Kapikian, MD, for their criticisms of the manuscript as well as Alan Sandler, DDS, Ruth Macklin, PhD, Eric Meslin, PhD, and Charles Weijer, MD, PhD, for helpful discussion and suggestions on the ideas contained in the manuscript.

REFERENCES

1. Childress J. The place of autonomy in bioethics. *Hastings Cent Rep*. 1984;14:12-16.
2. Dworkin G. *The Theory and Practice of Autonomy*. New York, NY: Cambridge University Press; 1988.
3. Beauchamp TL, Childress J. *The Principles of Biomedical Ethics*. New York, NY: Oxford University Press; 1996:chap 3.
4. Vanderpool HY, ed. *The Ethics of Research Involving Human Subjects*. Frederick, Md: University Publishing Group; 1996:45-58.
5. Freedman B. Scientific value and validity as ethical requirements for research. *IRB*. 1987;9:7-10.
6. Office of the Secretary. Protection of human subjects: informed consent and waiver of informed consent requirements in certain emergency research; final rules. 61 *Federal Register* 51498-51533 (1996).
7. Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized, controlled trials? *N Engl J Med*. 1999;340:804-807.
8. US Department of Health and Human Services. Protections of human subjects. 45 CFR §46 (1991).
9. Angell M. The ethics of clinical research in the third world. *N Engl J Med*. 1997;337:847-849.
10. Lurie P, Wolfe S. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *N Engl J Med*. 1997;337:853-856.
11. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *N Engl J Med*. 1997;337:1003-1005.
12. Grady C. Science in the service of healing. *Hastings Cent Rep*. 1998;28:34-38.
13. Crouch R, Arras J. AZT trials and tribulations. *Hastings Cent Rep*. 1998;28:26-34.
14. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med*. 1994;331:394-398.
15. Freedman B. Placebo-controlled trials and the logic of clinical purpose. *IRB*. 1990;12:1-6.
16. Weijer C. Placebo-controlled trials in schizophrenia. *Schizophr Res*. 1999;35:211-218.
17. Lipsett M. On the nature and ethics of phase I clinical trials of cancer chemotherapies. *JAMA*. 1982;248:941-942.
18. Freedman B. Cohort-specific consent. *IRB*. 1990;12:5-7.
19. Annas GJ. The changing landscape of human experimentation. *Health Matrix*. 1992;2:119-140.
20. Lehrman S. Jewish leaders seek guidelines. *Nature*. 1997;389:322.
21. Levine C, Dubler NN, Levine RJ. Building a new consensus. *IRB*. 1991;13:1-17.
22. Weijer C, Goldsand G, Emanuel EJ. Protecting communities in research. *Nat Genet*. 1999;23:275-280.
23. Juengst ET. Groups as gatekeepers to genomic research. *Kennedy Institute J Ethics*. 1998;8:183-200.
24. Weijer C. Protecting communities in research. *Camb Q Healthc Ethics*. 1999;8:501-513.
25. Kopelman LM, Moskop JC, eds. *Children and Health Care*. Dordrecht, the Netherlands: Klumer; 1989:73-87.
26. Freedman B, Fuks A, Weijer C. In loco parentis. *IRB*. 1993;15:13-19.
27. Leikin S. Minors' assent, consent, or dissent to medical research. *IRB*. 1993;15:1-7.
28. Grodin MA, Glantz LH, eds. *Children as Research Subjects*. New York, NY: Oxford University Press; 1994:81-101.
29. Committee on Drugs, American Academy of Pediatrics. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics*. 1995;95:286-294.
30. Levine RJ. *Ethics and Regulation of Clinical Research*. 2nd ed. New Haven, Conn: Yale University Press; 1988.
31. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Summing Up*. Washington, DC: US Government Printing Office; 1983.
32. Katz J. *Experimentation With Human Beings*. New York, NY: Russell Sage Foundation; 1972.
33. Wertheimer A. *Exploitation*. Princeton, NJ: Princeton University Press; 1996: chap 1.
34. DeCastro LD. Exploitation in the use of human subjects for medical experimentation. *Bioethics*. 1995;9:259-268.
35. The Nuremberg Code. *JAMA*. 1996;276:1691.
36. World Medical Association. Declaration of Helsinki. *JAMA*. 1997;277:925-926.
37. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report*. Washington, DC: US Government Printing Office; 1979.
38. Council for International Organizations of Medical Sciences. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Switzerland: CIOMS; 1993.
39. Brody BS. *The Ethics of Biomedical Research*. New York, NY: Oxford University Press; 1998:chap 9.
40. Fluss S. *International Guidelines on Bioethics*. Geneva, Switzerland: European Forum on Good Clinical Practice/CIOMS; 1998.
41. Sugarman J, Mastroianni A, Kahn JP. *Research With Human Subjects*. Frederick, Md: University Publishing Group; 1998.
42. World Health Organization. Guidelines for good clinical practice for trials on pharmaceutical products. In: *The Use of Essential Drugs*. Appendix 3. Geneva, Switzerland: WHO; 1995.
43. Council of Europe (Direcorate of Legal Affairs). *Convention for the Protection of Human Rights and Dignity of the Human Being With Regard to the Application of Biology and Medicine*. Strasbourg, France: Council of Europe; 1996.
44. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Good clinical practice: consolidated guidance, 62 *Federal Register* 25692 (1997).
45. European Forum for Good Clinical Practice. *Guidelines and Recommendations for European Ethics Committees*. Leuven, Belgium: EFGCP; 1997.
46. Medical Research Council (UK). *Guidelines for Good Clinical Practice in Clinical Trials*. London, England: MRC; 1998.
47. Uganda National Council of Science and Technology (UNCST). *Guidelines for the Conduct of Health Research Involving Human Subjects in Uganda*. Kampala, Uganda: UNCST; 1998.
48. Medical Research Council of Canada, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada. *Tri-Council Policy Statement*. Ottawa, Ontario: Public Works and Government; 1998.
49. National Health and Medical Research Council. *National Statement on Ethical Conduct in Research Involving Humans*. Canberra, Australia: NHMRC; 1999.
50. Levine RJ. The impact of HIV infection on society's perception of clinical trials. *Kennedy Institute J Ethics*. 1994;4:93-98.

51. Vanderpool HY, ed. *The Ethics of Research Involving Human Subjects*. Frederick, Md: University Publishing Group; 1996:235-260.
52. Levine RJ. The need to revise the Declaration of Helsinki. *N Engl J Med*. 1999;341:531-534.
53. Jones J. *Bad Blood*. New York, NY: Free Press; 1992.
54. Rothman D, Rothman S. *The Willowbrook Wars*. New York, NY: Harper & Row; 1984.
55. Krugman S. The Willowbrook hepatitis studies revisited. *Rev Infect Dis*. 1986;8:157-162.
56. Advisory Committee on Human Radiation Experiments. *The Human Radiation Experiments*. New York, NY: Oxford University Press; 1996.
57. Christakis N, Panner M. Existing international ethical guidelines for human subjects. *Law Med Health Care*. 1991;19:214-220.
58. Lasagna L. The Helsinki declaration. *J Clin Psychopharmacol*. 1995;15:96-98.
59. Glantz LH, Annas GJ, Grodin MA, et al. Research in developing countries. *Hastings Cent Rep*. 1998;28:38-42.
60. Committee on the NIH Research Priority-Setting Process. *Scientific Opportunities and Public Needs*. Washington, DC: National Academy Press; 1998.
61. Rutstein DD. The ethical design of human experiments. In: Fruend PA, ed. *Experimentation With Human Subjects*. New York, NY: Braziller Library; 1970: 383-402.
62. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Appendix*. Vol 1. Washington, DC: US Government Printing Office; 1978:chap 9.
63. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med*. 1987;317:141-145.
64. National Institutes of Health. NIH policy and guidelines on the inclusion of children as participants in research involving human subjects. Available at: http://grants.nih.gov/grants/guide/notice-files/not98-024.html. Accessed April 28, 2000.
65. Dresser R. Wanted: single, white male for medical research. *Hastings Cent Rep*. 1992;22:21-29.
66. Merton V. The exclusion of pregnant, pregnable, and once pregnable (a.k.a. women) from biomedical research. *Am J Law Med*. 1993;19:369-451.
67. DeBruin D. Justice and the inclusion of women in clinical studies. *Kennedy Institute J Ethics*. 1994;4: 117-146.
68. Mastriani AC, Faden RR, Federman DD. *Women and Health Research*. Washington, DC: National Academy Press; 1994.
69. Vanderpool HY, ed. *The Ethics of Research Involving Human Subjects*. Frederick, Md: University Publishing Group; 1996:105-126.
70. Weijer C. Evolving issues in the selection of subjects for clinical research. *Camb Q Healthc Ethics*. 1996; 5:334-345.
71. Weijer C, Fuks A. The duty to exclude. *Clin Invest Med*. 1994;17:115-122.
72. Merkatz RB, Temple R, Sobel S, et al. Women in clinical trials of new drugs. *N Engl J Med*. 1993;329: 292-296.
73. National Institutes of Health. NIH Guidelines for the inclusion of women and ethnic minorities in research, 59 *Federal Register* 14508-14513 (1994).
74. Barry M, Molyneux M. Ethical dilemmas in malaria drug and vaccine trials. *J Med Ethics*. 1992;18: 189-192.
75. Kahn J, Mastroianni A, Sugarman J. *Beyond Consent*. New York, NY: Oxford University Press; 1998.
76. Annas G, Grodin M. Human rights and maternal-fetal HIV transmission prevention trials in Africa. *Am J Public Health*. 1998;88:560-563.
77. Freedman B, Fuks A, Weijer C. Demarcating research and treatment. *Clin Res*. 1992;40:653-660.
78. Anderson E. *Value in Ethics and Economics*. Cambridge, Mass: Harvard University Press; 1993:chap 9.
79. Weijer C. Thinking clearly about research risks. *IRB*. 1999;21:1-5.
80. Sen A, Williams B, eds. *Utilitarianism and Beyond*. Cambridge, England: Cambridge University Press; 1982.
81. MacLean D, ed. *Values at Risk*. Totowa, NJ: Rowman & Allanheld; 1985:31-48.
82. Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine*. New York, NY: Oxford University Press; 1996.
83. Sen A. *Choice, Welfare, and Measurement*. Cambridge, Mass: Harvard University Press; 1982:264-284.
84. Relman AS. Economic incentives in clinical investigations. *N Engl J Med*. 1989;320:933-934.
85. Porter RJ, Malone TE. *Biomedical Research*. Baltimore, Md: Johns Hopkins University Press; 1992.
86. Thompson D. Understanding financial conflicts of interest. *N Engl J Med*. 1993;329:573-576.
87. Spece RG, Shimm DS, Buchanan AE. *Conflicts of Interest in Clinical Practice and Research*. New York, NY: Oxford University Press; 1996.
88. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *Institutional Review Boards*. Washington, DC: US Government Printing Office; 1978.
89. Curran WJ. Government regulation of the use of human subjects in medical research. In: Freund PA, ed. *Experimentation With Human Subjects*. New York, NY: George Braziller; 1970:402-455.
90. Edgar H, Rothman D. The institutional review board and beyond. *Milbank Q*. 1995;73:489-506.
91. Moreno J, Caplan AL, Wolpe PR, et al. Updating protections for human subjects involved in research. *JAMA*. 1998;280:1951-1958.
92. Fried C. *Medical Experimentation*. New York, NY: American Elsevier Co; 1974.
93. Freedman B. A moral theory of informed consent. *Hastings Cent Rep*. 1975;5:32-39.
94. President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research. *Making Health Care Decisions*. Washington, DC: US Government Printing Office; 1982.
95. Katz J. Human experimentation and human rights. *St Louis University Law J*. 1993;38:1-54.
96. Donagan A. Informed consent in therapy and experimentation. *J Med Philos*. 1977;2:318-329.
97. Faden RR, Beauchamp TL. *A History and Theory of Informed Consent*. New York, NY: Oxford University Press; 1986:chap 5-9.
98. Applebaum PA, Lidz CW, Meisel A. *Informed Consent*. New York, NY: Oxford University Press; 1987.
99. Grisso R, Applebaum PS. *Assessing Competence to Consent to Treatment*. New York, NY: Oxford University Press; 1998.
100. Buchanan AE, Brock DW. *Deciding for Others*. New York, NY: Cambridge University Press; 1990: chap 2.
101. American College of Physicians. Cognitively impaired subjects. *Ann Intern Med*. 1989;111:843-848.
102. Dresser R. Mentally disabled research subjects. *JAMA*. 1996;276:67-72.
103. National Bioethics Advisory Commission. *Research Involving Persons With Mental Disorders That May Affect Decisionmaking Capacity*. Washington, DC: US Government Printing Office; 1998.
104. Michels R. Are research ethics bad for our mental health? *N Engl J Med*. 1999;340:1427-1430.
105. Capron AM. Ethical and human rights issues in research on mental disorders that may affect decision-making capacity. *N Engl J Med*. 1999;340:1430-1434.
106. Weijer C, Shapiro S, Fuks A, Glass KC, Skrutkowska M. Monitoring clinical research. *CMAJ*. 1995; 152:1973-1980.
107. Biros MH, Lewis R, Olson C, et al. Informed consent in emergency research. *JAMA*. 1995;273:1283-1287.
108. Levine RJ. Research in emergency situations. *JAMA*. 1995;273:1300-1302.
109. Council on Ethical and Judicial Affairs, American Medical Association. *Waiver of Informed Consent for Emergency Research*. CEJA Report 1-A-7, June 1997.
110. Macklin R. *Against Relativism*. New York, NY: Oxford University Press; 1999.
111. Scanlon TM. *What We Owe to Each Other*. Cambridge, Mass: Harvard University Press; 1999: chap 1, 8.
112. Kymlicka W. *Liberalism, Community and Culture*. New York, NY: Oxford University Press; 1989.
113. Angell M. Ethical imperialism? *N Engl J Med*. 1988;319:1081-1083.
114. Levine RJ. Informed consent. *Law Med Health Care*. 1991;19:207-213.
115. Ijsselmuiden CB, Faden RR. Research and informed consent in Africa. *N Engl J Med*. 1992;326: 830-833.
116. Cubeddu LX, Hoffmann IS, Fuenmayor NT, Finn AL. Efficacy of ondansetron (GR 38032F) and the role of serotonin in cisplatin-induced nausea and vomiting. *N Engl J Med*. 1990;322:810-816.
117. Gandara DR, Harvey WH, Monaghan GG, et al. The delayed-emesis syndrome from cisplatin. *Semin Oncol*. 1992;19:67-71.
118. Beck TM, Ciociola AA, Jones SE, et al. Efficacy of oral ondansetron in the prevention of emesis in outpatients receiving cyclophosphamide-based chemotherapy. *Ann Intern Med*. 1993;118:407-413.
119. Temple R. Government viewpoint of clinical trials. *Drug Inform J*. 1982:1610-1617.
120. Marty M, Pouillart P, Scholl S, et al. Comparison of 5-hydroxytryptamine3 (serotonin) antagonist ondansetron (GR38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *N Engl J Med*. 1990;322:816-821.
121. Hainsworth J, Harvey W, Pendergrass K, et al. A single-blind comparison of intravenous ondansetron, a selective serotonin antagonist, with intravenous metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. *J Clin Oncol*. 1991;9:721-728.
122. Ondansetron and cisplatin-induced nausea and vomiting. *N Engl J Med*. 1990;323:1486.
123. Hait WN. Ondansetron and cisplatin-induced nausea and vomiting. *N Engl J Med*. 1990;323:1485-1486.
124. Citron ML. Placebos and principles. *Ann Intern Med*. 1993;118:470-471.
125. Rennels MB, Glass RI, Dennehy PH, et al. Safety and efficacy of high dose rhesus-human reassortant rotavirus vaccines. *Pediatrics*. 1996;97:7-13.
126. Bernstein DK, Glass RI, Rodgers G, et al. Evaluation of rhesus rotavirus monovalent and tetravalent reassortment vaccines in US children. *JAMA*. 1995; 273:1191-1196.
127. Joensuu J, Koskenniemi E, Pang XL, Vesikari T. Randomized placebo-controlled trial of rhesus-human reassortment rotavirus vaccine for prevention of severe rotavirus gastroenteritis. *Lancet*. 1997; 350:1205-1209.
128. Intussusception among recipients of rotavirus vaccine—United States, 1998-1999. *MMWR Morb Mortal Wkly Rep*. 1999;48:577-581.
129. Bern C, Martines J, de Zoysa I, Glass RI. The magnitude of the global problem of diarrheal disease. *Bull World Health Organ*. 1992;70:705-714.
130. Bresee JS, Glass RI, Ivanoff B, Gentsch JR. Current status and future priorities for rotavirus vaccine development, evaluation and implementation in developing countries. *Vaccine*. 1999;17:2207-2222.

Ethics and Research on Laboratory Animals

Jeffrey Kahn

Required Reading

David DeGrazia, "The Ethics of Animal Research: What are the Prospects for Agreement," Cambridge Quarterly of Healthcare Ethics 8(1) (1999): 23-34. doi: https://doi.org/10.1017/S0963180199801054

Hugh LaFollette, "Animal Experimentation in Biomedical Research," in Tom L. Beauchamp and R.G. Frey, eds., The Oxford Handbook of Animal Ethics, (Oxford University Press 2012).

Daniel Strech and Ulrich Dirnagl, "3Rs missing: animal research without scientific value is unethical," BMJ Open Science 3 (2019): e000035. doi:10.1136/bmjos-2018-000048.

Suggested Further Reading

Baruch A. Brody, "Defending Animal Research: An International Perspective," in Jeremy R. Garrett, ed., The Ethics of Animal Research: Exploring the Controversy, (MIT Press, 2012) Chap.4.

Jeffrey Kahn, "Lessons learned: challenges in applying current constraints on research chimpanzees to other animals," Theoretical Medicine and Bioethics 35(2) (2014):97-104. doi: 10.1007/s11017-014-9284-6.

The Ethics of Animal Research: What Are the Prospects for Agreement?

DAVID DEGRAZIA

Few human uses of nonhuman animals (hereafter simply "animals") have incited as much controversy as the use of animals in biomedical research. The political exchanges over this issue tend to produce much more heat than light, as representatives of both biomedicine and the animal protection community accuse opponents of being "Nazis," "terrorists," and the like. However, a healthy number of individuals within these two communities offer the possibility of a more illuminating discussion of the ethics of animal research.

One such individual is Henry Spira. Spira almost single-handedly convinced Avon, Revlon, and other major cosmetics companies to invest in the search for alternatives to animal testing. Largely due to his tactful but persistent engagement with these companies — and to their willingness to change — many consumers today look for such labels as "not tested on animals" and "cruelty free" on cosmetics they would like to buy.

Inspired by Spira, this paper seeks common ground between the positions of biomedicine and animal advocates. (The term "biomedicine" here refers to everyone who works in medicine or the life sciences, not just those conducting animal research. "Animal advocates" and "animal protection community" refer to those individuals who take a major interest in protecting the interests of animals and who believe that much current usage of animals is morally unjustified. The terms are not restricted to animal activists, because some individuals meet this definition without being politically active in seeking changes.) The paper begins with some background on the political and ethical debate over animal research. It then identifies important points of potential agreement between biomedicine and animal advocates; much of this common ground can be missed due to distraction by the fireworks of the current political exchange. Next, the paper enumerates issues on which continuing disagreement is likely. Finally, it concludes with concrete suggestions for building positively on the common ground.

Background on the Debate over Animal Research

What is the current state of the debate over the ethics of animal research? Let us begin with the viewpoint of biomedicine. It seems fair to say that biomedicine has a "party line" on the ethics of animal research, conformity to which may feel like a political litmus test for full acceptability within the professional community. According to this party line, animal research is clearly justified

My thanks to Arlene Klotzko and Peter Singer for their suggestions regarding this paper.
Cambridge Quarterly of Healthcare Ethics (1999), **8**, 23–34. Printed in the USA.

because it is necessary for medical progress and therefore human health — and those who disagree are irrational, antiscience, misanthropic "extremists" whose views do not deserve serious attention. (Needless to say, despite considerable conformity, not everyone in biomedicine accepts this position.)

In at least some countries, biomedicine's leadership apparently values conformity to this party line more than freedom of thought and expression on the animal research issue. (In this paragraph, I will refer to the American situation to illustrate the point.) Hence the unwillingness of major medical journals, such as *JAMA* and *The New England Journal of Medicine,* to publish articles that are highly critical of animal research. Hence also the extraordinary similarity I have noticed in pro-research lectures by representatives of biomedicine. I used to be puzzled about why these lectures sounded so similar and why, for example, they consistently made some of the same philosophical and conceptual errors (such as dichotomizing animal welfare and animal rights, and taking the latter concept to imply identical rights for humans and animals). But that was before I learned of the "AMA [American Medical Association] Animal Research Action Plan" and the AMA's "White Paper." Promoting an aggressive pro-research campaign, these documents encourage AMA members to say and do certain things for public relations purposes, including the following: "Identify animal rights activists as anti-science and against medical progress"; "Combat emotion with emotion (eg [sic], 'fuzzy' animals contrasted with 'healing' children)"; and "Position the biomedical community as moderate — centrist — in the controversy, not as a polar opposite." [1]

It is a reasonable conjecture that biomedicine's party line was developed largely in reaction to fear — both of the most intimidating actions of some especially zealous animal advocates, such as telephoned threats and destruction of property, and of growing societal concern about animals. Unfortunately, biomedicine's reaction has created a political culture in which many or most animal researchers and their supporters do not engage in sustained, critical thinking about the moral status of animals and the basic justification (or lack thereof) for animal research. Few seem to recognize that there is significant merit to the opposing position, fewer have had any rigorous training in ethical reasoning, and hardly any have read much of the leading literature on animal ethics. The stultifying effect of this cultural phenomenon hit home with me at a small meeting of representatives of biomedicine, in which I had been invited to explain "the animal rights philosophy" (the invitation itself being exceptional and encouraging). After the talk, in which I presented ideas familiar to all who really know the literature and issues of animal ethics, several attendees pumped my hand and said something to this effect: "This is the first time I have heard such rational and lucid arguments for the other side. I didn't know there were any."

As for the animal protection community, there does not seem to be a shared viewpoint except at a very general level: significant interest in animal welfare and the belief that much current animal usage is unjustified. Beyond that, differences abound. For example, the Humane Society of the United States opposes factory farming but not humane forms of animal husbandry, rejects current levels of animal use in research but not animal research itself, and condemns most zoo exhibits but not those that adequately meet animals' needs and approximate their natural habitats.[2] Meanwhile, the Animal Liberation Front, a clandestine British organization, apparently opposes all animal hus-

bandry, animal research, and the keeping of zoo animals.[3] Although there are extensive differences within the animal protection community, as far as our paper topic goes, it seems fair to say that almost everyone in this group opposes current levels of animal research.

That's a brief sketch of the perspectives of biomedicine and animal advocates on the issue of animal research. What about the state of animal ethics itself? The leading book-length works in this field exhibit a near consensus that the status quo of animal usage is ethically indefensible and that at least significant reductions in animal research are justified. Let me elaborate.

Defending strong animal rights positions in different ways, Tom Regan and Evelyn Pluhar advocate abolition of all research that involves harming animals.[4] Ray Frey and Peter Singer, by contrast, hold the use of animals to the very stringent utilitarian standard — accepting only those experiments whose benefits (factoring in the likelihood of achieving them) are expected to outweigh the harms and costs involved — where the interests of animal subjects (e.g., to avoid suffering) are given the same moral weight that we give comparable human interests.[5]

Without commiting either to a strong animal rights view or to utilitarianism, my own view shares with these theories the framework of equal consideration for animals: the principle that we must give equal moral weight to comparable interests, no matter who has those interests.[6] But unlike the aforementioned philosophers, I believe that the arguments for and against equal consideration are nearly equal in strength. I therefore have respect for progressive views that attribute moral standing to animals without giving them fully equal consideration. The unequal consideration view that I find most plausible gives moral weight to animals' comparable interests in accordance with the animals' cognitive, affective, and social complexity — a progressive, "sliding scale" view. Since I acknowledge that I might be mistaken about equal consideration, my approach tracks the practical implications both of equal consideration and of the alternative just described.

Arguing from pluralistic frameworks, which are developed in different ways, Steve Sapontzis, Rosemary Rodd, and Bernard Rollin support relatively little animal research in comparison with current levels.[7] Drawing significantly from feminist insights, Mary Midgley presents a view whose implications seem somewhat more accepting of the status quo of animal research but still fairly progressive.[8] Of the leading contributors to animal ethics, the only one who embraces the status quo of animal research and does not attribute significant moral status to animals is Peter Carruthers.[9] (It is ironic that while biomedicine characterizes those who are critical of animal research as irrational "extremists," nearly all of the most in-depth, scholarly, and respected work in animal ethics supports such a critical standpoint at a general level.)

In discussing the prospects for agreement between biomedicine and animal advocates, I will ignore political posturing and consider only serious ethical reflection. In considering the two sides of this debate, I will assume that the discussants are morally serious, intellectually honest, reflective, and well informed both about the facts of animal research and about the range of arguments that come into play in animal ethics. I will not have in mind, then, the researcher who urges audiences to dismiss "the animal rights view" or the animal activist who tolerates no dissent from an abolitionist position. The two representative interlocutors I will imagine differ on the issue of animal research, but their

views result from honest, disciplined, well-informed ethical reflection. Clearly, their voices are worth hearing.

Points on Which the Biomedical and Animal Protection Communities Can Agree

The optimistic thesis of this paper is that the biomedical and animal protection communities can agree on a fair number of important points, and that much can be done to build upon this common ground. I will number and highlight (in bold) each potential point of agreement and then justify its inclusion by explaining how both sides can agree to it, without abandoning their basic positions, and why they should.

1. The use of animals in biomedical research raises ethical issues. Today very few people would disagree with this modest claim, and any who would are clearly in the wrong.[10] Most animal research involves harming animal subjects, provoking ethical concerns, and the leading goal of animal research, promotion of human health, is itself ethically important; even the expenditure of taxpayers' money on government-funded animal research raises ethical issues about the best use of such money. Although a very modest assertion, this point of agreement is important because it legitimates a process that is sometimes resisted: *discussing* the ethics of animal research.

It is worth noting a less obvious claim that probably enjoys strong majority support but not consensus: that animals (at least sentient ones, as defined below) have moral status. To say animals have moral status is to say that their interests have moral importance independently of effects on human interests. ('Interests' may be thought of as components of well-being. For example, sentient animals have an interest in avoiding pain, distress, and suffering.) If animals have moral status, then to brutalize a horse is wrong because of the harm inflicted on the horse, not simply because the horse is someone's property (if that is so) or because animal lovers' feelings may be hurt (if any animal lovers find out about the abuse). The idea is that gratuitously harming the horse *wrongs the horse.* Although nearly every leader in animal ethics holds that animals have moral status — and though most people, on reflection, are likely to find this idea commonsensical — Carruthers argues that it is mistaken.[11]

2. Sentient animals, a class that probably includes at least the vertebrates, deserve moral protection. Whether because they have moral status or because needlessly harming them strongly offends many people's sensibilities, sentient animals deserve some measure of moral protection. By way of definition, sentient animals are animals endowed with any sorts of feelings: (conscious) sensations such as pain or emotional states such as fear or suffering. But which animals are sentient? Addressing this complex issue implicates both the natural sciences and the philosophy of mind. Lately, strong support has emerged for the proposition that at least vertebrate animals are very likely sentient.[12] This proposition is implicitly endorsed by major statements of principles regarding the humane use of research animals, which often mention that they apply to vertebrates.[13] (Hereafter, the unqualified term "animals" will refer to sentient animals in particular.)

3. Many animals (at the very least, mammals) are capable of having a wide variety of aversive mental states, including pain, distress (whose forms include discomfort, boredom, and fear), and suffering. In biomedical circles, there has

been some resistance to attributing suffering to animals, so goverment documents concerned with humane use of animals have often mentioned only pain, distress, and discomfort.[14] Because "suffering" refers to a *highly* unpleasant mental state (whereas pain, distress, and discomfort can be mild and transient), the attribution of suffering to animals is morally significant. An indication that resistance may be weakening is the attribution of suffering to sentient animals in the National Aeronautics and Space Administration's "Principles for the Ethical Care and Use of Animals."[15] Whatever government documents may say, the combined empirical and philosophical case for attributing suffering to a wide range of animals is very strong.[16]

4. Animals' experiential well-being (quality of life) deserves protection. If the use of animals raises ethical issues, meaning that their interests matter morally, we confront the question of what interests animals have. This question raises controversial issues. For example, do animals have an interest in remaining alive (life interests)? That is, does death itself — as opposed to any unpleasantness experienced in dying — harm an animal? A test case would be a scenario in which a contented dog in good health is painlessly and unwittingly killed in her sleep: Is she harmed?

Another difficult issue is whether animal well-being can be understood *entirely* in terms of experiential well-being — quality of life in the familiar sense in which (other things equal) pleasure is better than pain, enjoyment better than suffering, satisfaction better than frustration. Or does the exercise of an animal's natural capacities count positively toward well-being, even if quality of life is not enhanced? A test case would be a scenario in which conditioning, a drug, or brain surgery removes a bird's instinct and desire to fly without lowering quality of life: Does the bird's transformation to a new, nonflying existence represent a harm?

Whatever the answers to these and other issues connected with animal well-being, what is not controversial is that animals have an interest in experiential well-being, a good quality of life. That is why animal researchers are normally expected to use anesthesia or analgesia where these agents can reduce or eliminate animal subjects' pain, distress, or suffering.

5. Humane care of highly social animals requires extensive access to conspecifics. It is increasingly appreciated that animals have different needs based on what sorts of creatures they are. Highly social animals, such as apes, monkeys, and wolves, need social interactions with conspecifics (members of their own species). Under normal circumstances, they will develop social structures, such as hierarchies and alliances, and maintain long-term relationships with conspecifics. Because they have a strong instinct to seek such interactions and relationships, depriving them of the opportunity to gratify this instinct harms these animals. For example, in some species, lack of appropriate social interactions impedes normal development. Moreover, social companions can buffer the effects of stressful situations, reduce behavioral abnormalities, provide opportunities for exercise, and increase cognitive stimulation.[17] Thus in the case of any highly social animals used in research, providing them extensive access to conspecifics is an extremely high moral priority.

6. Some animals deserve very strong protections (as, for example, chimpanzees deserve not to be killed for the purpose of population control). Biomedicine and animal advocates are likely to disagree on many details of ethically justified uses of animals in research, as we will see in the next section.

Still, discussants can agree that there is an obligation to protect not just the experiential well-being, but also the lives, of at least some animals. This claim might be supported by the (controversial) thesis that such animals have life interests. On the other hand, it might be supported by the goal of species preservation (in the case of an endangered species), or by the recognition that routine killing of such animals when they are no longer useful for research would seriously disturb many people.[18]

Without agreeing on all the specific justifications, members of the National Research Council's Committee on Long-Term Care of Chimpanzees were able to agree (with one dissent) that chimps should not be killed for the purpose of population control, although they could be killed if suffering greatly with no alternative means of relief.[19] This recommended protection of chimps' lives is exceptional, because animal research policies generally state no presumption against killing animal subjects, requiring only that killings be as painless as possible.[20] Since this committee represents expert opinion in biomedicine, it seems correct to infer that biomedicine and the animal protection community can agree that at least chimpanzees should receive some very strong protections — of their lives and of certain other components of their well-being, such as their needs for social interaction, reasonable freedom of movement, and stimulating environments.[21]

7. Alternatives should now be used whenever possible and research on alternatives should expand. Those who are most strongly opposed to animal research hold that alternatives such as mathematical models, computer simulations, and in vitro biological systems should replace nearly all use of animals in research. (I say "nearly all" because, as discussed below, few would condemn animal research that does not harm its subjects.) Even for those who see the animal research enterprise more favorably, there are good reasons to take an active interest in alternatives. Sometimes an alternative method is the most valid way to approach a particular scientific question; often alternatives are cheaper.[22] Their potential for reducing animal pain, distress, and suffering is, of course, another good reason. Finally, biomedicine may enjoy stronger public support if it responds to growing social concern about animal welfare with a very serious investment in nonanimal methods. This means not just using alternatives wherever they are currently feasible, but also aggressively researching the possibilities for expanding the use of such methods.

8. Promoting human health is an extremely important biomedical goal. No morally serious person would deny the great importance of human health, so its status as a worthy goal seems beyond question. What is sometimes forgotten, however, is that a worthy goal does not automatically justify all the means thereto. Surely it would be unethical to force large numbers of humans to serve as subjects in highly painful, eventually lethal research, even if its goal were to promote human health. The controversy over animal research focuses not on the worthiness of its principal goal — promoting human health — but rather on the means, involving animal subjects, taken in pursuit of that goal.

9. There are some morally significant differences between humans and other animals. Many people in biomedicine are not aware that the views of animal advocates are consistent with this judgment. Indeed, some animal advocates might not realize that their views are consistent with this judgment! So let me identify a couple of ideas, to which all should agree, that support it.

First, the principle of respect for autonomy applies to competent adult human beings, but to very few if any animals. This principle respects the self-regarding

decisions of individuals who are capable of autonomous decisionmaking and action. Conversely, it opposes paternalism toward such individuals, who have the capacity to decide for themselves what is in their interests. Now, many sentient beings, including human children and at least most nonhuman animals, are not autonomous in the relevant sense and so are not covered by this principle.[23] Thus it is often appropriate to limit their liberty in ways that promote their best interests, say, preventing the human child from drinking alcohol, or forcing a pet dog to undergo a vaccination. We might say that where there is no autonomy to respect, the principles of beneficence (promoting best interests) and respect for autonomy cannot conflict; where there is autonomy to respect, paternalism becomes morally problematic.

Second, even if sentient animals have an interest, others things equal, in staying alive (as I believe), the moral presumption against taking human life is stronger than the presumption against killing at least some animals. Consider fish, who are apparently sentient yet cognitively extremely primitive in comparison with humans. I have a hard time imagining even very committed animal advocates maintaining that killing a fish is as serious a matter as killing a human being. Leaders in animal ethics consistently support — though in interestingly different ways — the idea that, ordinarily, killing humans is worse than killing at least some animals who have moral status. (It is almost too obvious to mention that it's worse to kill humans than to kill animals, such as amoebas, that *lack* moral status.[24])

The only notable exception seems to be Sapontzis, who tries to undermine the major arguments proffered to support such comparative claims. But the comparisons he opposes always involve humans and other mammals or birds.[25] The farther one goes down the phylogenetic scale, the more incredible it becomes to hold that it is equally prima facie wrong to kill humans and to kill other animals. At the very least, someone like Sapontzis will have to admit that killing humans tends to be worse than killing fish in that (1) humans tend to live much longer, so that untimely death generally robs them of more good years, and (2) untimely human death causes deep social sorrow and anguish to others in a way that is not paralleled in the fish world. So I believe that the comparative judgment I have made is well justified and embraceable by all parties to the present debate. There may be other morally interesting differences to which all should agree,[26] but these examples will suffice for present purposes.

10. Some animal research is justified. Many animal advocates would say that they disagree with this statement. But I'm not sure they do. Or, if they really do, they shouldn't. Let me explain by responding to the three likeliest reasons some animal advocates might take exception to the claim.

First, one might oppose all uses of animals that involve *harming them for the benefit of others* (even other animals) — as a matter of absolute principle — and overlook the fact that some animal research does not harm animal subjects at all. Although such nonharmful research represents a tiny sliver of the animal research enterprise, it exists. Examples are certain observational studies of animals in their natural habitats, some ape language studies, and possibly certain behavioral studies of other species that take place in laboratories but do not cause pain, distress, or suffering to the subjects. And if nonsentient animals cannot be harmed (in any morally relevant sense), as I would argue, then any research involving such animals falls under the penumbra of nonharming research.

Moreover, there is arguably no good reason to oppose research that imposes only *minimal* risk or harm on its animal subjects. After all, minimal risk research on certain human subjects who, like animals, cannot consent (namely, children) is permitted in many countries; in my view, this policy is justified. Such research might involve a minuscule likelihood of significant harm or the certainty of a slight, transient harm, such as the discomfort of having a blood sample taken.

Second, one might oppose all animal research because one believes that none of it actually benefits human beings. Due to physical differences between species, the argument goes, what happens to animal subjects when they undergo some biomedical intervention does not justify inferences about what will happen to humans who undergo that intervention. Furthermore, new drugs, therapies, and techniques must always be tried on human subjects before they can be accepted for clinical practice. Rather than tormenting animals in research, the argument continues, we should drop the useless animal models and proceed straight to human trials (with appropriate protections for human subjects, including requirements for informed or proxy consent).

Although I believe a considerable amount of current animal research has almost no chance of benefitting humans,[27] I find it very hard to believe that no animal research does. While it is true that human subjects must eventually be experimented on, evidence suggests that animal models sometimes furnish data relevant to human health.[28] If so, then the use of animal subjects can often decrease the risk to human subjects who are eventually involved in experiments that advance biomedicine, by helping to weed out harmful interventions. This by itself does not justify animal research, only the claim that it sometimes benefits humans (at the very least human subjects themselves and arguably the beneficiaries of biomedical advances as well).

Note that even if animal research never benefited humans, it would presumably sometimes benefit conspecifics of the animals tested, in sound veterinary research.[29] It can't be seriously argued that animal models provide no useful information about animals! Moreover, in successful *therapeutic* research (which aims to benefit the subjects themselves), certain animals benefit directly from research and are not simply used to benefit other animals. For that reason, blanket opposition to animal research, including the most promising therapeutic research in veterinary medicine, strikes me as almost unintelligible.

Almost unintelligible, but not quite, bringing us to the third possible reason for opposing all animal research. It might be argued that, whether or not it harms its subjects, all animal research involves *using animals (without their consent) for others' benefit,* since — qua research — it seeks *generalizable knowledge.* But to use animals in this way reduces them to *tools* (objects to be used), thereby *disrespecting* the animals.

Now the idea that we may never use nonconsenting individuals, even in benign ways, solely for the benefit of others strikes me as an implausibly strict ethical principle. But never mind. The fact that some veterinary research is intended to benefit the subjects themselves (as well as other animals or humans down the road) where no other way to help them is known shows that such research, on any reasonable view, is *not* disrespectful toward its subjects. Indeed, in such cases, the animals *would* consent to taking part, if they could, because taking part is in their interests. I fully grant that therapeutic veterinary research represents a minuscule portion of the animal research conducted today. But my arguments are put forward in the service of a goal that I think I have now

achieved: demonstrating, beyond a shadow of a doubt, that some animal research is justified.

If animal advocates and representatives of biomedicine were aware of these ten points of potential agreement, they might perceive their opponents' views as less alien than they had previously taken them to be. This change in perception might, in turn, convince all parties that honest, open discussion of outstanding issues has a decent chance of repaying the effort.

Points on Which Agreement between the Two Sides Is Unlikely

Even if biomedicine and the animal protection community approach the animal research issue in good faith, become properly informed about animal ethics and the facts of research, and so forth, they are still likely to disagree on certain important issues. After all, their basic views differ. It may be worthwhile to enumerate several likely points of difference.

First, disagreement is likely on the issue of *the moral status of animals in comparison with humans*. While representatives of biomedicine may attribute moral status to animals, they hold that animals may justifiably be used in many experiments (most of which are nontherapeutic and harm the subjects) whose primary goal is to promote human health. But for animal advocates, it is not at all obvious that much animal research is justified. This suggests that animal advocates ascribe higher moral status to animals than biomedicine does.[30]

Second, disagreement is likely to continue on the issue of *the specific circumstances in which the worthy goal of promoting human health justifies harming animals.* Biomedicine generally tries to protect the status quo of animal research. Animal advocates generally treat not using animals in research as a presumption, any departures from which would require careful justification. Clearly, animal advocates will have many disagreements with biomedicine over when it is appropriate to conduct animal research.

Third, in a similar vein, continuing disagreement is likely on the issue of *whether current protections for research animals are more or less adequate.* Biomedicine would probably answer affirmatively, with relatively minor internal disagreements over specific issues (e.g., whether apes should ever be exposed to diseases in order to test vaccines). Animal advocates will tend to be much more critical of current protections for research animals. They will argue, for example, that animals are far too often made to suffer in pursuit of less than compelling objectives, such as learning about behavioral responses to stress or trauma.

In the United States, critics will argue that the basic principles that are supposed to guide the care and use of animals in federally funded research ultimately provide very weak protection for research animals. That is because the tenth and final principle begins with implicit permission to make exceptions to the previous nine: "Where exceptions are required in relation to the provisions of these Principles, ..."[31] Since no limits are placed on permissible exceptions, this final principle precludes any absolute restraints on the harm that may be inflicted on research animals — an indefensible lack of safeguards from the perspective of animal advocates. (Although similar in several ways to these American principles, including some ways animal advocates would criticize, the *International Guiding Principles for Biomedical Research Involving Animals* avoids this pitfall of a global loophole. One of its relatively strong protections

is Principle V: "Investigators and other personnel should never fail to treat animals as sentient, and should regard their proper care and use and the avoidance or minimization of discomfort, distress, or pain as ethical imperatives."[32])

Although protections of research animals are commonly thought of in terms of preventing unnecessary pain, distress, and suffering, they may also be thought of in terms of protecting animal life. A fourth likely area of disagreement concerns *whether animal life is morally protectable.* Return to a question raised earlier: whether a contented animal in good health is harmed by being painlessly killed in her sleep. Since government documents for the care and use of research animals generally require justification for causing pain or distress to animal subjects, but no justification for painless killing, it seems fair to infer that biomedicine generally does not attribute life interests to animals. Although I lack concrete evidence, I would guess that most animal advocates would see the matter quite differently, and would regard the killing of animals as a serious moral matter even if it is justified in some circumstances.

The four issues identified here as probable continuing points of difference are not intended to comprise an exhaustive list. But they show that despite the fact that the biomedical and animal protection communities can agree on an impressive range of major points, given their basic orientations they cannot be expected to agree on every fundamental question. Few will find this assertion surprising. But I also suggest, less obviously, that even if both sides cannot be entirely right in their positions, differences that remain after positions are refined through honest, open-minded, fully educated inquiry can be reasonable differences.

What Can Be Done Now to Build upon the Points of Agreement

Let me close with a series of suggestions offered in the constructive yet critical-minded spirit of Henry Spira's work for how to build on the points of agreement identified above. For reasons of space, these suggestions will be stated somewhat tersely and without elaboration.

First, biomedical organizations and leaders in the profession can do the following: openly acknowledge that ethical issues involving animals are complex and important; educate themselves or acquire education about the ethical issues; tolerate views departing from the current party line; open up journals to more than one basic viewpoint; and stop disseminating one-sided propoganda.

Second, the more "militant" animal advocates can acknowledge that there can be reasonable disagreement on some of the relevant issues and stop intimidating people with whom they disagree.

Third, biomedicine can openly acknowledge, as NASA recently did in its principles, that animals can suffer and invite more serious consideration of animal suffering.

Fourth, the animal protection community can give credit to biomedicine where credit is due — for example, for efforts to minimize pain and distress, to improve housing conditions, and to refrain from killing old chimpanzees who are no longer useful for research but are expensive to maintain.

Fifth, animal researchers and members of animal protection organizations can be required by their organizations to take courses in ethical theory or animal ethics to promote knowledgeable, skilled, broad-minded discussion and reflection.

Sixth, the animal protection community can openly acknowledge that some animal research is justified (perhaps giving examples to reduce the potential for misunderstanding).

Seventh, more animal research ethics committees can bring aboard at least one dedicated animal advocate who (unlike mainstream American veterinarians) seriously questions the value of most animal research.

Eighth, conditions of housing for research animals can be improved — for example, with greater enrichment and, for social animals, more access to conspecifics.

Ninth, all parties can endorse and support the goal of finding ways to *eliminate* animal subjects' pain, distress, and suffering.[33]

Tenth, and finally, governments can invest much more than they have to date in the development and use of alternatives to animal research, and all parties can give strong public support to the pursuit of alternatives.

Notes

1. American Medical Association. Animal Research Action Plan. (June 1989), p. 6. See also American Medical Association. White Paper (1988).
2. See the Humane Society of the United States (HSUS). *Farm Animals and Intensive Confinement.* Washington, D.C.: HSUS, 1994; *Animals in Biomedical Research.* Washington, D.C.: HSUS, revised 1989; and *Zoos: Information Packet.* Washington, D.C.: HSUS, 1995.
3. Animal Liberation Front. Animal Liberation Frontline Information Service: the A.L.F. Primer. (website)
4. Regan T. *The Case for Animal Rights.* Berkeley: University of California Press, 1983; Pluhar E. *Beyond Prejudice.* Durham, North Carolina: Duke University Press, 1995.
5. Frey RG. *Interests and Rights.* Oxford: Clarendon, 1980; Singer P. *Animal Liberation,* 2d ed. New York: New York Review of Books, 1990.
6. DeGrazia D. *Taking Animals Seriously.* Cambridge: Cambridge University Press, 1996.
7. Sapontzis SF. *Morals, Reason, and Animals.* Philadelphia: Temple University Press, 1987; Rodd R. *Biology, Ethics, and Animals.* Oxford: Clarendon, 1990; and Rollin BE. *Animal Rights and Human Morality,* 2d ed. Buffalo, New York: Prometheus, 1992.
8. Midgley M. *Animals and Why They Matter.* Athens, Georgia: University of Georgia Press, 1983.
9. Carruthers P. *The Animals Issue.* Cambridge: Cambridge University Press, 1992.
10. In a letter to the editor, Robert White, a neurosurgeon well known for transplanting monkeys' heads, asserted that "[a]nimal usage is not a moral or ethical issue . . ." (White R. Animal ethics? [letter]. *Hastings Center Report* 1990;20(6):43). For a rebuttal to White, see my letter, *Hastings Center Report* 1991;21(5):45.
11. See note 9, Carruthers 1992. For an attempt to undermine Carruthers' arguments, see note 6, DeGrazia 1996:53–6.
12. See Rose M, Adams D. Evidence for pain and suffering in other animals. In: Langley G, ed. *Animal Experimentation.* New York: Chapman and Hall, 1989:42–71; Smith JA, Boyd KM. *Lives in the Balance.* Oxford: Oxford University Press, 1991:ch. 4. See also note 7 Rodd 1990:ch. 3; and DeGrazia D, Rowan A. Pain, suffering, and anxiety in animals and humans. *Theoretical Medicine* 1991;12:193–211.
13. See, e.g., U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training. In: National Research Council. *Guide for the Care and Use of Laboratory Animals.* Washington, D.C.: National Academy Press, 1996:117–8; National Aeronautics and Space Administration. *Principles for the Ethical Care and Use of Animals.* NASA Policy Directive 8910.1, effective 23 March 1998; and Council for International Organizations of Medical Sciences. *International Guiding Principles for Biomedical Research Involving Animals.* Geneva: CIOMS, 1985:18.
14. See note 13, National Research Council 1996; CIOMS 1985.
15. See note 13, NASA 1998.
16. See note 12, Rose, Adams 1989; DeGrazia, Rowan 1991. And see note 7, Rodd 1990:ch. 3. There is also much evidence that at least mammals can experience anxiety. (See note 12, DeGrazia, Rowan 1991; note 12, Smith, Boyd 1991:ch. 4.)

17. See note 13, National Research Council 1996:37.
18. Note that the term "euthanasia," which means a death that is good for the one who dies, is inappropriate when animals are killed because they are costly to maintain or for similarly human-regarding reasons.
19. National Research Council Committee on Long-Term Care of Chimpanzees. *Chimpanzees in Research*. Washington, D.C.: National Academy Press, 1997:38.
20. Such policies typically state that animals who would otherwise experience severe or chronic pain or distress should be painlessly killed. See, e.g., note 13, National Research Council 1996:117; CIOMS 1985:19; and [British] Home Office. *Home Office Guidance on the Operation of the Animals [Scientific Procedures] Act 1986*. London: Home Office, 1986. Although this directive addresses what to do with animals who could survive only in agony, it does not state any presumption against killing animals who could live well following research.
21. The committee addresses these chimpanzee interests in note 19, National Research Council 1997:ch. 3.
22. See note 12, Smith, Boyd 1991:334.
23. See note 6, DeGrazia 1996:204–10.
24. Admittedly, some unusual individuals would claim that amoebas have moral status, either because they think amoebas are sentient or because they think that sentience is unnecessary for moral status. I know of no one, however, who would claim that killing amoebas is as serious a matter as killing humans.
25. See note 7, Sapontzis 1987:216–22.
26. For example, if I am right, just as the moral presumption against taking life can differ in strength across species, so can the presumption against confining members of different species (the interest at stake being freedom). See note 6, DeGrazia 1996:254–6.
27. That is, except those humans who benefit directly from the conduct of research, such as researchers and people who sell animals and laboratory equipment.
28. See, e.g., note 12, Smith, Boyd 1991:ch. 3.
29. Peter Singer reminded me of this important point.
30. The idea of differences of moral status can be left intuitive here. Any effort to make it more precise will invite controversy. (See note 6, DeGrazia 1996:256–7.)
31. See note 13, National Research Council 1996:118.
32. See note 13, CIOMS 1985:18.
33. This is the stated goal of a new initiative of the Humane Society of the United States, which expects the initiative to expand to Humane Society International.

Animal Experimentation in Biomedical Research

Hugh LaFollette

The Oxford Handbook of Animal Ethics
Edited by Tom L. Beauchamp and R. G. Frey

Print Publication Date: Oct 2011 Subject: Philosophy, Moral Philosophy, Philosophy of Science
Online Publication Date: May 2012 DOI: 10.1093/oxfordhb/9780195371963.013.0030

Abstract and Keywords

This article discusses the conditions under which it is permissible and advisable to use animals in biomedical experimentation. The "Common View" is that there are moral limits on what we can do to nonhuman animals, but humans can use them when doing so advances significant human interests. This view entails that animals have some moral status, but not a demandingly high status. The idea also states that most people believe that medical experiments using animals do wind up benefiting humans. The "Lenient View" holds that even if animals have moral worth, their worth is so slight that humans can use them virtually any way we wish. The "Demanding View" holds that the moral worth of animals is so high that it bars virtually all uses of animals in biomedical research.

Keywords: biomedical experimentation, moral limits, human interests, moral status

SHOULD we use animals in biomedical experimentation? Most people think so. They embrace the Common View, which includes both moral and empirical elements. The two-part moral element is that although (a) there are moral limits on what we can do to (some) nonhuman animals, (b) humans can use them when doing so advances significant human interests.[1] Put differently, they think nonhuman animals have some moral worth—that their interests count morally—although that worth is not especially high. The empirical element is that biomedical experiments using animals significantly benefit humans. The truth of these claims would morally justify the practice.

The Common View is one among many views about the moral permissibility of biomedical experimentation using animals. This view is best seen as resting near the center of a moral continuum, with the Lenient View at one extreme and the Demanding View on the other.[2] The Lenient View holds that even if animals have moral worth, their worth is so slight that humans can use them virtually any way we wish and for any reason we wish. The Demanding View holds that the moral worth of animals is so high that it bars virtually all uses of animals in biomedical research. The Lenient and the Demanding Views share one significant claim: each thinks we need to determine only the moral worth ofnonhu-

man animals to morally evaluate the practice of animal experimentation. However, few people would agree. Most people think we must also know the extent to which biomedical research (p. 797) on animals benefits humans. Perhaps they are mistaken. Still, since this view is so common, it is a prudent place to begin.[3]

The Moral Status of Nonhuman Animals

Historically, few people have had moral qualms about using animals for their purposes.[4] Even so, most would not have harmed their nonhuman animals frivolously. It would be imprudent for a farmer to fail to feed the pigs she planned to eat or to fail to care for the ox she needed to pull her plow. That would be unwise, just as it would normally be unwise for us to let our houses or automobiles deteriorate. However, few people would have thought that there is anything *intrinsically* wrong with killing an animal or making it suffer,[5] just as few people today would think there is anything *intrinsically* wrong with taking a sledgehammer to their cars. To that extent, the Historical View is a form of the Lenient View. By the mid-1700s, that view began to give way to the Common View. (For a more detailed historical accounting, see the first two chapters in this *Handbook*.)

Indirect Limits on What We Do to Animals

Since what we do to nonhuman animals often benefits or harms humans, we have a reason to be morally concerned about them. Killing someone else's dog is wrong because it harms the animal's owner—much as someone harms her by throwing acid on her Saab or burning her favorite coat. Killing millions of honeybees or overfishing the ocean is wrong because these actions diminish limited resources humans need—much as we would by burning a million acres of Sequoias for a campfire. Disemboweling one's own dog in public would be wrong because it would offend many humans—much as someone would by belching loudly and repeatedly in a quiet romantic café. Finally, hitting, taunting, or killing animals is arguably wrong since people who do so are thereby more likely to mistreat humans.[6] All these considerations limit what we can permissibly do to or with nonhuman animals.

Although these provide plausible human-based reasons for not harming some nonhuman animals, most people do not think these considerations capture the most important moral consideration: harming animals is wrong because of what it does to the animals themselves. In this way the Common View diverges from the Historical View.

Direct Limits

Few people think it is morally acceptable to nail a fully conscious and unanesthetized dog to a board and then slowly disembowel it so we can determine the layout of its organs or see how its blood flows. Few think it is morally acceptable to roast an unanesthetized, fully conscious pig to slightly enhance the taste of pork tenderloin. (p. 798) According to the Common View, the wrongness of these actions cannot be exhaustively explained by the fact that such actions indirectly harm humans; they are also—indeed primarily—wrong

because they harm animals. The harm, according to most people, is that such actions cause pain to animals. How is this relevant to an assessment of biomedical experimentation using animals? Mammals and birds—the most common laboratory animals—can feel pain, and most experiments cause lab animals pain.[7] Most people think we must consider this pain when deciding how to act; they think we should not make these animals suffer needlessly.

Many other people think this is only part of the moral story. They think it is also wrong to kill some animals, at least to kill them without good reason. They believe that animals' lives are valuable. Of course, there are important disagreements about just how valuable nonhuman animals' lives are, and there are disagreements about what counts as a good reason for killing them. Some think we are justified in killing a nonhuman animal only for the same reasons that would justify killing another human—for example, in self-defense. Many others would not go nearly so far, but they would think humans need a compelling reason to take an animal's life. Still others think that any minor human interest would suffice. Still, this much seems true: most people would be appalled at a neighborhood child who shoots squirrels with his BB gun just so that he can watch them writhe in pain and at a businessman who kills a wild gorilla so that he can use its shellacked skull as a spittoon.

How might we explain the idea that nonhuman animals have a valuable life that counts morally? Those who embrace this view likely endorse Tom Regan's claims that some nonhuman animals are "subjects-of-a-life." Regan claims animals have:

> beliefs and desires; perception, memory, and a sense of the future, including their own future; an emotional life, together with feelings of pleasure and pain; preference- and welfare-interests; the ability to initiate action in pursuit of their desires and goals; a psychophysical identity over time; and an individual welfare in the sense that their experiential life fares well or ill for them, logically independent of their utility for others and logically independent of their being the subject of anyone else's interests.[8]

In this view, if we kill a nonhuman animal, we deprive it of a future it desires; we ignore its legitimate interests. Some with moral misgivings about killing nonhuman animals will not buy this explanation. They think nonhuman animals' lives are morally valuable, albeit less valuable that those of humans. "Normal (adult) human life is of a much higher quality than animal life, not because of species, but because of richness; and the value of a life is a function of its quality."[9] In this view, animals' lives cannot be taken cavalierly, but they can be taken if necessary for a significant public good.

Since Regan's view is highly controversial, we might make more progress if we begin by examining animal experimentation assuming only the weaker view that it is wrong to cause an animal needless pain, coupled with the idea that many laboratory animals' lives —especially mammals—have some value, even if that value is not high. After all, virtually all sides of this debate embrace these views—researchers as (p. 799) well as animal activists, and, according to the Gallup poll, also the American public. Of course, there are still significant disagreements about (a) how valuable nonhuman animals' lives are, (b)

what constitutes a good reason for taking their lives or causing them pain, and (c) whether most biomedical experiments using animals provide such a reason.

Knowing that animals have moral worth only lets us know that their interests should count. It does not tell us how *much weight* their interests have or *how* those interests should be counted. These questions are distinct, in part because they usually reflect different theoretical stances. Those who speak of nonhuman animals' interests as having *weight* often embrace some form of consequentialism where the animals' interests, whatever they happen to be, are balanced against competing human interests. If their interests are sufficiently weighty, then we are morally limited in what we can do to animals.

Regan will reject this approach; he will reject any talk of "balancing interests." He thinks that animal interests—like human interests—are not subject to moral calculation, but are rather morally protected by rights.[10] On his deontological view, it is not just that rights are weightier than other considerations; they are trumps that can never be overridden in the pursuit of human goods.

Those who embrace this view think that discussing potential benefits of biomedical experiments using animals is morally irrelevant. On their view, it wouldn't matter if experiments benefitted humans enormously. They would be immoral in precisely the same way and for the same reason that we think nonconsensual experiments on humans, including those performed by the Nazis or in the Tuskegee syphilis study, would be immoral.[11] Right or wrong, most people reject this defense of abolitionism. They think that the benefits of animal experimentation matter morally. It is to this issue that I now turn.

Benefits of Animal Experimentation

The empirical element of the Common View holds that the practice of biomedical experiments using animals substantially benefits humans. This claim, when conjoined with the second moral component of the Common View—the claim that we can use animals when doing so significantly benefits humans—is thought to justify the practice. Notice, though, what follows from saying that the benefits to humans *outweigh* moral costs to animals. It acknowledges that the interests of nonhuman animals carry moral weight.

Since nonhuman animals' interests have moral weight, their interests will sometimes constrain the pursuit of human interests. Clearly they do. All sides of the debate think that we should not keep lab animals in squalid conditions, and all sides think that we should anesthetize laboratory animals against substantial pain, unless there are compelling scientific reasons why we cannot. These are important concessions. (p. 800) For in the world of limited finances, the money experimenters use to care for (and anesthetize) animals is money they cannot use to conduct more experiments. All sides to the debate thereby acknowledge that respecting the interests of animals limits animal experimentation. Therefore, the issue is not *whether* the interests of animals should constrain animal experimentation. The issue is *how much* and *under which conditions* they should constrain it.

The Prima Facie Case for Animal Experimentation

The case for thinking that experimenting on animals will significantly benefit humans rests on three interlinked pillars: (1) the common sense idea that we can legitimately generalize what we learn from animals to human beings; (2) the claim by many medical historians that animal experiments have been essential for most major biomedical advances; and (3) plausible methodological reasons supporting the common sense and historical arguments. I examine each pillar in turn.

Common Sense Argument

The common sense argument is plausible. We see broad biological similarities between humans and animals, particularly other mammals. Given that, we infer that: the skeletal structure of humans will resemble that of chimpanzees; the blood of humans and rats will circulate in similar ways; the mechanisms whereby rabbits and humans exchange gasses with the air will be comparable; and the reactions of humans and guinea pigs to toxic substances will be akin.

This argument form is plausible. Disputants on all sides of this debate use it. Researchers use these analogical arguments to explain why they think we can safely generalize from animals to humans. Defenders of animals' interests use them to show that nonhuman animals morally resemble human beings. They claim that chimpanzees reason, that dogs scheme, and that rats grieve because these animals act in the same ways humans act when they reason, scheme, or grieve. I suspect, in the end, that the precise forms of these analogical arguments are relevantly different. Still, as a starting point of inquiry, and in the absence of contrary evidence, it is reasonable to make inferences from animals to humans.

Historical Evidence

Historical evidence reinforces the common sense view. According to the American Medical Association:

> [V]irtually every advance in medical science in the 20th century, from antibiotics and vaccines to antidepressant drugs and organ transplants, has been achieved either directly or indirectly through the use of animals in laboratory experiments. The result of these experiments has been the elimination or control of many infectious diseases—smallpox, poliomyelitis, measles—and the development of numerous life-saving techniques—blood transfusions, burn therapy, open-heart and brain surgery. This has meant a longer, healthier, better life with much less pain and suffering. For many, it has meant life itself.[12]

(p. 801) Biomedical advances are not simply the result of research seeking a cure to a specific disease or condition (applied research). Basic research—research aimed at understanding "how living organisms function, without regard to the immediate relation of their research to specific human disease—also prompts biomedical discoveries."[13] Finally, it is not just that animal experimentation was necessary for past discoveries, but also it

will be essential for future ones. As Sigma Xi claims: "an end to animal research would mean an end to our best hope for finding treatments that still elude us."[14]

Scientific Rationale Supports History and Common Sense

There are good methodological reasons reinforcing the common sense and historical pillars of the argument.

Good Science Requires Controlled Experiments. Scientists want tightly controlled experiments where they can exclude any factors that might skew the study's results. Only then can they be confident they have discovered a causal relationship rather than a mere correlation. However, meeting this scientifically high standard with human subjects is scientifically difficult and often morally impermissible. Suppose researchers want to know if smoking causes heart disease in humans. (a) They cannot merely compare the incidence of smokers who die from heart disease to that of nonsmokers. There may be other factors (e.g., lifestyle choices) that are the primary culprit. (b) Researchers can design reasonably reliable epidemiological studies that exclude many extraneous features (e.g., patients' diets) that could skew the study's results. However, these studies face two problems: (1) designers cannot be confident they know which factors are relevant; (2) even if they knew all relevant factors, they often rely on patients' self-reports to determine if those factors are present (if they smoke or drink and how much they exercise, etc.). However, self-reports are notoriously unreliable. These factors explain why epidemiological studies, although valuable, have several marks against them. (c) In principle, scientists *could* conduct wholly controlled studies on humans: they could seriously limit subjects' motion, their exposure to relevant environmental factors, and their diets. However, controlling humans in these ways would be morally unacceptable. So what is a serious and moral scientist to do?

Intact Systems. Some have suggested that we could use human cells and tissue cultures rather than humans or animals. For some purposes and at some testing stages, we can. However, defenders of biomedical research using animals claim these micro methods are insufficient when we need detailed information about the causes of, or possible cures for, a human disease. Humans and animals are not, they note, loose associations of biological parts; rather, they are intricately related "intact systems." Just as one cannot model the workings of a computer by looking at chips and hard drives lying on a table, one cannot model complex human biomedical behavior by looking at detached human body parts. Only one intact system can reliably model another.[15]

An Intermediate Conclusion

The prima facie case for the validity and importance of biomedical experimentation using animals is plausible. To challenge the case, objectors must show that the (p. 802) status of nonhuman animals is greater than, or that the benefits of experimentation are less than, most people suppose. In the next section, I address the second possibility, starting with concerns about the prima facie empirical argument.

Evaluation of the Prima Facie Case

The Common Sense View

The common sense argument for the effectiveness of biomedical experiments using animals is sensible. Animals and humans are similar in obvious ways; the issue is whether they are sufficiently similar to justify biomedical inferences from animals to humans. Whether they are depends on the other pillars of the argument. That is where the real work of the prima facie argument is being done.

The Historical Argument

Those defending animal experimentation claim that virtually every medical advance is attributable to that practice. In a minimal sense they are correct. The history of most biomedical discoveries during the last seventy-five years will reveal at least some experiments using animals. However, simply because something is part of a development's history does not mean that it was a causally significant—let alone a necessary—element of that history. Virtually all biomedical scientists drank milk as infants. However, that does not establish that milk drinking leads to biomedical knowledge. Not every element of a history is a significant causally contributory factor of that history.

Researchers are, in most cases, *legally required* to use animals for most biomedical experiments. Given the law, *of course* the use of animals is part of the history of biomedical discovery. So we must determine the degree to which the correlation reflects facts about scientific discovery rather than the state of the law. Defenders of experimentation would argue that it is the former. They contend that surveys of primary research show that this correlation is not simply, or even primarily, an epiphenomenon of the legal system.

There are good reasons to take these surveys seriously, but there are also good reasons to be careful in accepting their findings unquestioningly. Although academic journals and books will report some dissimilarities between animals and humans, they likely underreport them. When scientists are working within a guiding paradigm, we should expect failures to be underreported. If a researcher is trying to discover the nature of human hypertension, and conducts a series of experiments on a gazelle, only to discover that gazelle rarely develop hypertension, then she will likely not report her findings, not because she wants to suppress relevant information, but because most scientists won't be interested (unless, of course, they had (p. 803) thought about developing a gazelle model of hypertension). Even when scientists do report negative findings, others are less likely to discuss them—especially if the results do not explain the failure. Therefore, these failures, even if common, will rarely be well-known parts of the history of biomedical discovery, although occasionally failures are mentioned if researchers explain why the experiment failed.[16]

We have similar reasons to be careful when interpreting standard histories of biomedical research. When historians of medicine discuss the history of a biomedical advance, they

typically underreport failed experiments, even experiments that appear in the primary research literature. This, too, is normal. Historians chronicle events that they think illuminate history. For instance, American historians do not mention the vast majority of events in our country's past—for example, a two-minute extemporaneous stump speech Adlai Stevenson gave during his second failed run for the presidency. Barring some unusual reason, describing this speech in detail would be a distraction. We do the same thing when telling our personal stories: we focus on events that elucidate our current understanding of ourselves. We downplay, forget, or omit elements of our histories we consider tangential. Biomedical historians likely will not mention (even if they know about) most failed experiments; they see them as diversions from, rather than illuminating elements of, the scientific narrative. Since the use of nonhuman animals is integral to the current biomedical paradigm, we should expect histories to emphasize the successes of that paradigm.

These considerations give us grounds for caution when interpreting both primary research and historians' claims, especially since most of us seek evidence supporting our antecedently held views.[17] We often fall prey to the shotgun effect or we unintentionally engage in selective perception. If I fire a shotgun in the general direction of a target, several pellets will likely hit it. Since researchers conduct thousands of experiments annually, we would expect some substantial successes when surveying the practice over decades. The researcher then commits the fallacy of selective perception if she counts the hits and ignores the misses. For instance, researchers have been trying to understand ALS (Lou Gehrig's disease) for more than seventy years. Yet in "terms of therapeutic treatment of this disorder, we're not that much further along than we were in 1939 when Lou Gehrig was diagnosed."[18] To date, investigators have only found one drug that benefits humans with the disease, and that benefit is slight: it helps extend the patient's life for a few months. Yet researchers continue to employ the same mouse model of ALS that has guided research for years. Even advocates of these experiments acknowledge "previously, medications that have been found to be effective in the mouse model of ALS have not shown benefit when brought to human clinical trials."[19] Given advocates' belief in the power of animal models, they do not construe these failures as a mark against the practice. They continue to hope that each new drug with beneficial results in mice will have similar affects in humans. When they eventually find a beneficial drug, then advocates of biomedical research using animals will doubtless cite the success as proof of animal experimentation's enormous value, despite the previous significant failures.[20]

Opponents of animal experimentation often commit the same fallacies by focusing exclusively on the practice's failures; and failures there are. However, critics (p. 804) often forget that failures are common in science. We need more than just lists of putative successes and failures. We need to discuss evolution—the overarching biological theory. Why? Although particular scientific "facts" inform and shape theories, theories give us a framework for understanding, interpreting, and evaluating putative facts, especially when the facts are conflicting.

In later sections, I explain how evolution informs this debate. First, I offer some additional "facts" that suggest the limitations of the practice. I want it to be clear that the failure of the mouse model of ALS is not unique.

Some Empirical Evidence Undermining the Reliability of Animal Experimentation

Many people have heard about problems with animal testing on thalidomide, a drug that caused serious physical defects in more than ten thousand children worldwide, but did not appear to have any adverse effects in standard laboratory animals (although researchers later found some species in which the effects were similar). I want to mention other findings that, although less well known, are more instructive. Rats and mice are closely related species; they resemble each other far more than either resembles humans. Despite their close relationships, chemicals that induce cancers in rats produce cancers in mice in only 70% of the time.[21] That is not a wholly insignificant correlation, of course, but it is far from perfect. Then, in roughly a third of these cases, chemicals that produce cancer in both animals do not produce cancer at the same site. This is extremely troubling when we are trying to understand the causes of and mechanisms for treating cancer, sufficiently troubling that it prompted a leading team of researchers to conclude that, in its current form, "the utility of a rodent bioassay to identify a chemical as a 'potential human carcinogen' is questionable."[22]

The problem even pervades the history of one of researchers' vaunted successes. In the early years of polio research, scientists focused almost exclusively on one animal model of the disease, a form of the disease in rhesus monkeys. This obsession, according to researcher and medical historian J. R. Paul, made research focus on the wrong route of infection, and therefore likely delayed the discovery of a treatment for polio by twenty-five years.[23]

There is especially strong evidence of significant biomedical differences between humans and nonhuman animals in teratology (study of abnormal development): "False positives and false negatives abound. Once one has established that a drug is a teratogen for man, it is usually possible to find, retrospectively, a suitable animal model. But trying to predict human toxicity—which is after all what the screening game is about—is quite another matter."[24] It is difficult to find a suitable animal model even in nonhuman primates, our closest relatives.[25] These differences are so profound that we cannot safely generalize findings in animals to humans even for drugs within the same chemical or pharmacologic class.

Finally, species' differences are common in the endocrine system. "[G]enerally the same or very similar hormones are produced by corresponding glands of different (p. 805) vertebrates. Despite the general similarities, hormones do many different things in different vertebrates."[26] Because the endocrine system plays such a central role in overall function of the body, differences in these systems are amplified elsewhere in the organism. "The poor predictiveness of animal studies for humans thus becomes comprehensible in terms

of interspecific variations in endocrinology."[27] These variations are the products of evolution, are conservative inasmuch as they "use" the same biochemical building blocks across species, but they are radical inasmuch as they use those endocrinal blocks for different functional ends.

These brief examples do not show that biomedical experiments using animals are worthless. All areas of even mature sciences have experimental failures. However, these examples do indicate that there are important differences between species. We need a theoretical framework to interpret empirical results, a theory to explain just why we should expect significant species differences. It is to evolutionary theory that I now turn for this framework.

Evolution and Its Influences

Understanding Similarities and Differences Between Species

The current practice of biomedical research is grounded in the work of eighteenth-century French physiologist Claude Bernard.[28] Bernard wanted to make physiology a *real* science by adopting the methods of physics. For him that meant that all life—like all matter—was fundamentally the same. By testing on one species, we can straightaway discover important biological information about another:

> Experiments on animals, with deleterious substances or in harmful circumstances, are very useful and *entirely conclusive* [emphasis mine] for the toxicology and hygiene of man. Investigations of medicinal or of toxic substances also are wholly applicable to man from the therapeutic point of view; for as I have shown, the effects of these substances are the same on man as on animals, save for differences in degree.[29]

Bernard is partly right. There are clear commonalities between species. Having discovered that numerous species of mammals, reptiles, amphibians, and birds have blood circulating throughout their bodies, we can infer that the same will be true of a related species we have not yet examined. To that degree we can generalize from species to species. However, this fact can easily mislead us. We are considering a much narrower issue: Can we reliably infer details of specific human diseases by experimenting on laboratory animals?

To address this question, I must explain the nature and use of animal models of human biomedical phenomena. Researchers seek to identify or create a condition in laboratory animals (AIDS, cancer, etc.) that resembles some human condition they (p. 806) want to understand. They then proceed in two different ways. Some seek to better understand the nature of the condition in nonhuman animals.[30] This is a form of basic research with no direct application to humans, although the knowledge gained may eventually be used in humans. We will explore this use of animals later.

Other researchers engage in applied research. They directly seek a cure for some human disease or condition. After identifying a potential animal model of the human disease, they may give the animal a drug or excise a growth, or see if implanting stem cells alters that condition. If the intervention cures the animals or attenuates the disease, then others may try the same intervention in a small number of humans—first to see if it is relatively safe (it doesn't cause any significant adverse effects), then to see if it is efficacious. If it is both safe and efficacious, then the researcher will try the intervention in a larger sample of humans. If it is significantly unsafe or demonstrably inefficacious, then they will either modify or abandon the idea.

Two Issues about Models in Applied Research

We now see that to assess the benefits of biomedical experimentation using animals we must answer two different empirical questions. One, is the disease in the laboratory animal relevantly similar to the human condition it supposedly models (the *similarity problem*)? Two, if the models are similar, can we reliably generalize from animals to humans (the *inference problem*)? These issues are clearly related, albeit distinct.

There are always some similarities and some differences between a condition or disease in animals and in humans. I earlier noted obvious ways in which species are similar. They are also different, and different in ways that are biomedically significant. Mice are the standard model of human cancer. However, although 80% of human cancers are carcinomas, sarcomas and leukemia are more common in mice.[31] Additionally, most AIDS research has been guided by animal models in primates, despite important differences between the conditions in the two species: "The only nonhuman primate species that can be reproducibly infected by HIV is the chimpanzee .... [However] HIV does not replicate persistently in chimpanzees, nor does HIV consistently cause AIDS in this species."[32]

Of course, not all differences undermine inferences from animals to humans. Although a human femur is different from a gorilla femur, most differences will be irrelevant if orthopedists simply want to know how to repair a fractured human femur. On the other hand, seemingly miniscule differences may turn out to be highly significant. Therefore, before we can rely on a model, we must know if the condition in the animal model is *relevantly* similar to the human condition. That is not easy to do.

Suppose, though, we do know that they are highly similar. We must still determine if the methods which prevent, control, or cure the disease in nonhuman animals will do the same in humans (the inference problem). In a not-insignificant number of cases, the answer is "No." As I noted earlier, ALS researchers have long relied on what they deemed a promising mouse model of the disease. Yet after years (p. 807) of study, the interventions that work in the mouse have been, with one minor exception, unsuccessful in humans.

Although these two questions are independent, they are linked. We often know if differences are relevant only after we discover if research leads to a cure for, or at least an attenuation of, the human condition. However, we cannot know that it leads to a cure or an attenuation until we have conducted tests in both animals and humans. That shows why

experiments on animals cannot do what they aim to do—that is, give us *confidence* in predictions about human biomedical phenomena prior to human testing. Still, it may be that animal models are sufficiently similar to the corresponding human condition so that we can make qualified, albeit still useful, inferences about humans. Before we can ascertain that fact, we must determine how common and how deep species differences are. That requires understanding the profound ways that evolutionary forces shape biological organisms.

Evolutionary Influences Prompt Changes

Over evolutionary time, the environments in which animals lived and competed changed. Some animals' food sources either died or became more plentiful. Animals that adapted to their new environments survived or even flourished, while those that did not adapt either disappeared or became less successful. Evolutionary processes prompted biological differences between closely related species, differences that go all the way to the building blocks of life: "[T]he genomes and chromosomes of modern-day species have each been shaped by a unique history of seemingly random genetic events, acted on by selection pressures over long evolutionary times." [33] This history is relevant for assessing biomedical experimentation using animals.

Organizational Complexity Amplifies Adaptive Changes

Defenders of animal experimentation note that animals and humans are highly organized, intact systems. That fact, they claim, is why we must experiment on animals rather than on human parts. They are right by half. Since animals are intact systems, we should be cautious when making inferences from experiments on isolated tissues to humans. However, what this fact gives with one hand, it takes away with the other. The same factors also give us reason to be cautious about making biomedically significant inferences from nonhuman animals to humans. Evolutionary pressures reward species that have advantageous adaptations. These adaptations are frequently biomedically significant. Because humans are intact systems, the adaptations' biological significance is often amplified in one or more of the following four ways.

First, structures and processes interacting with adaptations must change to accommodate them. "New parts evolved from old ones and have to work well with the parts that have already evolved."[34] These accommodations partly explain why beneficial adaptations are rarely unqualifiedly beneficial. Changes advantageous in one niche may become detrimental if the climate changes, a new predator appears on the scene, or the individuals relocate to a new environment. For instance, a single (p. 808) gene for sickle-cell anemia is highly beneficial in a malaria-prone environment. The same trait is highly detrimental (because offspring with two sickle-cell anemia genes usually die before fifty years of age) once malaria has been controlled or people susceptible to the trait relocate to a malaria-free area.

Second, a beneficial adaptation might prompt potentially detrimental changes elsewhere in the organism. Humans are more fit because they have relatively large brains. Brain size, though, is limited by skull size. Therefore, humans could develop larger brains only if there were compromises elsewhere within the organism. When human skulls became larger to permit larger brains, human infants had to be born earlier; they were therefore more dependent on parental care than are most mammals. Having more developed cognitive skills is beneficial. Being wholly dependent on one's parents for longer makes human infants especially vulnerable. For instance, more than half of deaths from hunger-related problems are in children under five years of age. Such compromises are ubiquitous. "The body is a bundle of compromises, compromises which, even if they currently serve (or once served) some fitness advantage, now cause disease."[35]

Third, organisms often retain elements of their evolutionary pasts even when those elements no longer promote survival—for example, the human appendix. These structures may affect biochemical processes or create the possibility of detrimental, even life-threatening, conditions, such as appendicitis. Other elements of their evolutionary pasts may significantly influence cellular and metabolic functions.[36]

Fourth, resulting differences between two species may be exaggerated if their "molecular clocks" (the rate at which their DNA and proteins evolve) are different. Although the human and mouse genomes are approximately the same size, "There has been a much longer period over which [genomic] changes have had a chance to accumulate—approximately 80 million years versus 6 million years .... [Moreover] rodent lineages ... have unusually fast molecular clocks. Hence, these lineages have diverged from the human lineage more rapidly than otherwise expected."[37]

In concert, these factors lead to important differences between species, differences greater than those we might initially expect. These give us a reason to think that the results of animal experiments will rarely be straightforwardly applicable to human beings.

Functional, Explanatory, and Causal Properties

To understand the effects of evolutionary change, we must distinguish three perspectives from which we can describe biological phenomena. In talking about ways in which all life is the same we mask these differences. (1) Sometimes we talk about ways an organism functions within its environment: that it moves, exchanges gases with the air, takes in nourishment, and the like. In so doing, we are talking about an organism's *functional properties*. (2) At other times, we describe an organism's mechanisms for achieving these functions. In so doing, we are talking about its *causal properties*. Finally, (3) we sometimes describe an organism's mid-level properties, properties we can see as either causal or functional. For instance, breathing is (p. 809) a functional property inasmuch as it identifies the fact that an organism exchanges gasses with the air, and it is a causal property inasmuch as it describes (albeit abstractly) a mechanism for performing that function (the *way* the organism oxygenates its blood). I call these dual-purpose properties *explanatory properties*.

Each way of describing an organism's properties serves a different but important purpose. Evolutionary theorists focus on organisms' functional properties to describe how natural selection favored a creature within its environmental niche. Functional properties are also key to understanding a creature's moral status, since, as I noted earlier, a creature counts morally if it can feel pain, think, or emote.

However, biomedical researchers are not currently investigating either functional or explanatory properties since these do not explain disease or uncover cures. In the early years of biomedical discovery, researchers did seek to understand common biological functional properties like the circulation of the blood.[38] Now they are only tangentially interested in these properties. Researchers know *that* the blood circulates; now they want to know the ways blood absorbs oxygen or the way it responds to certain chemicals. In short, they want to identify and understand an organism's causal mechanisms.

Researchers evidence this focus both explicitly and implicitly. They study biological systems to understand what causes or exacerbates a disease or condition. Then they implicitly demonstrate this focus when making inferences from animals to humans. Unless researchers assume that laboratory animals and humans have relevantly similar causal mechanisms, they have no reason to think that a drug or chemical that is harmful to animals will also be harmful to humans. As researchers with the Carcinogenic Potency Project put it, "Without data on the *mechanism* of carcinogenesis, however, the true human risk of cancer at low dose is highly uncertain and could be zero."[39]

Unfortunately, although the distinction between these three perspectives is important, researchers and their apologists either do not notice or appreciate them, or else they assume that if two animals share any properties then they must share all related ones. Neither assumption is plausible. Of course most animals share abstract functional properties: they move within their respective environments, they gain nourishment, and they excrete wastes. Many share the same explanatory properties: most use lungs to exchange gasses with the air. However, only someone guided by the Bernardian paradigm would infer that humans and nonhuman mammals therefore have similar causal mechanisms for all or even most biomedically significant phenomena.

For instance, although cats, rats, pigs, and humans all successfully metabolize phenol (metabolizing phenol could be a functional or even an explanatory property), the mechanism of metabolism varies widely between species. There are two primary mechanisms. Some species metabolize phenol primarily using only one mechanism. For example, pigs rely entirely on one while cats use only the other. Other species use both mechanisms roughly equally.[40] Species differences are evident even in closely related species: humans and New World monkeys use different metabolic pathways.[41] Why do these differences matter? Because researchers often speak as if the condition or disease being studied in laboratory animals strongly (p. 810) resembles the condition in humans. Evolutionary theory suggests that is not a plausible expectation. We thus have reason to think that nonhuman animals are not, in general, strong models of human biomedical phenomena.

Strong Models

This claim that animals are strong models of human biomedical phenomena might be true if we were talking about functional or explanatory properties. Those properties *are* broadly similar across most mammalian species. However, biomedical researchers using animals study creatures' biomedically significant (causal) mechanisms. It is only by studying these that researchers can understand the causes of, and identify potential cures for, human disease. However, inferences from animals to humans will be questionable if the condition in the laboratory animal differs causally from the human condition. Given the myriad ways that evolutionary forces shape an organism's biological systems, we should expect causal differences. Many differences run all the way to the genome.[42] These differences are not simply, or even primarily, in the number of genes a species has, but in whether, when, and how those genes are expressed (the particular order and manner in which genes turn on or off).[43] That explains why even two seemingly similar animals may be so different biomedically.

In short, evolutionary theory—the theoretical glue of modern biology—gives us reason to expect that a biomedically significant condition in an animal will never be exactly like the condition in humans. Researchers are usually satisfied if they can find or create a condition in laboratory animals that symptomatically resembles the human condition. However, symptomatic similarity does not guarantee causal similarity. That is why interventions that cure a disease or condition in laboratory animals not infrequently fail in humans. The history of biomedicine is littered with such cases. Researchers have tested 85 potential AIDS vaccines in 197 different human clinical trials. However, although many of these were promising in animal trials (that's why they proceeded to clinical trials), "just 12% of these trials have reached Phase II [an early phase of human testing with a small number of human subjects], only seven (3.5%) have reached Phase III [a later phrase with more human subjects], and altogether, 18 trials were prematurely terminated."[44] One vaccine seemed especially promising given its effects in animals. However, researchers had to stop the clinical trial midstream because it appeared to increase people's susceptibility to HIV/AIDS.[45]

As I was completing this paper, researchers reported one study in which a new vaccine was 31% effective.[46] Some defenders of research have hinted that this just shows how successful animal experimentation is. However, believing that a single and relatively minor success demonstrates the predictive power of animal models simply illustrates the psychological power of the shotgun effect and of selection attention. If this is a success, and we cannot be confident that it is since this is a single study, it comes only after twenty-five years of failures. Perhaps some advocates will claim that all the failures are worth the eventual success. However, that is a (p. 811) separate question and a moral issue I address shortly. The issue here is the predictive power of animal models. A single minor success (if it is a success) after a quarter century of failures is hardly proof of the predictive power of animal studies.

Where does this situation leave us? Concrete examples and evolutionary processes give us reason to think that animal models are always different to some degree from the human condition they model. Inferences from animals to humans are never certain. In the end, I suspect all serious researchers know that. Talk about animal models being "entirely conclusive for the toxicology and hygiene of man"[47] is just an artifact of the public debate over biomedical experimentation using animals.

Most cautious defenses of the practice usually employ another strategy when defending biomedical experimentation using animals: (1) they emphasize the value of basic research, or (2) they claim that animal models, although causally different from the human condition they model, are similar enough to that condition to justify inferences from animals to humans. I will examine each suggestion in turn.

Other Defenses of the Practice

Basic Research. Many defenders of biomedical experimentation using animals claim that basic research has been profoundly beneficial to humans.[48] Basic research does not directly seek a cure for any disease. Rather it seeks to understand fundamental biomedical phenomena—although this understanding, advocates say, empowers other researchers to find cures for human diseases or conditions. For instance, if basic research explains the causal mechanisms whereby mutant superoxide dismutase 1 induces motor neuron death in a mouse, then clinicians and applied researchers may have insight into ways to prevent, control, or cure human patients with this disease. I have no doubt that some basic research yields applied biomedical fruit. However, we must be careful not to overestimate these benefits. While Comroe and Dripps claimed that well over half of all clinical advances were traceable to basic research, the Health Economics Research Group found that the real figure is much lower, somewhere between 2% and 21%.[49]

Additionally, basic research is also partly vulnerable to the previous arguments about species differences. Knowing how mutations cause neuronal death in a mouse might be scientifically interesting, but on its own, it will not illuminate the mechanisms in humans if the mouse and the human are causally relevantly different. To that extent, basic research will not predictably have the indirect benefits often attributed to it.

Weak Models and Dynamical Systems Theory. We might also think that animal models are valuable if the conditions in animals and humans are *sufficiently* similar to *generally* justify inferences from one to the other. This would be plausible, if, as Bernard thought, biological systems were simple systems, ones where small differences between the model and the condition modeled make little if any difference. However, we have strong evidence that biological systems in higher animals are not simple; they are complex with extensive interactions and feedback mechanisms. Even a small change one place in an organism can have significant effects elsewhere (p. 812) in that organism. The behavior of complex systems is best explained by *dynamical systems theory*—or what is colloquially called "chaos theory."[50] This theory explains why even seemingly minor differences between two creatures may result in widely different reactions. "Among rodents and pri-

mates, zoologically closely related species exhibit markedly different patterns of metabolism."[51]

Where does this leave us? Both empirical evidence and evolutionary theory give us reason to think that inferences from nonhuman animals to humans are never certain. However, it does not show that the practice of using animals as models of human disease does not have reasonable levels of probability or that it has not benefitted humans. The moral question is whether any benefits are morally worth the costs. I now turn now to that question.

The Moral Costs of Animal Experimentation

I begin by combining two strands of argument. Some defenders of biomedical research using animals offer deontological arguments for the practice—arguments that seek to explain why humans can use animals for their purposes. I say a bit more about those arguments at the end of the paper. However, since virtually everyone now acknowledges that nonhuman animals have some moral status, most defenders of the practice employ in significant measure a consequentialist justification of the practice. They claim that biomedical experimentation using animals is justified because of its enormous benefits to human beings. As Carl Cohen, who begins by offering a deontological justification of the practice, puts it:

> When balancing the pleasures and pains resulting from the use of animals in research, we must not fail to place on the scales the terrible pains that would have resulted, would be suffered now, and would long continue had animals not been used. Every disease eliminated, every vaccine developed ... indeed, virtually every modern medical therapy is due, in part or in whole, to experimentation using animals.[52]

Most defenders of biomedical experimentation think that this point supplies a devastating response to any criticism of animal experimentation. They think everyone (a) will acknowledge the enormous benefits of the practice and (b) will acknowledge that such benefits morally justify that practice. These are highly debatable assumptions. One, the earlier arguments suggest that claims about animal experimentation's benefits are bloated. Two, even if animal experimentation has significant benefits, there are enormous moral costs of the practice that defenders do not acknowledge or address. These costs might well be sufficiently great to undermine the legitimacy of the practice, no matter what its benefits. This position might be an alternative route to defending some form of abolitionism. I am unable to fully (p. 813) evaluate that claim here. What seems minimally true is that defenders must establish profound, and perhaps overwhelming, benefits of experimentation to morally justify the practice.

The Moral Scales

Researchers need to demonstrate the success of animal experimentation even if animals had no moral worth. If animal experimentation were only marginally beneficial, the practice would be a terrible waste of scarce public resources. Our need to demonstrate its success increases once we note that researchers, like most of us, think that nonhuman animals—at least mammals, the most common laboratory animals—have moral status. If nonhuman animals were devoid of value, or if their value were morally negligible, then the impact of experimentation on them would not enter the moral equation. Defenders of research accept that the costs to animals must be given due consideration—not only before permitting the general practice of biomedical experiments using animals, but arguably before we determine if any particular line of experimentation is morally justifiable.[53] For present purposes, I assume that although nonhuman animals have non-negligible moral status or value, their value is considerably less than that of humans. Even granting them minimal value raises potent moral objections to animal experimentation. If arguments against research are potent on this minimalistic assumption, then defenders of research will be vulnerable to arguments showing that the moral value of animals remotely resembles that of humans.

As Cohen's claim suggests, we often think about the choice as two options resting on an old-fashioned set of scales, with the benefits to humans on the right pan of the scales, and the costs to animals on the left. When we ordinarily make a utilitarian calculation, we assume that the creatures in each pan have the same moral worth. Therefore, when deciding what to do, we need consider only (a) the extent of the harms and benefits and (b) the number of creatures harmed or benefitted. However, since I am plausibly assuming that nonhuman animals have less moral worth than humans do, we must modify the relative costs and benefits accordingly. Although this is difficult to specify with precision, we can take inspiration from "cruelty to animal" statutes on the books in most developed countries. Although what counts as "cruelty to animals" varies from jurisdiction to jurisdiction, we can definitely say that it is wrong to inflict excruciating pain on an animal merely to bring a human some tinge of pleasure. Most people think it wrong to roast a chimpanzee alive to make a bookend from its hand or to slowly kill an elephant so we can use its tusks for a paperweight.

Here's the idea. Even if creatures$_A$ have less moral worth than creatures$_H$, as long as the former have non-negligible worth—of the sort specified by "cruelty to animal" statutes—then there are circumstances under which morality demands that we favor them over the latter creatures. If the harm to creatures$_A$ is considerably greater than the benefits to creatures$_H$—or if there are considerably greater numbers of creatures$_A$ suffering that harm—then morality demands that we favor (p. 814) the former in those circumstances. With this adjustment in place, a utilitarian would hold that the moral permissibility of an action would be the product of (a) the moral worth of the creatures that suffer and benefit, (b) the seriousness of the wrong and the significance of the benefit of those respective creatures, and (c) the number of such creatures that suffer and benefit.[54]

That shows that the calculation is more complicated than defenders of animal experimentation suggest. In the public debate, they often cast the choice as one between "your baby or your dog." Since the baby is worth more than the dog, then everyone will choose the baby. However, the choice has not been, nor will it ever be, between "your baby and your dog." Single experiments, and certainly not lone experiments on single animals, will *never* lead to any medical discovery. Only coordinated sequences of experiments can lead to discovery. This is a point about the nature of science; it is not unique to biomedical experimentation. All scientific experiments are part of a pattern of activity—an institutional practice—and discoveries are made though an organized pattern of experimentation. Therefore, the core issue is whether that practice or institution significantly benefits humans. Consequently, we must reformulate the moral question: is this practice—or some attenuated version of it—morally justified even though it kills and causes pain to a significant number of animals?

Two Moral Assumptions

This way of framing the issue still makes it appear that we begin with the scales evenly balanced. Or, if they are tipped, they are tipped in favor of humans since we think that humans have greater moral worth than nonhuman animals. Doubtless that is why defenders such as Cohen claim the benefits of research "incalculably outweigh the evils."[55] However, this claim ignores two widely held moral views, which, if true, tip the scales sharply in favor of nonhuman animals. If I am correct, then defenders of biomedical research using animals must show significant benefits of experimentation to even the scales, let alone to tip them in favor of experimentation. Even if they can do that, we should fully appreciate the moral costs of such research. These costs are generally overlooked or ignored by those defending the practice.

Acts Are Morally Weightier than Omissions

Imagine any morally bad condition. Most people assume it is worse to bring that condition about than allowing it to happen. It is morally worse to kill someone than to let her die, to steal than to fail to prevent theft, and to lie rather than to fail to correct a lie. This claim comes in two forms. The absolute view holds that it is categorically worse to do harm than to fail to prevent it: it is always worse to cause a harm than to fail to stop another harm from occurring, no matter how benign the first and how serious the second. The relative view holds that it is worse to cause a harm than to fail to prevent one, although not categorically so. In some circumstances it is permissible to do a small harm to prevent a much greater one.

(p. 815) Regardless of which form one holds, most people think that it is not only worse to do harm than to fail to prevent harm, but that it is *much* worse. Although specifying how much worse is difficult, I can illustrate. Although most people would be aghast if Ralph failed to save a drowning child, particularly if he could have done so with little effort, they would not think Ralph nearly as bad as his neighbor Bob who held a child's head under water until she drowned. Minimally, "much worse" means this: the person who drowns the child should be imprisoned for a long time—if not executed—while the person who al-

lowed the child to drown should not be punished at all, although perhaps she should be morally censured.

If the person had some special duties to the child—for instance, if she were a lifeguard at the pond—then we might hold her liable for the child's death, although even then we would not charge her with first-degree murder. If we did punish her, we would claim her obligation arose because of her special status: she voluntarily assumed responsibility for people swimming in her pond. The current issue we are discussing, however, is about the function the difference between doing and allowing plays in our moral thinking when people have not assumed any special responsibility for those who are harmed. Here the situation is quite different. Even in European cultures with "Good Samaritan" laws, someone who violates such laws—say, by not saving a drowning child—may be punished, but far less severely than someone who kills a child.[56] That signals a profound moral difference.

How is this relevant to the current debate? The researchers' calculation requires rejecting this widely held belief that there is a significant moral difference between harm we do and harm we do not prevent.[57] The experimenter knowingly kills—and often inflicts pain and suffering on—creatures with non-negligible moral worth to prevent future harm to humans. Put more abstractly, she causes harm to prevent future harm. Experimenters would likely contend that the moral asymmetry between doing and allowing is applicable only if the wrong perpetrated is morally equal to the wrong not prevented. Since animals are not as valuable as humans, then the wrong permitted is morally weightier than the wrong perpetrated.

However, the doing/allowing distinction has moral bite even if the harm not prevented is worse than the harm perpetrated. Although it is worse for a child to die than for a child to be spanked for inappropriate reasons, most people think this difference in moral weight is outweighed by the moral asymmetry between what we do and what we allow. That is, most people will think an adult has done something worse if he spanks his child (or worse still, a strange child) for inappropriate reasons than if he fails to feed a starving child on the other side of the world.[58]

A defender of research might respond that this example is irrelevant since both cases involve children—creatures of the same moral worth. For reasons offered earlier, this objection is misguided. Although the relative worth of creatures enters the moral equation, it is not the only factor. We must also include the seriousness of the harm (significance of the benefit), the number of creatures subjected to that harm (benefitted), and, especially relevant to the current discussion, whether we cause or merely permit the harm. For instance, Ralph intentionally chooses not to send money that would keep a starving Pakistani child alive. His next door neighbor, (p. 816) Bob, picks up a stray puppy, takes it home and kills it slowly, causing it great pain. Although the law would do nothing whatsoever to Ralph, Bob would be charged with cruelty to animals. Finally, although most people in the community would not condemn Ralph for his inaction, they would roundly condemn Bob for his cruelty and callousness. They would not want to live next door to Bob, nor to have him as a veterinarian.

Some animal researchers might argue that they have special obligations to people—obligations that override the force of this asymmetry. That is not plausible. Lifeguards are hired to save those specific people swimming in their pools from drowning. Animal researchers are not hired to save particular people from kidney disease. They are hired to conduct experiments on animals. Everyone may hope that these experiments would benefit anyone who happens to have the disease. However, that does not mean that the researchers have special obligations to these as-yet-unidentified people. Special obligations are just, that, special: direct obligations to particular, identifiable individuals. Here's a clear way to see the point. If a lifeguard fails to rescue someone swimming in his pool, he can be subject to both civil and criminal penalties. No one who dies of renal failure could sue (let alone successfully sue) an animal experimenter who failed to find a cure for the disease.

Finally, even if we could make sense of the claim that researchers have special obligations to humans who might benefit from their research, it is more plausible to think that they have special obligations to their laboratory animals, since by law investigators are specifically required to care for them.[59]

Consequently, if this asymmetry is morally relevant, it is relevant even given the presumed difference in moral worth. Therefore, unless the benefits to humans are substantially greater than the costs to animals, then these will not outweigh the special immorality of causing harm. How much greater the benefits must be depends in part on whether defenders hold the absolute or relative form of the distinction. However, it is enough to acknowledge that experiments that kill numerous animals and yield only slight benefits to humans will not cut the moral mustard.

Some theorists do not accept this moral distinction; they think there is no moral difference between what we do and what we permit. For them, this asymmetry provides no objection to animal experimentation. Although I have sympathies with this claim, it is not a position most defenders of research embrace. If defenders of animal experimentation do not think that doing harm is worse than failing to prevent harm, then they think that we should pursue any activity that yields benefits greater than that activity's costs. If we could achieve extremely important biomedical benefits only by invasive, nonconsensual experiments on humans, then these would be morally justified. This is a most unwelcomed consequence for most defenders of animal experimentation since they categorically reject nonconsensual invasive biomedical experiments on humans.[60] That denial cannot be defended by those who reject the first asymmetry. At most they can say that such experimentation could be justified only if the benefits were substantial, and because such conditions are rarely satisfied, then nonconsensual experiments on humans are rarely justified.

(p. 817) Even this line of defense will be difficult to hold. It is implausible to think that invasive experiments on non-consenting humans would never yield substantial biomedical benefits to many humans. Apparently, German experiments on inmates taught us a fair bit about treating burns and Japanese experiments on prisoners of war taught us about infec-

tious agents. This should not be surprising. Humans are the best test subjects. If invasive nonconsensual experiments on humans are justified if the benefits are high enough, then nonconsensual experiments will sometimes be justified.

I am not taking a stance on the moral significance of the doing/allowing distinction. My claim is that most defenders of research will be uncomfortable either embracing or denying its significance. If advocates categorically reject invasive nonconsensual experiments on humans, then they must (a) think that nonhuman animals are devoid of moral worth or (b) believe it is categorically worse to commit an evil than to fail to prevent one. The first option clashes with their claim that animals' interests go on the moral scales. The second raises an additional justificatory hurdle to defending the practice since experimenters do harm to prevent harm. Perhaps, though, experimentation is acceptable if the benefits of experimentation are overwhelming.

Definite Harms are Morally Weightier than Possible Benefits

To make matters worse for consequentialist defenders of experimentation, the trade-off is not between harm we do to animals and human suffering we fail to alleviate. That description masks the fact that the suffering of animals is definite while benefits to humans are merely possible. It is sometimes legitimate to give up some definite benefit B in the hope of obtaining a greater benefit B_1—if B_1 is sufficiently great. For instance, I might give up $10 to obtain a 10% chance of gaining $200. Generally speaking, it is reasonable for me to forego a definite benefit B for another benefit B_1, if the product of the utility and probability of B_1's occurring is much greater than the utility of B (being definite, its probability is 1). Therefore, researchers must show that the product of the probability and utility of benefits to humans is greater than the product of animals' definite harm (adjusted for their diminished value) and the number of animals who suffer.

Demanding that researchers establish that any particular experiment will be successful is too stringent. The issue is whether we can reliably predict that the *practice* of experimentation will produce sufficient benefits for humans, benefits that outweigh the costs to nonhuman animals. We will have difficultly doing so because both the utility and the probability of the practice are unknown, while the harm to animals is substantial and definite.

Rejecting this second assumption also comes at considerable cost. It would be the height of foolishness to give up any good G1 for the mere chance of obtaining some other good G2 if G2 were not greater than G1. Abandoning this assumption would be to abandon rationality itself.

(p. 818) What Really Goes on the Scales?

Cohen's accounting of what goes on the moral scales is incomplete. When determining the benefits and costs of animal experimentation, we must include not only the costs to animals (which are direct and substantial), but also the costs to humans (and animals) of misleading experiments. I earlier noted that J. R. Paul claimed that adherence to animal

models of polio delayed the development of a vaccine for more than two decades. Many lives were lost or ruined because of this delay.

Animal experiments also seriously misled us about the dangers of smoking. By the early 1960s, human epidemiological studies showed a strong correlation between lung cancer and smoking.[61] Nonetheless, Northrup brushed off the claim that smoking caused cancer thusly, "The failure of many ... investigators to induce experimental cancers, except in a handful of cases, during fifty years of trying, casts serious doubt on the validity of the cigarette-lung cancer theory."[62] Finally, an AIDS vaccine researcher has concluded, "The lack of an adequate animal model has hampered progress in HIV vaccine development."[63] These three cases show that there will be substantial costs *to humans* of relying so heavily on animal experimentation. We should count these costs.

Researchers insist that we should put possible benefits on the scales, since no benefits are certain. That is reasonable, at least if we also include possible costs. For instance, some people speculated that AIDS was transferred to the human population through an inadequately screened oral polio vaccine given to 250,000 Africans in the late 1950s. Such a claim has been widely repudiated.[64] However, even if it is false, something like it might be true. After all, we know that one dangerous simian virus (SV40) entered the human population through inadequately screened vaccine.[65]

Finally, and perhaps most importantly, what is crucial is not the benefits animal experimentation did and will produce, but the benefits that only it could produce. We must determine (a) the role that medical intervention played in lengthening life and improving health,[66] (b) the contribution of animal experimentation to medical intervention, and (c) the benefits of animal experimentation relative to those of nonanimal research. In sum, what goes on the moral scales are not all the purported benefits of experimentation, but only the *increase* in benefits relative to alternatives. Since we do not know what the alternatives would have yielded, determining that increase will be difficult. Minimally, though, we have no reason to think that none of the advances attributable to animal research would have been made without that research.

A Final Dilemma

Deontological Concerns

The previous discussion explores consequentialist concerns about animal experimentation. The practice also faces deontological objections. I mentioned the most obvious one earlier. Tom Regan claims that animals are subjects of a life, and, as such, cannot be used for human purposes.[67] Many animal activists embrace Regan's (p. 819) idea, though, rightly or wrongly, a majority of people reject it.[68] However, we can combine elements of Regan's view with some empirical arguments in this essay to frame a dilemma for defenders of animal experimentation.

Biomedical researchers claim (1) that biomedical experiments using animals are *scientifically* justified because (carefully selected) nonhuman animals are good models of human

biomedical phenomena, and (2) that these experiments are *morally* justified because humans and nonhuman animals are morally relevantly different. To scientifically justify inferences from animals to humans, defenders must identify substantial and pervasive *causal* similarities between humans and nonhuman animals. To morally justify the practice they must find sufficient relevant *functional* differences between humans and nonhuman animals. Defenders of research claim it is easy to do the latter: humans have cognitive and emotional abilities that nonhuman animals lack, at least in sufficient degree.[69] As Cohen put it, "Animals ... lack this capacity for free moral judgment. They are not beings of a kind capable of exercising or responding to moral claims. Animals therefore have no rights, and they can have none."[70]

As it turns out, there is mounting evidence that the mental lives of nonhuman animals are far richer than people historically supposed.[71] However, we can sidestep this question. Defenders of experimentation will have trouble supporting the combination of (1) and (2), whether the differences in mental abilities are great or slight.

To see why, we must understand how scientists explain the presence of cognitive and emotional traits in humans and their absence in animals. The usual answer is that humans have an advanced cerebral cortex, which nonhuman animals lack. Human mental superiority is reflected in differences between our respective "encephalization quotient" (EQ), the ratio of the "brain weight of a species with the brain weight of an average animal of the same approximate body weight .... According to this formula, the actual brain size of humans comes out to six times what we would expect of a comparable mammal."[72] There is little doubt that the average human is more cognitively sophisticated than the average nonhuman animal, and that we can best explain this difference by differences in our respective brains. However, because biological systems are highly interconnected intact systems, it is implausible to think that human brains, and thus cognitive abilities, evolved without significant biological changes elsewhere in the organism. To think this could have happened researchers must embrace bio-Cartesianism.

Bio-Cartesianism

Descartes claimed that the mind and the brain are ontologically distinct substances operating in wholly different domains and then had a problem getting these substances to interact. Animal experimenters have unconsciously adopted a biological corollary—what Niall Shanks and I call bio-Cartesianism.[73] Animal researchers assume that the brain, although formed by the same evolutionary pressures that shape other biological systems, somehow developed independently of those other systems. This makes no evolutionary sense. Higher-order cognitive abilities evolved (p. 820) because they were advantageous to the creatures' survival, and, having developed, shaped those creature's biological systems and behavior:

> [S]ome types [of monkeys] have higher EQs than others and [that connects] ... with how they make their living: insect-eating and fruit-eating monkeys have bigger brains for their size, than leaf-eating monkeys. It makes some sense to argue that an animal needs less computing power to find leaves, which are abundant all

> around, than to find fruit, which may have to be searched for, or to catch insects, which take active steps to get away.[74]

These evolved cognitive differences affect noncognitive biological systems; we must consider these differences in the practice of biomedicine. As one animal research handbook cautions:

> When selecting nonhuman primates because of their close relationship to humans, choice of species of nonhuman primate is important. For example, a completely vegetarian species may not be as useful because of differences in microflora of the intestine, which may affect drugmetabolism.[75]

Once we understand the ways that cognitive functioning is related to other biological systems, we can state this deontological dilemma for defenders of research: they must embrace bio-Cartesianism to morally defend their practice and they must reject it to scientifically defend their practice. They embrace it by claiming that humans and animals are sufficiently different to morally permit animals' use as experimental subjects. They reject it by invoking the "intact systems" argument to scientifically defend the practice. Defenders of experimentation cannot have it both ways. If nonhuman animals and humans are sufficiently similar to think that inferences from the former to the latter are scientifically legitimate, then they are likely sufficiently similar cognitively to think that nonhuman animals have significant moral worth. If nonhuman animals and humans are sufficiently different functionally to morally justify the practice, then they are likely sufficiently different biologically so that we have greater reason to suspect that inferences from animals to humans will often be suspect.

Conclusion

I have tried to identify and evaluate arguments for biomedical experimentation using animals. Animal experimentation is not useless as critics sometimes aver. However, neither are the benefits of the practice as clear, direct, or compelling as defenders commonly claim. Likewise, I do not think that the moral arguments defending the practice are wholly wanting, nor are they as persuasive as defenders claim. There are significant moral costs of the practice.

Defenders of the practice carry the moral burden of proof. The moral onus always rests on anyone who wishes to harm sentient creatures, to do what is, all things being equal, a moral wrong. Because people on both sides ofthis debate (p. 821) acknowledge at least some level of moral status for nonhuman animals, defenders must provide clear evidence that the value of the institution of research exceeds its moral costs. I suspect that their most promising way of scientifically defending the practice would emphasize limited and focused basic research. The results of that research will rarely yield immediate and direct benefits. However, they arguably provide a broad understanding of biological processes

that may suggest promising curative strategies. Whether such benefits are sufficient to morally defend the practice is another question.[76]

Suggested Reading

BEAUCHAMP, TOM L. "Opposing Views on Animal Experimentation: Do Animals Have Rights?" *Ethics and Behavior* 7 (1997): 113–21.

BEKOFF, MARK, **COLIN ALLEN**, and **GORDON BURGHARDT**, eds. *The Cognitive Animal*. Cambridge, Mass.: MIT Press, 2002.

BERNARD, CLAUDE. *An Introduction to the Study of Experimental Medicine*. Paris: Henry Schuman, Inc., 1949.

CAIRNS-SMITH, A. G. *Seven Clues to the Origin of Life*. Cambridge: Cambridge University Press, 1985.

COHEN, CARL. "The Case for the Use of Animals in Biomedical Research." *New England Journal of Medicine* 315 (1986): 865–70.

COMROE JR., J. H., and **R. D. DRIPPS**. "Scientific Basis for the Support of Biomedical Science." *Science* 192 (1976): 105–11.

DEGRAZIA, DAVID, and **ANDREW ROWAN**. "Pain, Suffering, and Anxiety in Animals and Humans." *Theoretical Medicine* 12 (1991): 193–211.

(p. 825) **DRESSER, REBECCA**. "Standards for Animal Research: Looking at the Middle." *Journal of Medicine and Philosophy* 13 (1988): 123–43.

EDEY, MAITLAND A., and **DONALD C. JOHNSON**. *Blueprints: Solving the Mystery of Evolution*. New York: Penguin Books, 1989.

FOX, MICHAEL A. *Case for Animal Experimentation: An Evolutionary and Ethical Perspective*. Berkeley and Los Angeles: University of California Press, 1986.

GRANT, JONATHAN, **LIZ GREEN**, and **BARBARA MASON**. *From Bedside to Bench: Comroe and Dripps Revisited*. Uxbridge, U.K.: Health Economics Research Group, Brunel University, 2003.

LAFOLLETTE, HUGH, and **NIALL SHANKS**. *Brute Science: Dilemmas of Animal Experimentation*. New York: Routledge, 1996.

MAYR, ERNST. *Toward a New Philosophy of Biology*. Cambridge, Mass.: Harvard University Press, 1988.

NESSE, RANDOLPH M., and **GEORGE C. WILLIAMS**. *Why We Get Sick: The New Science of Darwinian Medicine*. New York: Crown Publishers, 1995.

NORCROSS, ALASDAIR. "Animal Experimentation." In *Oxford Handbook of Bioethics*, edited by Bonnie Steinbock, pp. 648–67. Oxford: Oxford University Press 1997.

REGAN, TOM. *The Case for Animal Rights*. Berkeley and Los Angeles: University of California Press, 1983.

SHANKS, NIALL, and **RAY GREEK**. *Animal Models in Light of Evolution*. Boca Raton, Fla.: Brown Walker Press, 2009.

SIGMA XI. "Sigma Xi Statement of the Use of Animals in Research." *American Scientist* 80 (1992): 73–76.

SINGER, PETER. *Animal Liberation: A New Ethics for Our Treatment of Animals*. 2nd ed. New York: New York Review, 1975.

SMITH, J. A., and **KENNETH M. BOYD**, eds. *Lives in the Balance: The Ethics of Using Animals in Biomedical Research*. Oxford: Oxford University Press, 1991.

Notes:

(1.) A 2003 Gallup poll found "96% of Americans saying that animals deserve at least some protection from harm and exploitation," even if many reject the idea of "animal rights." "Public Lukewarm about Animal Rights," http://www.gallup.com/poll/8461/Public-Lukewarm-Animal-Rights.aspx (accessed January 18, 2010).

(2.) As far as I know, no one has ever used this particular classificatory scheme. However, I think it will soon become apparent that it nicely categorizes the range of moral views.

(3.) I am not using claims about "what most people believe" as a surreptitious way of grounding controversial moral claims. However, I think ethicists should begin by addressing common moral views, even if we later conclude that these views are mistaken. What justifies the claim that this is what most people believe? I am a competent speaker of the English language who has discussed these issues with thousands of students at dozens of universities worldwide.

(4.) Keith Thomas, *Man and the Natural World: Changing Attitudes in England 1500–1800* (London: Allen Lane, 1980), pp. 17, 25, and 31.

(5.) Lori Gruen, "Moral Status of Animals," *Stanford Encyclopedia of Philosophy*, ed. Edward N. Zalta (Summer 2003), http://plato.stanford.edu/entries/moral-animal/ (accessed February 17, 2010).

(6.) Immanual Kant, *Lectures on Ethics* (Indianapolis, Ind.: Hackett Pub. Co., 1980), p. 239.

(7.) David DeGrazia and Andrew Rowan, "Pain, Suffering, and Anxiety in Animals and Humans," *Theoretical Medicine* 12 (1991): 193–211.

(8.) Tom Regan, *The Case for Animal Rights* (Berkeley and Los Angeles: University of California Press, 1983), pp. 243–48.

(9.) R. G. Frey, "Moral Standing, the Value of Lives, and Speciesism," in *Ethics in Practice: An Anthology*, 3rd ed., ed. H. LaFollette (Oxford: Blackwell Publishers, 2007), pp. 192–204.

(10.) Regan, *Case for Animal Rights*, pp. 151–55.

(11.) R. J. Lipton, *Nazi Doctors: Medical Killing and the Psychology of Genocide* (New York: Perseus Publishing, 2000); Tuskegee Syphilis Study Legacy Committee, "A Request for Redress of the Wrongs of Tuskegee," (1996), http://hsc.virginia.edu/hs-library/historical/apology/report.html (accessed May 15, 2003).

(12.) American Medical Association, *Use of Animals in Biomedical Research: The Challenge and Response* (Chicago: American Medical Association, 1992), p. 11.

(13.) J. H. Comroe Jr. and R. D. Dripps, "Scientific Basis for the Support of Biomedical Science," *Science* 192 (1976): 105–11; J. H. Comroe Jr. and R. D. Dripps, "Ben Franklin and Open Heart Surgery," *Circulation Research* 35 (1974): 661–69; S. Zola, "Basic Research, Applied Research, Animal Ethics, and the Animal Model of Human Amnesia," in *Why Animal Experimentation Matters: The Use of Animals in Medical Research*, ed. E. F. Paul and J. Paul (New York: Transaction Publishers, 2001), pp. 79–92.

(14.) Sigma Xi, "Sigma Xi Statement of the Use of Animals in Research," *American Scientist* 80 (1992): 73–76.

(15.) American Medical Association, *Use of Animals in Biomedical Research*, p. 27.

(16.) The first meta-analysis of the standard mouse model of ALS reveals that " 'positive' results are often considered more interesting and hence more likely to be published." Michael Benatar, "Lost in Translation: Treatment Trials in the SOD1 Mouse and in Human ALS," *Neurobiology of Disease* 26 (2007): 6.

(17.) Psychologists claim that humans are often mislead by "confirmatory biases." See David Dunning's *Self-Insight: Roadblocks and Detours on the Path to Knowing Thyself* (New York: Psychology Press, 2005), pp. 46ff.

(18.) B. Patoine, "Pitfalls and Promise on the Road to ALS Therapeutics," The Dana Foundation (2009), http://www.dana.org/news/publications/detail.aspx?id=19766 (accessed September 12, 2009).

(19.) ALS Association, "Trial of Arimoclomol in SOD1–Positive Familial ALS Opens for Enrollment," (2009), http://www.alsa.org/patient/drug.cfm?id=1414 (accessed July 27, 2009).

(20.) Jim Schnabel, "Standard Model," *Nature* 454 (2008): 683.

(21.) L. B. Lave, F. K. Ennever, H. S. Rosencrantz, and G. S. Omenn, "Information Value of the Rodent Bioassay," *Nature* 336 (1988): 631–33.

(22.) L. S. Gold et al., *Misconceptions about the Causes of Cancer* (Vancouver: Fraser Institute, 2002), p. 35; L. S. Gold, T. Slone, N. Manley, and L. Bernstein, "Target Organs in Chronic Bioassays of 533 Chemical Carcinogens," *Environmental Health Perspectives* 93 (1991): 233–46.

(23.) J. R. Paul, *The History of Poliomyelitis* (New Haven, Conn.: Yale University Press, 1971), pp. 384–85.

(24.) L. Lasagna, "Regulatory Agencies, Drugs, and the Pregnant Patient," in *Drug Use in Pregnancy*, ed. L. Stern (Boston: ADIS Health Science Press, 1982), p. 15.

(25.) B. M. Mitruka, H. M. Rawnsley, and D. V. Vadehra, *Animals for Medical Research: Models for the Study of Human Disease* (New York: Wiley, 1976), pp. 467–68.

(26.) A. Gorbman et al., *Comparative Endocrinology* (New York: Wiley, 1983), p. 33.

(27.) J. Hart, "Endocrine Pathology of Estrogens: Species Differences," *Pharmacologial Therapy* 47 (1990): 203–18.

(28.) American Medical Association, *Use of Animals in Biomedical Research: The Challenge and Response*; Hugh LaFollette and Niall Shanks, *Brute Science: Dilemmas of Animal Experimentation* (New York: Routledge, 1996).

(29.) Claude Bernard, *An Introduction to the Study of Experimental Medicine* (Paris: Henry Schuman, Inc., 1949), p. 125.

(30.) Hugh LaFollette and Niall Shanks, "Two Models of Models in Biomedical Research," *Philosophical Quarterly* 45 (1995): 141–60.

(31.) B. Alberts et al., *Molecular Biology of the Cell*, 5th ed. (New York: Taylor & Francis, 2008), p. 1207.

(32.) Lee, "Acquired Immunodeficiency Disease Vaccines: Design and Development," in *AIDS: Biology, Diagnosis, Treatment and Prevention*, fourth edition, edited by V. T. DeVita, Jr (Philadelphia, PA: Lippincott-Raven Publishers, 1997), p. 609.

(33.) Alberts et al., *Molecular Biology of the Cell*, p. 205.

(34.) Coyne, Jerry, *Why Evolution Is True* (New York: Viking, 2009) p. 81.

(35.) R. M. Nesse and G. C. Williams, *Why We Get Sick: The New Science of Darwinian Medicine* (New York: Crown Publishers, 1995), p. 4.

(36.) Coyne, *Why Evolution Is True*, pp. 57–79.

(37.) Alberts, et al. *Molecular Biology of the Cell*, p. 249.

(38.) Zola, "Basic Research, Applied Research, Animal Ethics, and the Animal Model of Human Amnesia," pp. 79–92.

(39.) Gold et al., *Misconceptions about the Causes of Cancer*, p. 34.

(40.) J. C. Caldwell, "Comparative Aspects of Detoxification in Mammals," in *Enzymatic Basis of Detoxication*, vol. 1, ed. W. Jakoby (New York: Academic Press, 1980), pp. 87–110.

(41.) E. A. Hodgson, *Textbook of Modern Toxicology* (Hoboken N.J.: Wiley Interscience, 2004), p. 177.

(42.) Alberts et al., *Molecular Biology of the Cell*, p. 205.

(43.) Coyne, *Why Evolution Is True*, pp. 62–80.

(44.) J. Bailey, "An Assessment of the Role of Chimpanzees in AIDS Vaccine Research," *Alternatives to Laboratory Animals* 36 (2008): 381–428. See pages 386–409 and 412–15 for detailed information drawn from the International AIDS Vaccine Initiative.

(45.) J. Lauerman, "Merck Aids Vaccine Failure May Doom Promising Study," *Bloomberg.com*, 2009, http://www.bloomberg.com/apps/news?pid=20601109&sid=axb42ai9OAlw (accessed August 22, 2009).

(46.) M. Falco, "Combo Vaccine Reduces Risk of HIV Infection, Researchers Say," *CNN*, 2009, http://www.cnn.com/2009/HEALTH/09/24/hiv.vaccine/index.html (accessed August 18, 2009).

(47.) Bernard, *Introduction to the Study of Experimental Medicine*, p. 125.

(48.) Comroe and Dripps, "Scientific Basis for the Support of Biomedical Science;" Comroe and Dripps, "Ben Franklin and Open Heart Surgery," pp. 661–69.

(49.) Health Economics Research Group (London: Brunel University, 2003), p. iii.

(50.) Stephen H. Kellert, *In the Wake of Chaos: Unpredictable Order in Dynamical Systems* (Chicago: University of Chicago Press, 1993).

(51.) J. C. Caldwell, "Comparative Aspects of Detoxification in Mammals," pp. 85–113 and 106.

(52.) Carl Cohen, "The Case for the Use of Animals in Biomedical Research," *New England Journal of Medicine* 315 (1986): 865–70, here p. 868.

(53.) J. Smith, and K. Boyd, *Lives in the Balance: The Ethics of Using Animals in Biomedical Research* (Oxford: Oxford University Press, 1991), pp. 138–39.

(54.) LaFollette and Shanks, *Brute Science*, pp. 247–61.

(55.) Cohen, "Case for the Use of Animals in Biomedical Research," p. 868.

(56.) H. M. Malm, "Bad Samaritan Laws: Harm, Help, or Hype," *Law and Philosophy* 19 (2000): 707–50, here pp. 744–45.

(57.) S. R. L. Clark, "How to Calculate the Greater Good," in *Animals' Rights: A Symposium*, ed. D. Patterson and R. Ryder (London: Centaur Press, 1977), pp. 96–105.

(58.) Such a view is clearly implied by John Arthur in his "Rights and the Duty to Bring Aid," in *World Hunger and Morality*, ed. Will Aiken and Hugh LaFollette (Upper Saddle River, N.J.: Prentice-Hall, 1996), pp. 39–50.

(59.) See Institute for Laboratory Animal Research, *Guide for the Care and Use of Laboratory Animals* (Washington, D.C.: National Academies Press, 1996), p. 2, http://www.nap.edu/openbook.php?record_id=5140&page=1.

(60.) Cohen, "Case for the Use of Animals in Biomedical Research," p. 866; American Medical Association, *Use of Animals in Biomedical Research*, pp. 1, 7.

(61.) See E. Brecher, and R. Brecher, *The Consumers Union Report on Smoking and the Public Interest* (Mount Vernon, N.Y.: Consumers Union Press, 1963).

(62.) E. Northrup, *Science Looks at Smoking: A New Inquiry into the Effects of Smoking* (New York: Coward McCann, 1957), p. 133.

(63.) Lee, "Acquired Immunodeficiency Disease Vaccines," p. 609.

(64.) For a different view, see B. F. Elwood, and R. B. Striker, "Polio Vaccine and the Origin of AIDS" (Letter to the Editor), *Research in Virology* 144 (1993): 175–77.

(65.) Leonard Hayflick, "Human Virus Vaccines: Why Monkey Cells?" *Science* 733 (1972): 813–14.

(66.) T. McKeown, *The Modern Rise of Populations* (New York: Academic Press, 1976), especially chapter 5.

(67.) Regan, *Case for Animal Rights*, pp. 243–45.

(68.) Gallup Poll, "Public Lukewarm about Animal Rights."

(69.) M. A. Fox, *The Case for Animal Experimentation: An Evolutionary and Ethical Perspective* (Berkeley and Los Angeles: University of California Press, 1986).

(70.) Cohen, "Case for the Use of Animals in Biomedical Research," p. 866.

(71.) D. G. Griffin, *Animal Minds* (Chicago: University of Chicago Press, 1992); R. J. Hoage, and L. Goldman, eds., *Animal Intelligence: Insight into the Animal Mind* (Washington, D.C.: Smithsonian Institution Press, 1986); C. Allen and M. Bekoff, *Species of Mind: The Philosophy and Biology of Cognitive Ethology* (Cambridge, Mass.: MIT Press,

1997); M. Bekoff, C. Allen, and G. Burghardt, eds., *The Cognitive Animal* (Cambridge, Mass.: MIT Press, 2002).

(72.) Fox, *Case for Animal Experimentation*, p. 38.

(73.) LaFollette and Shanks, *Brute Science,* pp. 238–41.

(74.) M. A. Edey and D. C. Johnson, *Blueprints: Solving the Mystery of Evolution* (New York: Penguin Books, 1989), pp. 189–90.

(75.) Mitruka et al., *Animals for Medical Research*, p. 342.

(76.) I am indebted to Niall Shanks for the collaborative work that informs important elements of this essay. I am grateful to Eva LaFollette for her insightful philosophical comments and stylistic suggestions. Finally, I thank Tom L. Beauchamp and R. G. Frey for helpful comments on an earlier version of this paper.

Hugh LaFollette

Hugh LaFollette, Cole Chair in Ethics, University of South Florida St. Petersburg

BMJ Open Science

3Rs missing: animal research without scientific value is unethical

Daniel Strech,[1,2] Ulrich Dirnagl [1,2,3]

Tocite: Strech D, Dirnagl U. 3Rs missing: animal research without scientific value is unethical. *BMJ Open Science* 2019;**3**:e000035. doi:10.1136/bmjos-2018-000048

► Prepublication and Review History is available online at http://dx.doi.org/10.1136/bmjos-2018-000048.

Received 6 September 2018
Revised 4 December 2018
Accepted 24 January 2019

[1]QUEST Center for Transforming Biomedical Research, Berlin Institute of Health (BIH), Berlin, Germany
[2]Charité - Universitätsmedizin Berlin, Berlin, Germany
[3]NeuroCure Clinical Research Center, Charité - Universitätsmedizin Berlin, Berlin, Germany

Correspondence to
Daniel Strech;
daniel.strech@charite.de

AbstrACt

The current, widely established 3R framework for the ethical use of animals in research consists of three guiding principles, that is, *R*eplacement, *R*eduction and *R*efinement, all aiming to safeguard the overarching ethical principle of animal welfare. However, animal welfare alone does not suffice to make animal research ethical if the research does not have sufficient scientific value. The scientific value of animal studies strongly decreases if they are not sufficiently robust, if their questions have already been sufficiently addressed or if the results are selectively reported. Against this background, we argue that three guiding principles are missing, that is, *R*obustness, *R*egistration and *R*eporting, all of which aim to safeguard and increase the scientific value of animal research. To establish a new 6R framework, we need a multistakeholder discourse to conceptualise the specific requirements of robustness, registration and reporting and to clarify responsibilities, competencies and legislation for auditing 6R compliance.

InTroducTIon

Framed by Russel and Burch more than 60 years ago, the 3Rs (*R*eplacement, *R*eduction and *R*efinement) have become the guiding principles for the ethical use of animals in research.[1] Although universally accepted, there is an ongoing discourse on their improvement, uptake and implementation.[2] Here, we argue that with their current focus on animal welfare, the 3Rs lack an important ethical dimension. Research on animals is only ethical if it generates value for science and society, a dimension that is not represented by the current 3Rs.

Individual research projects are only valuable if they enable a knowledge gain, apply robust study designs and report their results in a non-selective manner. Whether a research project will ultimately contribute to innovation in healthcare is hard to gauge for several reasons. One reason is that scientific breakthroughs may take years to manifest. Robustness, on the other hand, can be judged on the research project level. If we want to better understand what research questions are still insufficiently addressed, we need individual projects to be accessible via animal study registries open to the public. Furthermore, only if protocols are prospectively registered are we able to identify selective reporting of study results.

We posit that while the current 3Rs are important for upholding animal welfare, the dimension of scientific value needs to be considered when planning, reviewing and conducting animal research. We therefore propose the addition of three additional Rs, that is, *R*obustness, *R*egistration and *R*eporting, to the guiding principles for the ethical use of animals in research (figure 1).

Why do We need to Complement the 3r frAmeWork noW?

Over the past 5 years, several empirical studies and expert analyses have demonstrated that three challenges endanger the value of animal research. First, animal research often lacks measures to reduce validity threats such as biases or a lack of statistical power.[3 4] Second, animal research faces a substantial publication bias, that is, null and negative results often end up in the file drawer.[5 6] Third, publication of results often lacks important information that is needed for a critical appraisal (eg, information on study design or attrition of animals).[7 8] These challenges negatively affect the reproducibility of animal studies[9 10] and the relevance of animal studies in justifying early human research.[11 12] In summary, these threats reduce the value of the research results, potentially leading to inefficient allocation of public funds, to ill-advised clinical research and to the unnecessary use and suffering of experimental animals.

Why robustness, registrAtion And reporting?

Our core argument is that the current 3R principles for animal research, despite their importance, are limited because of their one-sided focus on the basic ethical principle 'animal welfare'. They lack an explicit and practice-oriented set of guiding principles promoting the second basic ethical

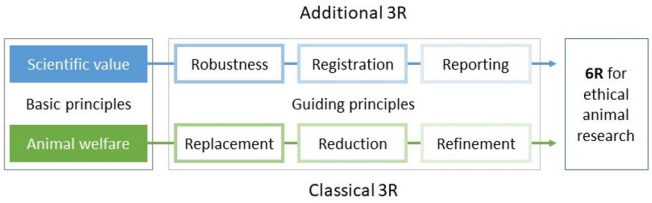


Figure 1 Two basic principles for animal research ethics translate into six practice-guiding principles (6R).

principle 'scientific value'. Furthermore, each of the additional 3R principles (robustness, registration and reporting) is important in itself and not replaceable by the other two. Animal studies, for example, can be robust but reported in a biased or otherwise inappropriate way. Alternatively, they can be appropriately reported but not robust. Both scenarios compromise the value of the study. In times where approximately 50% of animal studies are not reported,[13] only the preregistration of animal study protocols allows the identification of biased, delayed or unreported results. Finally, ethics frameworks for human research already address all three value principles for the same moral reasons. The Declaration of Helsinki, for example, includes registration (article 35) and reporting (article 36) as obligatory principles.[14] The widely acknowledged framework for clinical research 'What makes clinical research ethical' from Emanuel *et al* highlights robustness (scientific validity) as one of the basic ethical principles.[15]

hoW do We implement the neW 3rs in Current prACtiCes?

The reporting principle is relatively easy to implement. Beside standard peer-review journals, new publication formats allow accessible reporting of all types of research results, including null and negative results, such as preprint servers (eg, bioRxiv), Open Access journals (eg, BMJ Open Science, PLoS One), journals with postpublication review (eg, f1000research) or data repositories (eg, Open Science Framework, Dryad, figshare). Adherence to reporting guidelines, such as ARRIVE,[7] further aims to improve the evaluation and utilisation of study results. Several leading research funders such as the Wellcome Trust, the Horizon 2020 programme or the Bill and Melinda Gates Foundation just recently signed the WHO Joint Statement and thus indicated to make reporting requirements a part of funding decisions for clinical trials.[16] Similarly, ethics review and funding of individual animal studies could implement a requirement for timely and non-selective results reporting and evaluate compliance.

Dedicated tools for implementing the registration principle in animal research equivalent to registries for human studies (such as ClinicalTrials.gov) have already been launched by academic initiatives (eg, www.preclinicaltrials.eu) or just recently by a governmental organisation (www.animalstudyregistry.org). These platforms allow swift protocol registration with an embargoing option for several years. The registration principle will increase the value of research but how will it affect the efficiency of animal research? In a recent study, experts from all relevant stakeholder groups in animal research expressed their attitudes on potential strengths and weaknesses of animal study registries.[17] Some highlighted their concerns that animal study registration might aggravate administrative burdens and the theft of ideas. Others emphasised the opposite viewpoint that improved transparency via such registries might ultimately make animal research more efficient.

The robustness principle is more difficult to implement: How can we gauge robustness of individual animal studies? More specifically: When is sample size calculation or blinded outcome assessment necessary? How can the external and construct validity of individual studies be improved? Recent expert proposals to better distinguish between exploratory and confirmatory study designs in animal research have provided preliminary answers.[18 19] Initial guidance on how to implement a more systematic assessment of animal study robustness in standard review procedures was recently published by Würbel.[20] Würbel distinguishes three dimensions of validity (internal, external and construct validity) and recommends assessing each dimension within the harm–benefit analysis for individual animal studies. With this proposal, he is in line with recent guidance from Kimmelman on how to assess the validity of animal studies within approval procedures for phase I/II clinical trials.[21] Assessing robustness of individual studies requires complex judgements. Ethics review boards for animal studies, however, already require complex judgements regarding the welfare principles, and in many jurisdictions, already consider a study's robustness. Even Russel and Burch already included a section on 'The Design and Analysis of Experiments' in the chapter explaining the Reduction principle.[1] They emphasise the importance of statistics to determine the minimum number of animals needed for an experiment and they mention sequential analysis and randomisation as further means to reduce uncontrolled variance. They do not emphasise, however, robustness or scientific value as a principle in itself and they do not mention further measures to improve robustness such as blinding of outcome assessment.

In line with our recommendation to add guiding principles for scientific value to the ethical framework for animal research are recent activities from national centres for the 3Rs such as the UK National Centre for the Replacement Refinement & Reduction of Animals in Research (NC3Rs) or the German Centre for the Protection of Animals in Research (Bf3R). Both already promote the new 3R principles for scientific value in several ways. The revised NC3Rs guidelines for primate research, for example, explicitly require robustness and reporting.[22] The new NC3Rs Experimental Design Assistant (EDA) not only supports the development of robust study protocols but also allows to timestamp the resulting

protocols. With the option to make such timestamped protocols publicly available, the EDA facilitates preregistration of protocols on a voluntary basis.[23] In January 2019, Bf3R launched their Animal Study Registry. We very much welcome these recent developments but want to highlight that they do not derive directly from any of the three animal welfare principles. They make sense only when considering scientific value as a complementary set of ethical principles.

'rhumbA of rs'?

In the previous sections, we already commented on potential counterarguments against the introduction of a complementary set of 3R principles. These counterarguments addressed the relevance or implementability of registration, robustness, or reporting in a direct way. Another type of counterargument is more indirect: Does it make sense at all to add new R principles? At least two arguments were raised in our discussions with colleagues and reviewers: first, other papers already and unsuccessfully proposed new Rs such as Responsibility, Reproducibility or Rigour. These contributions did not impact on animal research but rather heat up a rhumba of Rs.[24] We think that former proposals of new Rs were unsuccessful because they were circular, too broad, or did not provide direct guidance. Responsibility as an R principle is clearly circular, as it cannot specify how to act responsibly. Reproducibility as an R principle does not provide direct guidance. It is a desired characteristic of animal research that strongly depends on robustness and non-selective reporting. Rigour as an R principle is too broad, at least in its current use. Rigour is often used interchangeably with scientific value as it comprises robustness, non-selective reporting and could also comprise registration.

The second counterargument against any modification of the 3R framework is based on the assumption that the current 3R framework is a strong concept especially because it is established all over the world. Adding new Rs bears the risk to dilute this widely accepted concept, ultimately leading to a weaker protection of animal welfare. However, we do not find it plausible to believe that a consistent set of three new guiding principles that all centre around the complementary basic principle of scientific value will dilute the very distinct basic principle of animal welfare. In contrast, we posit that the relatively narrow focus of the current 3R approach contributed to the fact that animal research often lacks scientific value.

summAry

Animal research is ethical only when it is of scientific and social value. The past years have demonstrated that this value of animal research and thus its capacity to improve human health are threatened by a lack of robustness and biased or unreported results. Three ethical principles (*R*obustness, *R*egistration and *R*eporting) help to safeguard the value of animal research. The current, widely established ethical framework for animal research (3Rs=*R*eplacement, *R*eduction and *R*efinement) misses this value dimension by solely focusing on the equally important animal welfare dimension. We recommend complementing the current 3R framework (for animal welfare) with the second set of 3Rs (for scientific value). Regulators, ethics boards, scientists and funders should add robustness, registration and reporting to their criteria when planning, licensing or funding animal experiments. Guidances such as the Basel Declaration should consider making the normative framework for animal research more comprehensive and coherent.[25] National centres for the 3R should consider revising their branding and explicitly addressing the ethical rationale underlying their recent policies for registration, robustness and reporting. To this end, a multistakeholder discourse and decisions are needed to (1) conceptualise the specifics of robustness, (2) develop frameworks detailing the mandatory information that is being registered as well as acceptable embargo periods, (3) clarify funding and approval requirements related to results reporting and (4) determine relevant responsibilities, competencies and legislation for auditing 6R compliance.

funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests DS is an associate editor and UD an editorial advisor, BMJ Open Science.

provenance and peer review Not commissioned, externally peer reviewed.

data availability statement All data relevant to the study are included in the article.

open peer review Prepublication and Review History is available online at http://dx.doi.org/10.1136/bmjos-2018-000048.

referenCes

1. Russell WMS, Burch RL. *The Principles of Humane Experimental Technique*. London: Methuen, 1959.
2. RSPCS, LASA. Guiding principles on good practice for Animal Welfare and Ethical Review Bodies. A report by the RSPCA Research Animals Department and LASA Education, Training and Ethics Section. 2015 http://www.lasa.co.uk/PDF/AWERB_Guiding_Principles_2015_final.pdf.
3. Vogt L, Reichlin TS, Nathues C, *et al*. Authorization of Animal Experiments Is Based on Confidence Rather than Evidence of Scientific Rigor. *PLoS Biol* 2016;14:e2000598.
4. Macleod MR, Lawson McLean A, Kyriakopoulou A, *et al*. Risk of Bias in Reports of In Vivo Research: A Focus for Improvement. *PLoS Biol* 2015;13:e1002273.
5. Sena ES, van der Worp HB, Bath PM, *et al*. Publication bias in reports of animal stroke studies leads to major overstatement of efficacy. *PLoS Biol* 2010;8:e1000344.
6. Mueller KF, Briel M, Strech D, *et al*. Dissemination bias in systematic reviews of animal research: a systematic review. *PLoS One* 2014;9:e116016.
7. Kilkenny C, Browne WJ, Cuthill IC, *et al*. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. *PLoS Biol* 2010;8:e1000412.
8. Holman C, Piper SK, Grittner U, *et al*. Where Have All the Rodents Gone? The Effects of Attrition in Experimental Research on Cancer and Stroke. *PLoS Biol* 2016;14:e1002331.

9. Begley CG, Ellis LM. Drug development: Raise standards for preclinical cancer research. *Nature* 2012;483:531–3.
10. Prinz F, Schlange T, Asadullah K. Believe it or not: how much can we rely on published data on potential drug targets? *Nat Rev Drug Discov* 2011;10:712.
11. Wieschowski S, Chin WWL, Federico C, *et al*. Preclinical efficacy studies in investigator brochures: Do they enable risk-benefit assessment? *PLoS Biol* 2018;16:e2004879.
12. Kimmelman J, Federico C. Consider drug efficacy before first-in-human trials. *Nature* 2017;542:25–7.
13. Kilkenny C, Parsons N, Kadyszewski E, *et al*. Survey of the quality of experimental design, statistical analysis and reporting of research using animals. *PLoS One* 2009;4:e7824.
14. World Medical Association. *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*: Fortaleza, 2013.
15. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 2000;283:2701–11.
16. WHO. Joint statement on public disclosure of results from clinical trials. 2017 www.who.int/ictrp/results/jointstatement/en/.
17. Wieschowski S, Silva DS, Strech D. Animal study registries: results from a stakeholder analysis on potential strengths, weaknesses, facilitators, and barriers. *PLoS Biol* 2016;14:e2000391.
18. Kimmelman J, Mogil JS, Dirnagl U. Distinguishing between exploratory and confirmatory preclinical research will improve translation. *PLoS Biol* 2014;12:e1001863.
19. Mogil JS, Macleod MR. No publication without confirmation. *Nature* 2017;542:409–11.
20. Würbel H. More than 3Rs: the importance of scientific validity for harm-benefit analysis of animal research. *Lab Anim* 2017;46:164–6.
21. Kimmelman J, Henderson V. Assessing risk/benefit for trials using preclinical evidence: a proposal. *J Med Ethics* 2016;42:50–3.
22. NC3R. Non-human primate accommodation, care and use. 2017 https://www.nc3rs.org.uk/sites/default/files/documents/Guidelines/NC3Rs%20guidelines%20-%20Non-human%20primate%20accomodation%20care%20and%20use.pdf.
23. du Sert NP, Bamsey I, Bate ST, *et al*. The Experimental Design Assistant. *Nat Methods* 2017;14:1024–5.
24. Steward O. A Rhumba of "R's": Replication, Reproducibility, Rigor, Robustness: What Does a Failure to Replicate Mean? *eNeuro* 2016;3.
25. Basel Declaration Society. Basel Declaration. 2010. available at https://www.basel-declaration.org/basel-declaration/.

Ethics and Genetics Research

Effy Vayena

Required Reading

Susan M. Wolf, “Return of individual research results and incidental findings: facing the challenges of translational science,” Annual review of genomics and human genetics 14 (2013): 557-77. doi:10.1146/annurev-genom-091212-153506

Mark Sheehan, et al., “Can Broad Consent be Informed Consent?,” Public health ethics, vol. 4,3 (2011): 226-235. doi:10.1093/phe/phr020

Can Broad Consent be Informed Consent?

Mark Sheehan*, Oxford BRC Ethics Fellow and James Martin Research Fellow, Oxford NIHR Biomedical Research Centre, the Ethox Centre and the Institute for Science and Ethics, University of Oxford

*Corresponding author: Mark Sheehan, Department of Public Health and Primary Care, The Ethox Centre, University of Oxford, Old Rd Campus, Badenoch Building, Headington, Oxford OX3 7LG, UK. Tel.: +44 (0) 1865 287848; Fax: +44 (0) 1865 287884; Email: mark.sheehan@ethox.ox.ac.uk

In biobanks, a broader model of consent is often used and justified by a range of different strategies that make reference to the potential benefits brought by the research it will facilitate combined with the low level of risk involved (provided adequate measures are in place to protect privacy and confidentiality) or a questioning of the centrality of the notion of informed consent. Against this, it has been suggested that the lack of specific information about particular uses of the samples means that such consent cannot be fully autonomous and so is unethical. My answer to the title question is a definite 'yes'. Broad consent can be informed consent and is justified by appeal to the principle of respect for autonomy. Indeed, I will suggest that the distinction between the various kinds of consent is not a distinction between kinds of consent but between the kinds of choice a person makes. When an individual makes a choice (of any kind) it is important that they do so according to the standards of informed consent and consistent with the choice that they are making.

Can Broad Consent be Informed Consent?

On the face of it biobanks offer a great deal of hope for the future progress of medical science (Oosterhuis *et al*., 2003; Hansson *et al*., 2006; Helgesson *et al*. 2007; Christensen, 2009). As repositories for various kinds of human biological collections, they can contain a broad range of material including DNA, tissue, tumour samples or blood. They are also likely to include linked clinical and/or phenotypic data on the donors of the samples so that the potential for useful, patient-related research is maximized. Though their specific purposes can vary widely the broad point of biobanks is to house and facilitate on-going research on samples that have already been collected. If the potential that is claimed for them is to be realised, biobanks need to be organized in such a way that their promise has the best chance of being fulfilled and that the individual rights and choices of the research partici- pants are respected as much as is possible. A good deal of this respect is shaped at the point of entry to the biobank in the form of the consent process.

Most easily, when we think of informed consent to participate in research we imagine being very specific about the nature of the research and of the participant's involvement in it.[1] This involves providing specific information about the nature of the research, who will be conducting it and what the specific anticipated outputs are. Quite clearly, however, this model of specific consent runs counter to the aims of broad, future-oriented collaborative research that might form part of the purpose of a biobank. In biobanks, a broader model of consent is often used and/or justified by a range of different strategies which make reference to the potential benefits brought by the research it will facilitate combined with the low level of risk involved (provided adequate measures are in place to protect privacy and confidentiality) or a questioning of the centrality of the notion of informed consent (Eriksson and Helgesson, 2005; Barr, 2006; Brekke and Sirnes, 2006; Hansson *et al*., 2006; Helgesson *et al*., 2007; Helgesson, 2008; Caulfield and Weijer, 2009; Otlowski, 2009; Hoppe, 2011). Against this, it has been suggested that the lack of specific information about particular uses of the samples means that such consent cannot be fully autonomous and so is unethical (Caulfield *et al*., 2003; Arnason, 2004; Hofmann, 2008, 2009; Hofmann *et al*., 2009).

My answer to the title question is a definite 'yes'. Broad consent can be informed consent and is justified by appeal to the principle of respect for autonomy. Indeed, I will suggest that the distinction between the various kinds of consent (broad, narrow/specific and open/blanket) is not a distinction between kinds of consent but between the kinds of choice a person

doi:10.1093/phe/phr020
Advance Access publication on 3 August 2011

makes. When an individual makes a choice (of any kind) it is important that they do so according to the standards of informed consent and consistent with the choice that they are making.

The plan in what follows is to first get clear about the concepts at issue. In this respect, I give an account of what I mean by broad consent as it applies in the context of biobanks. I will also give a brief account of the nature of informed consent and its ethical justification. This part of the article will cover familiar terrain but will highlight those aspects of these concepts that are relevant to the question at hand. The second part of the article considers the scope of decisions that we might legitimately—that is, autonomously—make with specific reference to an example that is analogous to broad consent in the biobank context. The third part of the article considers arguments about the right to genetic ignorance. If, as some have argued, there is no right to genetic ignorance—there is no right not to know—this might be used to undermine the ethical legitimacy of broad consent. In the final part of the article, I will consider two objections to my position.

The Nature of Broad Consent

Here, I will understand broad consent to encapsulate consent to a range of different kind of conditions. Perhaps the clearest and most distinct of these is consent to a particular kind of governance arrangement (Arnason, 2004; Kaye, 2004; Knoppers, 2005; Rothstein, 2005; Hansson, 2006; Wendler, 2006; Laurie, 2009; Hunter and Laurie, 2009). That is, when an individual gives 'broad consent' to the use of their sample or data in future research they are giving permission for someone else, usually in the form of the governing body of the biobank, to decide how to use that sample or data. Broad consent though can cover and include other elements besides consent to governance. Consent to governance is an important element to include in an account of broad consent because it helps us to isolate the kind of decisions involved. Other features that we might include here are an account of a general program of research, an account of the general goals of research or an account of the institutional values and aspirations of the biobank.

When we include reference to the governance arrangements in broad consent we acknowledge the importance of how future decisions will be made. When we include an account of the general program of research we acknowledge that in some contexts and for some biobanks the type of research conducted will be more focussed. For the broadest biobanks, like UK Biobank and other population biobanks the program of research may only be specifiable very generally if at all. In such cases, the broad consent may include reference to the goals of the research that will be conducted using the resources of the biobank or an account of the institutional values and aspirations. Overall, I will understand these four general kinds of consent contents as being elements of broad consent.

I will take it here that the inclusion of an element of consent to a process of governance is an important feature of broad consent though not, given the range of definitions of governance, a necessary one. Crucially, this element does not clearly separate broad consent from open consent—we can easily imagine cases in which there was a process of governance but that it was so minimal as to permit almost any kind of research: 'You give me your sample and I decide what research it would best serve'. The underlying point here is that the distinction between broad and open consent is probably impossible to draw. My main concern in what follows is to distinguish between narrow consent and the range of consents between broad and open. I will have something to say at the end of the last section about how we might settle the kind of information that it might appropriate to provide in the range of cases between broad and open consent.

Unsurprisingly, broad consent is not an ideal term for this process but it does make some sense. Arguably, the sense the term makes is connected to the breadth of research projects that are and will be included under the auspices of the biobank. It is unclear however that it does justice to the full and complex range of elements mentioned above. In any case, I am more concerned with the content of the kind of consent than with the terminology. I am particularly concerned to distinguish the category of broad consent, understood as described above, from specific or narrow consent.

Informed Consent

Countless pages have been written about the nature and justification of informed consent, the specifics of which are not relevant here. On the standard understanding, the important elements of informed consent are the provision of information, the voluntariness of the choice and the competence of the chooser to make the choice—so the potential research participant should be provided with information relevant to the decision to participate, they should be able to choose freely about their participation and they should be competent to decide

(Allen and McNamara, 2011). There are two key elements of the standard account that are worth emphasizing here. First, when we speak of obtaining informed consent we are invoking a process in which the potential research subject is, among other things provided with information of various sorts about the research and asked to make a decision about entering the trial (Cambon-Thomsen, 2004). The emphasis here is rightly on the decision, one way or the other, to be a part of the research. Second, when considering the proper provision of information it is not enough that the prospective research subject is given the information. There should be some allowance or provision for understanding (Allen and McNamara, 2011). What matters is that the decision is informed by the relevant details of the research and that the individual chooser comprehends and assimilates them into their own set of values, desires and preferences. Again, a good deal has been written about the amount and specificity of the information that is required—the material relevance requirement is here intended to be a version of the subjective standard of information provision (Hoeyer, 2008). In sum, it is important to bear in mind that 'giving informed consent to X' is in certain respects shorthand for 'making a decision, with appropriate understanding, to X'.

In the context of consent to participate in a biobank much of the discussion revolves around the amount of information that is given (and indeed can be given) to prospective participants. The general worry is that the details of the research are unknown at the time of donation so the donor cannot be informed about the precise nature of the research in which they (and their samples) are involved. Importantly, at the time of donation the information about future research is not available and so cannot be disclosed (Allen and McNamara, 2011). The research participant then, does not know the relevant facts of the specific research and so does not know to what they consent. This is the fundamental objection to broad consent to participate in a biobank (and one which the argument of this article directly addresses).

The primary justification of the requirement to obtain informed consent is respect for autonomy (O'Neill, 2002; Beauchamp and Childress, 2008; Kihlbom 2008). On the standard understanding of autonomy as the capacity for self-governance, the general idea is that an individual's capacity to govern their own life is of significant value and worthy of respect. That is, we attribute moral worth to the individual's ability to determine the shape and course of their lives—from the very general, 'policy' decisions to very particular preferences and whims (Manson and O'Neill, 2007). Since we attribute value to the capacity to make these decisions, asking the individual to choose whether or not to participate in research amounts to the proper respect of this capacity. It is crucial that the capacity that is being respected, the capacity for autonomy, is a general decision-making one that applies just as much to the very important 'life' decisions that a person makes as it does to particular, local decisions about daily life choices.

The moral obligation to obtain informed consent can also be justified by appeal to a concern for the welfare of the research participant. That is, by asking the individual to decide whether to participate we allow them assess and value the various risks and benefits by their own lights, thus generally achieving a better, more personalised assessment of the risk of harm balanced against the potential benefits. However, if we were primarily concerned with protecting people from harm then sometimes, perhaps often, we would ignore what they actually want precisely because it is harmful (e.g. smoking, drinking, etc.). In the research context, informed consent most clearly functions precisely to enable individual participants to choose to take on certain risks for the sake of the possible benefits and according to their own plan of the course of their lives (Edwards *et al*., 2004). Thus in research, the requirement to obtain informed consent is not primarily justified by the need for protection from harm or risk of harm, but by the requirement that we respect autonomy.

The Scope of the Choice

What is important about the respect for autonomy justification and the corresponding idea of self-governance is that it does not specify anything about the scope of the choices and decisions that an individual is entitled to make about the way in which they govern their life. Indeed 'governing' here involves 'laying down laws' to oneself at all levels not just making first order decisions. Indeed the various levels of choices that individuals might legitimately and actually make can be seen in discussions of weakness of will and addiction. In particular, the idea of second order desires to desire discussed by Frankfurt and others provides us with clear examples of precisely the kind of orders of decisions at issues here (Frankfurt, 1971). A person may decide that they do not want to eat cake and adopt a strategy which takes away the possibility of choice or, more simply, they may decide to decide not to eat cake any more. Two other more complex examples of choices of this kind are

career decisions and long-term relationship commitments like marriage. One might argue that the kind of choice that one makes in relationships like marriage is a choice to commit—a choice to continue to choose in particular ways. But even if this is not the case, the commitment to a marriage looks like a decision about, among other things, future choices. Moreover, these decisions look to be perfectly normal and reasonable decisions made by autonomous agents with full information relative to the kind of decision being made. Autonomy, here understood as self-governance, and its moral significance entitles an individual to make decisions, to make decisions about the kind of decisions they make, to decide about the way in which they make decisions and to decide not to make some decisions.

It is important to notice that these future-choice limiting or determining choices are not necessarily liberty restricting (Hofmann, 2008). In many cases, they simply change the range and nature of the choices that the individual will make. There are clearly cases where autonomous decisions that individuals make *do* restrict their future liberty. The case of Ulysses and the Sirens is a pertinent one: Ulysses' choice to be bound to the mast restricted his liberty to act when he heard the Sirens (Elster, 2000). Buying a house is an interesting example here. In some cases buying a house can be liberty restricting (no longer having the money or the same degree of freedom to move) but it need not. I may buy a house just because I wish to make a commitment to living in a particular area and no longer wish to have to make decisions about housing. These latter decisions do not undermine my actual capacity for autonomous decision making in the future irrespective of whether they restrict my liberty. Instead the decision to commit to living in area is an autonomous decision about the kinds of decisions that I am prepared to make in the future.

A useful way to see how the distinction between levels of decision works in the case of biobank consent is to consider an analogous case of broad consent. Fred is at a restaurant with a number of colleagues. Without having seen the menu, he gets called away to the telephone. He asks one of his dinner companions to choose from the menu for him. A brief discussion ensues about the general kind of food that he would like and any immediately obvious dietary or taste restrictions. Fred's companion orders his meal. Of course the idea is that Fred's decision is a perfectly ordinary one which plainly illustrates the exercise of autonomy and is analogous to broad consent to participate in a biobank.

There are various ways in which we can adjust this example to make it more specifically like broad consent in the biobanks case: for example, the designated companion might agree with Fred that he will consult with the other companions in the process of deciding (we could even suggest that in cases of dispute that all companions will vote)—this parallels the idea of consent to governance (Kaye 2004; Laurie 2009; Hunter and Laurie 2009). Fred's companion might also suggest some mechanism for handling the case where he orders someone that Fred doesn't want: it might be agreed that Fred can withdraw from the arrangement and that the companion will eat the food or it will be sent back—this parallels considerations about withdrawal from a biobank and the mechanisms for doing so (Eriksson and Helgesson, 2005). Finally, it might also be in the (collective) interest of the whole party that this person (or indeed any person) decides for Fred, in this way the whole party can expect to eat sooner (Hansson *et al*., 2006; Christensen 2009).

On the face of it then, there is nothing in the justification of the requirement to obtain informed consent that implies that the nature of the choice must be limited or restricted. There is certainly nothing that requires only specific consent—indeed, the idea that it could require such a thing looks unintelligible. Further, there are plenty of straightforward decisions that autonomous people make regularly that are decisions about future decisions that are analogous to the broad consent decision to participate in a biobank.

The Right Not to Know

Having made this very general claim, we can quickly see that there might be some important exceptions. There do look to be some kinds of choices that we generally think individuals are unable to make autonomously or at least, that give us pause for thought. The decision to give up all future choices or to sell oneself into slavery, look to be decisions that are in some way inconsistent with the nature of autonomy, properly understood.[2] We might also suspect that the concept of autonomy is more closely connected to an idea of rational valuing, so that there are some things that that one cannot autonomously value (Rhodes, 1998; O'Neill, 2002; Manson and O'Neil, 2007). On this view, decisions that aim at the fulfilment of these goals cannot be autonomous. One example that has received some discussion in the literature is the decision to remain ignorant about important genetic information about oneself—say, whether or not I carry a specific gene for a devastating disease, in the light of evidence that it is in my family.

Connecting this set of exceptions to the biobank context is, I take it, the best hope for a defence of the claim that broad consent is not informed consent. Such a connection proceeds by claiming that the decision involved in broad consent is just like the decision to give up all future choices or the decision not to know that I will develop a devastating genetic condition. Understanding these exceptions and possibility of a connection to the biobank context, involves reflecting on the arguments about the existence of a right not to know.

Much of the discussion about the existence of a right not to know occurs in the context of personal genetic information—hence, the right to genetic ignorance (Wilson, 1998). The question in this literature is whether it is justified to remain ignorant about certain (presumably important) genetic information about oneself. One immediate and perhaps relevant difference here is that the genetic information and the ability to retrieve it, already exists at the time of the choice. This is very often not the case in biobanks (Allen and McNamara, 2011). At the time of consent (just as at the time of delegation in the restaurant case), the actual research uses of the donated material are not determined.

An initial form of the argument here is that autonomy requires information, so decisions made without information are not autonomous and are not worthy of respect.[3] Someone who does not have the relevant genetic knowledge cannot make autonomous decisions. Of course, put in this way, the argument has the absurd consequence that the restaurant case provides us with an example of a non-autonomous decision.[4] The arguments here are more subtle that this suggests but there does remain a puzzle about ordinary cases like the restaurant case. Harris and Keywood point out that 'patients should be provided with an appropriate level of information to enable them to operate as rational "choosers"' (Harris and Keywood 2001: 422) where, clearly, knowing important genetic facts about oneself is taken to be an important part of being a rational chooser.

There are two key arguments that are presented by opponents of the right to genetic ignorance: (i) that ignorance (and specifically this kind of ignorance) is contradictory to autonomy and (ii) that autonomously deciding to take certain risks is irresponsible (i.e. deciding not to know certain things is irresponsible).[5] Harm to others is sometimes taken to a factor here, but we must be careful about how it features in relation to the arguments at issue here. Although it may be an important ethical issue in general, it is not relevant here because such harms would be candidates to overrule autonomous decisions not to show that they were not autonomous.

In terms of the irresponsibility of decisions to take on certain risks, even if it can be shown that some decisions fail to be autonomous on the grounds that they are irresponsible, it is hard to see how these risks are involved in the decision to participate in a biobank. We should of course be careful here about the judgement of responsibility. There might be certain situations in which deciding not to decide is irresponsible but where the decision is an autonomous one: autonomous individuals can make irresponsible and yet autonomous decisions.

So how might the contradiction argument play out? There are interesting difficulties that arise from cases like the deciding never to decide kind of case. The particular account of autonomy will in large part determine what counts as contradictory. It is also a distinct possibility that a contradiction is practically impossible. It is hard to imagine how the decision never to decide could be actualized without some liberty-limiting enforcement mechanism. But then the problem looks to rest with the mechanism rather than the decision—we ought not to limit our own decisions in this way (cf. Suicide or slavery). But a problem with the mechanism is not a problem with the exercise of autonomy. Instead, the contradiction argument reduces to the irresponsibility claim—it is not that the decisions in question fail to be autonomous, they fail to be worthy of respect.

Any account should do justice to common intuitions about or instances of what might count as rational choosing. I take it that the restaurant case is one such case. I also take it that this case points to a class of cases where we legitimately and autonomously decide not to decide or to defer decision. There are many other examples where we adopt a policy that means that others decide on our behalf (that is, without us having full information about all decisions). Of course, this does not rule out the idea that some decisions not to decide do undermine our ability to be rational choosers (selling oneself into slavery being one). I suspect that there are various relevant criteria that might be helpful here which guard against certain levels of harm and against basic incoherencies and that these criteria that are at issue in the debate about genetic ignorance. Broad consent to participate in a biobank reaches neither of these levels: it does not involve the levels of expected harms or failures of obligation to others of the significance of those being discussed in the genetic knowledge

case and nor does it involvea basic inconsistency of the kind involved in deciding never to decide.

Overall, the important distinction that I have suggested here is that between kinds of decisions (or the scope of the choice). This matters because if the decisions are of a different kind then the knowledge that is appropriately possessed by the decider in order to make such decisions autonomously is also different. So it is true that Fred cannot autonomously decide what to order for dinner because he does not have the appropriate information about the options. However the decision that matters here is of a different order—it is the decision to delegate decision making (about what to order). The information that is appropriately required to make this decision an informed one is not the same as the first order decision (deciding what to order). Here the relevant information is about the designated companion and the decision making process that will be used.

The force of this distinction is that it avoids the debate about the right not to know. The broad consent case is not one where a right not to know is being asserted, instead a different kind of decision is being made with entirely the appropriate level of information to make it an informed and so autonomous decision.

Objections

In this final section, I will consider two objections to the account and justification of broad consent as informed consent that I have outlined above. The first targets the analogy between the restaurant case and broad consent to participate in a biobank. The second suggests that my arguments are too strong and equally justify open or blanket consent.

The first objection targets the analogy between the restaurant case and broad consent to participate in a biobank. It might be objected that the restaurant example is importantly different from the biobank case and so cannot play the analogical role that I have given it.[6] The particular feature that is important here and which undermines the analogy is the role of the interests of the individual in each case. In therestaurant example we presume that the designated companion will choose an option that is, in his opinion, something that Fred will like and perhaps would choose himself—i.e. the designated chooser's goal is centrally taken to revolve around Fred's interests. In the biobank context this is not the case. Very clearly the biobank primarily serves the public interest and if any other interests are involved these are likely to include those of the individual researcher accessing the biobank and, depending on the governance arrangements, commercial interests. The individual donor's interests will be served primarily insofar as they are included in the public interest. Notice that in the restaurant case, Fred's interests may not always trump other considerations. The designated chooser might decide against ordering one of Fred's favourite dishes, the soufflé, on the grounds that it would delay everyone else's meal. Overall though, the point stands: the restaurant case is to be distinguished from the biobank case because the designated chooser is charged primarily with making a decision that is in the interests of the absent individual.

There are two points to make in response to this concern. First, this objection slightly misses the point of the analogy. The main thrust of the example is to demonstrate an overall kind of autonomous decision, namely, decisions to allow others decide. So although the nature of the decision to be made by the delegated chooser is different, the decision to delegate is of the same form. Moreover, the extensions to the restaurant case (which make it closer to the biobank situation) illustrate the kinds of information that might be important for the agent's decision to delegate. Second and perhaps most importantly, it is unclear what follows about my argument from this observation. Even if we think that the fact that the biobank-related decisions are ruled out as unethical because they are not in the donor's best interests, this is distinct from claims about whether the donor's decision to participate was autonomous. There are a whole range of motivations that an agent may autonomously have only one of which is their own best interests. I may for instance autonomously choose to behave in a way that will benefit others or I may do something because I think it is worthwhile or of value independently of the consequences. In each of these cases, my choice remains autonomous and, on the face of it, worthy of respect. It may be, of course, that the decision that I make is not in my best interests and may be overruled on paternalistic grounds. What matters here is that the decision made by the person delegating their future decisions is motivated by something that they value. Over and above this feature of autonomous decision making, the role played by best interests is separate from questions about the agent's consent.

A second way in which the restaurant decision differs from the biobank one is that the decision in the restaurant case is a one-off decision but the biobank decision is not. So when an individual agrees to participate in a biobank there samples are used multiple times for different research projects. Thus the biobank case is more akin to a case in which Fred agrees, for a certain

membership fee, to be a part of a diners club in which he will have no say in what food is served to him but where he is given information about the committee making the decisions and the kind of principles that govern their decisions.[7] Again this poses no problem for the analogy properly understood. The restaurant case provides an illustration of a kind of decision—the decision to allow others to decide (or the decision not to decide)—that can be autonomous and is dependent on the provision of a different sort of information. This dining club case alternative is another illustration of the kind of decision with the details adjusted to fit a different aspect of the biobank case.

A second objection claims that my defence of broad consent is too strong—it justifies open or blanket consent as well as broad consent. Indeed, it looks as though any kind of consent follows from this argument. So whereas I set out to show that broad consent is informed consent, I have produced an argument that shows that open or blanket consent can count as informed consent also.

In responding to this objection, we first need to be clear about the way in which the justifications function. There is always the possibility that the individual can opt out of taking in the information—by not reading it, by not paying attention, or by bluffing in some way about their knowledge. There is, to this extent, a certain amount of liberty that is maintained in the consent process irrespective of the kind of consent. Questions about when we might be entitled to restrict an individual's liberty in these cases will take us back to the issues about the relationship between the obligation to respect autonomy and the obligation to promote or to ensure maximal autonomy—specifically, under what circumstances we are justified in preventing an individual from exercising their liberty in this respect.

With this in mind, it is indeed true that the general form of my argument applies equally to open or blanket consent cases. That is, there do look to be cases where an individual can autonomously decide to allow anything at all to be done with their tissue. These will be cases where for example the relevant details are of no significance—say for a general type of research that the individual wholeheartedly supports and where there is complete anonymisation. Overall this is not surprising. My argument is primarily one that shows that specific consent is not the only morally legitimate form of informed consent and as such it argues that broad consent can be informed consent. I have not here been concerned to separate morally broad consent from open consent.

The argument that is required to show that broad consent is preferable to or more justified than open consent has a very different form and is outside the scope of this article. However, the main issue is about how biobank institutions ought to structure the consent process rather than what forms of consent are legitimate. The focus, then, is on what is a fair and legitimate process would be all things considered. Part of this argument will mimic the arguments given in the case of specific consent for the level of information that is required. So the information provided should include all relevant information that is material to the decision in questions—that is, the decision to allow someone else to decide. The other part of the argument will involve claims about how research should be conducted and, specifically, governed, in our society. I take it that there are substantial benefits to be accrued through the conduct of research and that biobanking may well assist in delivering these benefits. I also take it both that individuals are largely capable of and entitled to make their own decisions about participating in research but that society has a responsibility to ensure that the institutions supporting research are constructed to provide an appropriate degree of protection. These arguments require special attention but together, in my view, they form the outline of an argument which shows that broad consent in preferable to open consent to participate in a biobank.

Conclusion

In this article, I have argued for a view of the kind of decision involved in consenting to participate in a biobank that differs from a very significant proportion of the literature on the ethics of broad consent. Typically, the debate takes broad consent to be a lesser form of consent largely because it is undertaken without information about the specific research that will be conducted using the biobank's samples. This understanding has led to a marked split in the literature. In generalized terms, one side of this split maintains the over-riding ethical importance of the principle of respect for autonomy and its requirement of fully informed consent. Consequently, because broad consent is not fully informed, it is ethically problematic. The other side of this split broadly suggests that the principle of respect for autonomy and its requirement of fully informed consent can sometimes be justifiably weakened (or sacrificed altogether) in cases of minimal risk and/or significant public benefit. There is clearly scope for disagreement here about the level of risk and the

significance of the benefits associated with biobanks and so whether the deficiencies of broad consent are justified, but in principle such trade-offs can be ethically legitimate. In short, both sides take broad consent to be deficient.

The position articulated here suggests that broad consent involves a different kind of decision, a decision to allow others to decide, and correspondingly involves a different sort of information from that required for other kinds of decision. Broad consent, as described here, provides the appropriate information for the kind of decision involved and so counts as informed consent for those decisions. Just as I am justified in deciding to allow my dinner colleague to order my meal for me, so, broad consent is an acceptable form of consent to participate in a biobank. Even if we do think that the nature of autonomy is such as to make certain kinds of choices unintelligible or autonomy-defeating, these will not extend to the decision involved in broad consent to participate in a biobank.

Acknowledgements

The author is grateful for support from the Oxford NIHR Biomedical Research Centre. Thanks also to Nils Hoppe for his insightful comments on an earlier draft. Finally, thanks to two anonymous referees for this journal for their helpful comments.

Funding

This work was supported by the National Institute of Health Research through the Oxford Biomedical Research Centre.

Notes

1. In what follows I refer to informed consent rather than to valid consent. I take it that information provision (and hence informed consent) is one component of valid consent and that valid consent is the more accurate, morally significant term. However, the literature on the topic of broad consent in couched in terms of informed consent and, here, the focus is primarily on the informational element of the consent process.
2. I realize that that the more standard legal interpretation of this is that the reason we cannot sell ourselves into slavery is that we do not own our bodies. This has always seemed an odd construction when extended to ethics. Understanding this to be a case where one cannot autonomously choose seems more satisfactory and makes it more like the decision to give up future choices combined with the liberty-restricting enforcement of that decision. Indeed one might think, contra Harris and Keywood (2001), that what makes the decision to enslave oneself problematic is not that contradicts autonomy in some way but that involves the imposition of a certain kind of liberty-denying enforcement. The newly enslaved individual remains perfectly capable of autonomous choice but is now denied the freedom to exercise that ability. In this respect, choosing slavery is distinct from choosing suicide since in the latter the person ceases both to be autonomous and to have the exercise of that ability denied (because they are dead). The immediate consequence of this is that one can on the face of it consent to being enslaved. Such slavery would then be wrong only when it ceased being voluntary—that is, when the enslaved individual autonomously chose not to accept the liberty restricting sanctions and those sanctions continued to be applied.
3. The principle of respect for autonomy implies an obligation to respect autonomous decisions of agents which in turn implies a right that one's autonomous decisions are respected. If a decision is not autonomous then correspondingly there is no right for that decision to be respected. If the decision is to remain in ignorant of certain facts and this is not autonomous, then, on this argument there is no right for this decision to be respected (Kihlbom 2008; Foster and Herring, forthcoming).
4. The absurdity is generated by my original supposition that the Fred's choice is both rational and autonomous. I have indicated why this is a plausible assumption to make, but it is of course possible to bite the bullet and insist that Fred has not made an autonomous decision.
5. Harris and Keywood (2001) insist that such decisions are 'inimical' to autonomy but fail to elaborate on the ways in which this is case. It seems to me that they may mean a combination of the two mentioned.
6. Thanks to Christian Lenk for pointing out this objection.
7. Thanks to an anonymous referee for this helpful example.

References

Allen, J. and McNamara, B. (2011). Reconsidering the Value of Consent in Biobank Research'. *Bioethics*, 25, 155–166.

Arnason, V. (2004). Coding and Consent: Moral Challenges of the Database Project in Iceland. *Bioethics*, 18, 2–49.

Barr, M. (2006). I'm not Really Read up on Genetics: Biobanks and the Social Context of Informed Consent. *Biosocieties*, 1, 251–262.

Beauchamp, T. and Childress, J. (2008). *The Principles of Biomedical Ethics*. 6th edn. Oxford: Oxford University Press.

Brekke, O. and Sirnes, T. (2006). Population Biobanks: the Ethical Gravity of Informed Consent. *Biosocieties*, 1, 385–398.

Cambon-Thomsen, A. (2004). The Social and Ethical Issues of Post-Genomic Human Biobanks. *Nature Review Genetics*, 5, 6–13.

Caulfield, T. and Weijer, C. (2009). Minimal Risk and Large-scale Biobank and Cohort Research. *Health Law Review*, 17, 2–3.

Caulfield, T., Upshur, R. E. and Daar, A. (2003). DNA Databanks and Consent: a Suggested Policy Option Involving an Authorization Model. *BMC Medical Ethics*, 4, E1.

Christensen, E. (2009). Biobanks and our Common Good. In Solbakk, J. H., Holm, S. and Hofmann, B. (eds), *The Ethics of Research Biobanking*. Dordrecht: Springer, pp. 101–114.

Edwards, S. J. L., Kirchin, S. and Huxtable, R. (2004). Research Ethics Committees and Paternalism. *Journal of Medical Ethics*, 30, 88–91.

Elster, J. (2000). *Ulysses Unbound: Studies in Rationality, Precommitment, and Constraints*. Cambridge: Cambridge University Press.

Eriksson, S. and Helgesson, G. (2005). Potential Harms, Anonymization, and the Right to Withdraw Consent to Biobank Research. *European Journal of Human Genetics*, 13, 1071–1076.

Frankfurt, H. G. (1971). Freedom of the Will and the Concept of a Person. *Journal of Philosophy*, 68, 5–20.

Foster, C. and Herring, J. (forthcoming). "Please don't Tell me": The Right not to Know. *Cambridge Quarterly of Healthcare Ethics*.

Hansson, M., Dillner, J., Bartram, C., Carlson, J. and Helgesson, G. (2006). Should Donors be Allowed to give Broad Consent to Future Biobank Research?' *Lancet Oncology*, 7, 266–269.

Harris, J. and Keywood, K. (2001). Ignorance, Information and Autonomy. *Theoretical Medicine and Ethics*, 22, 415–436.

Helgesson, G. (2008). Reply to: Bypassing Consent for Research on Biological Material. *Nature Biotechnology*, 26, 980–981.

Helgesson, G., Dillner, J., Carlson, J., Bartram, C. R. and Hansson, M. G. (2007). Ethical Framework for Previously Collected Biobank Samples. *Nature Biotechnology*, 25, 973–976.

Hoeyer, K. (2008). The Ethics of Research Biobanking: A Critical Review of the Literature. *Biotechnology and Genetic Engineering Reviews*, 25, 429–452.

Hofmann, B. (2008). Bypassing Consent for Research on Biological Material. *Nature Biotechnology*, 26, 979–980.

Hofmann, B. (2009). Broadening Consent – and Diluting Ethics? *Journal of Medical Ethics*, 35, 125–129.

Hofmann, B., Solbakk, J. H. and Holm, S. (2009). Consent to Biobank Research: One Size Fits All?' In Solbakk, J. H., Holm, S. and Hofmann, B. (eds), *The Ethics of Research Biobanking*. Dordrecht: Springer, pp. 3–24.

Hoppe, N. (2011). Risky Business: Re-Evaluating Participant Risk in Biobanking. In Lenk, C., Hoppe, N., Beier, K. and Wiesemann, C. (eds), *Human Tissue Research: A European Perspective on the Ethical and Legal Challenges*. Oxford: Oxford University Press, pp. 35–45.

Hunter, K. and Laurie, G. (2009). Involving Publics in Biobank Governance: Moving Beyond Existing Approaches. In Widdows, H. and Mullen, C. (eds), *The Governance of Genetic Information: Who Decides?* Cambridge: Cambridge University Press, pp. 151–177.

Kaye, J. (2004). Broad Consent – the Only Option for Population Genetic Databases? In Arnason, G., Nordal, S. and Arnason, V. (eds), *Blood and Data: Ethical, Legal and Social Aspects of Human Genetic Databases*. Reykjavı`k: University of Iceland Press, pp. 103–109.

Kihlbom, U. (2008). Autonomy and Negatively Informed Consent. *Journal of Medical Ethics*, 34, 146–149.

Knoppers, B. M. (2005). Consent Revisited: Points to Consider. *Health Law Review*, 13, 33–38.

Laurie, G. (2009). Role of the UK Biobank Ethics and Governance Council. *The Lancet*, 374, 1676.

Manson, N. and O'Neill, O. (2007). *Rethinking Informed Consent in Bioethics*. Cambridge: Cambridge University Press.

O'Neill, O. (2002). *Autonomy and Trust in Bioethics*. Cambridge: Cambridge University Press.

Oosterhuis, J. W., Coebergh, J. W. and van Veen, E. B. (2003). Tumour Banks: Well-Guarded Treasures in the Interest of Patients. *Nature Reviews Cancer*, 3, 73–77.

Otlowski, M. (2009). Developing an Appropriate Consent Model for Biobanks: in Defence of 'Broad' Consent. In Kaye, J. and Stranger, M. (eds), *Principles and Practice in Biobank Governance*. Farnham: Ashgate, pp. 79–92.

Rhodes, R. (1998). Genetic Links, Family Ties and Social Bonds: Rights and Responsibilities in the Face of Genetic Knowledge. *Journal of Medicine and Philosophy*, 23, 10–30.

Rothstein, M. A. (2005). Expanding the Ethical Analysis of Biobanks. *Journal of Law, Medicine and Ethics*, 33, 89–101.

Wendler, D. (2006). One-time General Consent for Research on Biological Samples. *British Medical Journal*, 332, 544–547.

Wilson, J. (1998). To Know or not to Know? Genetic Ignorance, Autonomy and Paternalism. *Bioethics*, 19, 492–504.

HHS Public Access

Author manuscript

Annu Rev Genomics Hum Genet. Author manuscript; available in PMC 2015 June 02.

Published in final edited form as:

Annu Rev Genomics Hum Genet. 2013 ; 14: 557–577. doi:10.1146/annurev-genom-091212-153506.

Return of Individual Research Results & Incidental Findings: Facing the Challenges of Translational Science

Susan M. Wolf, J.D.

Abstract

The debate over return of individual research results and incidental findings to research participants is a key frontier in research ethics and practice. Fundamentally, this is a problem of translational science, a question of when information about an individual that is generated in research should be communicated for clinical attention, as the technology itself is moving into clinical care. There is growing consensus that investigators should offer participants at least those individual findings of high clinical importance and actionability. Increasing attention to what information biobanks and secondary researchers owe people who provide data and samples offers an opportunity to treat these source individuals as research partners. Cutting-edge issues include return of results in pediatric populations and return to kin and family, including after death of the proband. Progress will require facing the continuum linking research and clinical care and developing standards and models for return.

Keywords

genetics; genomics; research ethics; bioethics; biobank

Introduction

The question of whether to return individual research results (IRRs) and incidental findings (IF) to participants in genetic and genomic research is now recognized as one of the most difficult challenges facing investigators. When our research group at the University of Minnesota began funded work on this problem in 2005, the return of results debate in genetics and genomics was in its infancy. Indeed, that project was framed comparatively: using the more advanced debate at the time over management and return of incidental findings in neuroimaging research and CT colonography research (as the latter images most of the torso and customarily reveals extracolonic IFs), our national project group launched into consideration of how to define, anticipate, manage, and return IFs in genetic and genomic research. We published consensus recommendations[1] as part of a symposium offering papers on different pieces of this puzzle.

Corresponding author: Susan M. Wolf, J.D., McKnight Presidential Professor of Law, Medicine & Public Policy, Faegre Baker Daniels Professor of Law, Professor of Medicine, University of Minnesota, 229 19th Avenue South, Minneapolis, MN 55455, Tel. 612-377-3406, FAX 612-624-9143, swolf@umn.edu.

Disclosure Statement

The author receives research support from the National Human Genome Research Institute (NHGRI) and National Cancer Institute (NCI) at NIH, as well as the Robert Wood Johnson Foundation and the University of Minnesota. She has received honoraria in the last year from the Mayo Clinic and Boston Scientific.

Concern over how to handle incidental findings in research was preceded by a long history of attention to the question of how to handle IFs in clinical care. Probably every clinician has had the experience of a patient presenting with a certain complaint and the clinician discovering an additional and unrelated pathology. Indeed, the term "incidentaloma" is defined in medical dictionaries as an occult adrenal tumor, accidentally discovered.[23] Genetics has seen a long-standing debate on how to handle an incidental finding of misattributed paternity revealed by genetic testing.[4]

As this long-standing concern over clinical incidentalomas moved into the research sphere and edged toward genetics, the National Bioethics Advisory Committee (NBAC) published a report on stored tissue in 1999.[5] That report included a brief section on "Reporting Research Results to Subjects" and offered several recommendations. NBAC urged that Institutional Review Boards (IRBs) develop guidelines and require that protocols address this issue. However, the committee recommended that disclosure should be "an exceptional circumstance," and only if "the findings are scientifically valid and confirmed," "the findings have significant implications for subjects' health concerns," and "a course of action to ameliorate or treat these concerns is readily available." They also suggested that at the time of disclosure, "appropriate medical advice or referral should be provided," though later recommendations instead have counseled that investigators should offer the finding as a research finding, with referral for clinical follow-up. (1) This contemplates a "hand-off" of information from the domain of research to that of the clinic, in part to avoid mistaking research for clinical care.

NBAC cited few sources to show earlier attention to the problem of return of research results. The most prescient was a short article by Reilly from 1980.[6] As NBAC recounted, Reilly distinguished three types of findings: "1) 'findings that are of such potential importance to the subject that they must be disclosed immediately'; 2) 'data that are of importance to subjects…but about which [the investigator] should exercise judgment about the decision to disclose…[i]n effect, these are data that trigger a duty to consider the question of disclosure'; and 3) 'data that do not require special disclosure.'"

By the time NBAC published its report, a significant literature was already emerging on how to manage incidental findings in imaging research, where IFs can be visually obvious and hard to overlook. In 1997, for example, Yue et al. published a study of IFs discovered in imaging the brain[7] as did Katzman et al. in 1999.[8] The literature on IFs in imaging research became voluminous. In 2005, Illes led a workshop including investigators and policy-makers from the National Institutes of Health (NIH) focusing on IFs in neuroimaging research, which led to progress on consensus recommendations.[9] Consensus recommendations emerged for IFs discovered in CT colonography as well.[10] And in 2008, our project published consensus recommendations bridging from imaging research to genetic and genomic research. (1)

In the fast-moving work of genetics and genomics, the 1990's and even the mid-2000's is now a long time ago. With increasing reliance on large-scale genomic research using biobanks and archived data sets, the emergence of whole exome sequencing (WES) and whole genome sequencing (WGS), their increasing speed and plummeting cost, and

developments in informatics allowing increasingly automated analysis of potentially returnable variants and computer-supported communication to clinicians and even participants, the debate over return of IRRs and IFs has intensified. NIH, and especially the National Human Genome Research Institute (NHGRI), deserves great credit for recognizing the fundamental importance of these issues, committing significant funding to the research needed to build a strong evidence base for solutions, and speeding progress by linking funded investigators through a Return of Results (RoR) Consortium with targeted work groups.[11]

The importance of this issue has now been widely recognized. Both the professional literature (scientific, medical, ethics, and legal) as well as the popular media now regularly cover this unfolding story. A 2011 news article in *Science* reported that, "Whether to divulge results…, and how, is arguably the most pressing issue in genetics today."[12] In August 2012, the *New York Times* quoted NIH Director Francis Collins, calling the issue "one of the thorniest current challenges in clinical research."[13] An October 2012 report from the Presidential Commission for the Study of Bioethical Issues, which focused on the privacy challenges posed by the rise of WGS, included recommendations on return of IFs: "Researchers, clinicians, and commercial whole genome sequencing entities must make individuals aware that incidental findings are likely to be discovered in the course of whole genome sequencing. The consent process should convey whether these findings will be communicated…."[14] Many in the genetics and genomics community now await the recommendations of the American College of Medical Genetics and Genomics (ACMG) Workgroup on return of IFs (which the Workgroup also calls "secondary findings"). In the group's March 2012 preliminary report, they suggested a "minimum list of variants/ conditions that labs should look for and return."[15]

I have focused here on U.S. developments, but the debate over return of IFs and IRRs is international.[16,17,18] This article concentrates largely on developments in the context of American policy and regulations, but genetic and genomic research cross national boundaries. Ultimately, international exchange on policy and best practices will be crucial, as a route toward international harmonization of policies and standards.

Definitions

In 2008, our project group offered a definition of an *incidental finding* as "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of research but is beyond the aims of the study." (1) Since this definition was offered, it has been widely recognized that not only health and reproductive importance, but also personal utility to the research participant may suggest possible return of an IF.[19] Note that IFs discovered in the course of genetic or genomic research may not be limited to genetic findings. Screening individuals for possible enrollment in research, collecting baseline values on research participants, or gathering phenotypic information (for example, to search for genotype/phenotype associations) may yield a wide range of IFs such as abnormal blood pressure and other phenotypic findings.

In contrast to an IF, an *individual research result* is a finding concerning an individual research participant that has potential health or reproductive importance or personal utility and is discovered in the course of research on the focal variables under study in meeting the study's aims. Thus, in genetic or genomic research, IRRs are likely to be genetic or genomic findings on this individual.

Of course, distinguishing IFs from IRRs may be more difficult in discovery-driven rather than hypothesis-driven research, as the aims in the former may be broad and the method inductive. (1) For example, in some genome-wide association studies (GWAS) that search widely across the genome for genotype/phenotype correlations, it may be hard to discern what findings are beyond the aims of the study. For this reason, distinctions between management of IFs and that of IRRs should be carefully justified, especially because research participants may find it difficult to distinguish these two types of findings. (19) Indeed, when commentators reference the "return of results," they are typically referring to return of both IFs and IRRs, as I will in this review.

Both IFs and IRRs contrast with *aggregate research results*. These are findings concerning the research population (usually published) that are discovered in the course of research on the focal variables under study in meeting the study's aims. Beskow et al. discuss ethical obligations to offer aggregate research results to research participants and the relationship to return of individual research results.[20] Indeed, return of aggregate results to a research population (as in a newsletter or through a website) can lead individual participants to ask for their own findings.

There are a range of terms for the individuals whose findings are at issue. The literature variously calls them participants (or human subjects), donors, sources, and contributors. Some are indeed participants in research on human subjects as defined by the Common Rule, because they are a "living individual about whom an investigator…obtains data through intervention or interaction with the individual or identifiable private information").[21] However, much genetic and genomic research is performed on data and samples collected for clinical rather than research purposes and then deidentified. [22] Such research does not qualify as research on human subjects.[23] Indeed, the source individuals (the term I will use here, though our group has also used "contributor" (19)) may not know their materials are being used in research (though possible changes to the Common Rule have been published for comment, which would require at least rudimentary consent from source individuals[24]). Thus, "donor" seems the wrong term, as it suggests a past donation.

A final definition of *biobank* is useful. As in much of the literature, I use the term here to refer to a range of structured collections of human biological materials and/or data, archived for ongoing use in research. (19) Others offer similar definitions,[25] allowing for discussion of the role of biobanks in the return of results debate without getting lost in the welter of terms used for such structured collections, including biorepositories, tissue repositories, and DNA databanks.

Why has this issue become important?

Return of results has erupted into a major debate and focus for research. The importance of the issue stems in part from the gap between the preferences in favor of return that participants and the public appear to hold, and past research practice to avoid return. Research is still under way on the preferences of research participants, other individuals who serve as sources of data and specimens used in research, and the public. But data thus far indicate that most are interested in return. [262728293031] Indeed, one survey found that "90% of…respondents wanted their genetic or risk information even when there was nothing that currently could be done with that information."[32] (p. 836) While more data and analysis are needed to understand preferences in a range of research contexts, as well as the impact of return on actual participants, the gap between apparent preferences and research practice has led to concern over the ethics of withholding individual research results of clinical significance.

This concern has arisen at a time of broader attention to the problem of how to earn and sustain the trust of individuals recruited for research as well as those source individuals whose data and specimens are used. As Trinidad et al. have noted, "A spate of recent events – including several…conflicts over newborn blood samples; the return of biospecimens to the Yanomamö people; and the bestselling account of the origins of the HeLa human cell line widely used in research – have raised questions about trustworthiness of the research process at a time when new approaches to genomic research place a premium on study participation."[33] (references omitted) Kohane et al. have argued that withholding data from research participants, makes them "passive purveyors of biomaterials and data," not research partners.[34] Illes et al. have similarly maintained that researchers should return IFs based on respect for participant autonomy and interests, as well as a duty of reciprocity to those who make research possible through their participation.[35]

Richardson and Belsky have offered ethical analysis to translate these concerns into investigator duties to return IFs to research participants.[363738] They argue that participants permit researchers access to their private data, specimens, and bodies, access that researchers otherwise would not have. This grant of access represents an act of partial entrustment ("partial" because participants are not fully entrusting their medical welfare to the researcher, as they would to a clinician). Richardson and Belsky maintain that the scope of this partial entrustment creates researcher duties of ancillary care. These are not the full duties of care borne by clinicians, but neither are researchers "pure scientists" with no duty of care. Richardson has argued that this duty of ancillary care embraces a duty to return IFs: "Having gotten the participants to waive these privacy rights, the researchers correspondingly come to have duties of care with regard to the pieces of information — and in particular the incidental findings — that fall in their hands by doing the research procedures." (30)

Lurking here is a duty to warn or duty to rescue. Beskow and Burke explicitly embrace the notion of a duty to rescue, which they argue applies "when, in the course of research, an investigator discovers genetic information that clearly indicates a high probability of a serious condition for which an effective intervention is readily available."[3940] Ossorio has

questioned the extent of a duty to warn or rescue, at least a duty falling on secondary researchers, those most distant from any research interaction with participants. Yet even in the case of secondary researchers, she argues that there are cases in which the duty applies and return of results may be obligatory, as well as additional cases in which it may not be obligatory but would still be "morally superior to not doing so."[41]

The question of whether researchers bear duties to return IFs and IRRs has proved particularly vexing because it straddles the worlds of research and clinical care, with their different norms and objectives. The core question is whether information discovered in the course of research should be conveyed to the individual participant in order to trigger clinical evaluation and follow-up. In that sense, the return of results is a "bridge" problem, because it bridges from the world of research (with its own norms and objectives) into the world of clinical care (with very different norms and objectives). On the research side of the bridge, investigators debate whether information acquired in the course of research should be communicated across that bridge to the domain of clinical care.

The problem of whether to return IFs and IRRs thus challenges the dichotomy between research and clinical care that ethics (and law, for that matter) has long embraced.[42] On the clinical side, copious work on medical ethics as well as court decisions and legislation have established that the physician owes the patient a robust duty of clinical care. The physician's goal is to serve the patient's interests. A great deal follows from this, including informational obligations to disclose to the patient the diagnosis, treatment options, and other information material to treatment decisions. However, on the research side, the researcher's core goal is to seek generalizable knowledge for the benefit of the many. The researcher owes a much thinner duty of clinical care, focused on averting and addressing research-caused harm. Researchers are obliged to seek research participants' informed consent to be part of the research, but they currently have had no duty to seek consent from individuals whose clinically derived data and samples are used without identifiers. And what information the researchers should report back to the participant or individual source of data and specimens is the precise question posed by the return of results debate.

This dichotomous vision of the contrasting worlds of research and clinical care is rooted in the history of human subjects research. Traditionally, research asked narrow, circumscribed questions in time-limited investigation, aimed at advancing aggregate knowledge and welfare. In contrast, medical care addressed all of the patient's health issues, extended over the patient's life-time, and was provided by clinicians committed to advance the patient's individual welfare. However, newer research realities now alter this contrast. Genetic and genomic research may now ask broad, uncircumscribed questions in GWAS discovery research and analysis of the full exome or genome. Research may no longer be time-limited, now that specimens and data sets are archived and re-analyzed indefinitely. Research technologies are so powerful that they routinely generate findings of potential clinical importance, and researchers may acquire data highly important to individual welfare.

The return of results problems is thus one of many signs that the old, dichotomous vision of research and clinical care widely separated will need to evolve into a new more translational vision of connected realms. The rise of genomic medicine and pharmacogenomics are

interdigitating research and clinical care as well. Rather than relying on the old dichotomous vision, we may need to reconceptualize research and clinical care along a translational continuum. The problem of return of IFs and IRRs has become a central catalyst to forging this new vision.

How IRRs and IFs Arise

Both IFs and IRRs can arise throughout the course of research. This is true over the course of an individual study, starting at the beginning with recruitment and ascertaining eligibility. It is also true as data and specimens from multiple studies or those left over from clinical care are collected and aggregated, stored in biobanks or archived data sets, and used in secondary research. In 2012, our group published the results of a project on managing IFs and IRRs in genomic research involving biobanks and archived data sets. (19) Addressing this issue forced our project group to conceptualize how IFs and IRRs arise as data and specimens flow through what we called a *biobank research system*. Figure 1 depicts a biobank research system, comprised of three types of entities. At Stage 1, data and specimens from contributors are collected by primary research and collection sites. The initial collection may be in research or in clinical care. Research may itself occur at the Stage 1 sites.

At Stage 2, the data and/or specimens are fed into a biobank for curation, annotation, storage, and making them available for subsequent research. (Note that some biobanks collect their own data/specimens, eliminating the Stage 1 collection sites.) The research on banked data and specimens may take place at the biobank, multiple secondary research sites, or both.

Those secondary research sites comprise Stage 3 of the biobank research system.

IFs and IRRs can arise at all three stages of this biobank research system. At Stage 1 primary research or collection sites, IFs may arise in ascertaining an individual's eligibility to participate and collecting baseline information, as noted above. In addition, IFs and IRRs may arise in any subsequent research conducted at these Stage 1 sites.

At Stage 2 sites, where data and specimens are archived and processed to be made available for further research, IFs may arise in biobank processing of data/specimens. For example, a biobank that processes tumor specimens by reconfirming the reported pathology may discover an erroneous diagnosis (sometimes called a "discrepant diagnosis"). Biobank quality control (QC) is another potential source of IFs. For example, a biobank conducting routine QC by chromosomal confirmation that a contributor reported as female is indeed XX, may discover sex chromosome abnormalities and wonder whether these should be offered to the contributor or her physician. In addition, any research conducted at the biobank may yield IFs or IRRs. These may be discovered in the genetic data or in the phenotypic data about an individual, including in their electronic medical record, if that is used in the research.

At Stage 3 sites, secondary researchers using data/specimens obtained through the biobank may discover IFs or IRRs in the course of performing research. These are particularly

challenging to handle, as secondary research may be far removed from data and specimen collection in time and geographically, secondary researchers may have no relationship with the source individuals, and the data and specimens are likely to be deidentified before being conveyed to the secondary researchers.

Conceptualizing the flow of data and specimens through the entire research system is important. It allows consideration of the proper stage for stripping identifiers, and what entity (if any of them) should hold the codes to allow reidentification. It also allows consideration of how the documents that structure the relationships between the Stage 1 sites and the Stage 2 biobank, and then the biobank and Stage 3 secondary researchers (documents including Material Transfer Agreements (MTAs) and Data Access Agreements (DAAs)) should address responsibilities for return of IFs and IRRs.

Most of the literature to date on IFs and IRRs in genetic and genomic research focuses on those that arise in Stage 1 primary research or does not specify the context in which the findings arise and must be addressed. However, much genomic research now occurs in a biobank research system and has to be addressed in this context. That was the focus of our 2012 consensus paper (19) and associated symposium. To address the more complex reality of genomic research conducted on a large scale through a biobank research system requires first examining the analysis that has emerged to date on how to handle IFs and IRRs in primary research.

Recommendations for Primary Research

The key questions that have structured the debate over return of IFs and IRRs in primary research have included:

What findings are we talking about?

What criteria should define returnable IFs and IRRs? Do returnable findings include only those of clinical significance? What about findings of reproductive significance (such as carrier status)? And what about findings of personal utility (such as a variant predicting serious illness and early death, that might prompt an individual to put their affairs in order and alter life decisions)? If a finding must be "actionable" to warrant return, how should "actionability" be defined?

How are these findings ascertained?

Do investigators have a duty to "hunt" for these findings, or should return of IFs and IRRs be limited to those that investigators and others stumble upon?

What should investigators do once they spot a suspected IF or IRR?

What personnel and procedures are needed to set up a responsible process for ascertaining these findings? Should the research team include (or arrange access to) a clinician with relevant expertise to examine the research findings of concern and confirm whether they warrant communication to participants for potential clinical evaluation and follow-up?

What further steps are needed to raise confidence in the finding to the level necessary for return?

Given that false positives occur even in clinical testing, what level of confidence in a research finding is required for return, given that return itself should then trigger clinical evaluation? Does return require confirmation of genetic IFs or IRRs in a lab certified to return findings for diagnosis or treatment use under the Clinical Laboratory Improvement Amendments (CLIA)? (19, [43]) If so, how is this best accomplished?

To whom should return be offered?

Should return only be offered to research participants themselves? Are there circumstances under which return should be offered to the participant's clinician, in addition or instead of the participant? Should return be offered only to participants who consent? Are there findings of such gravity and actionability that they should be returned even if the participant has not consented? How should participant consent for return be sought?

What systems and processes should be set up to support ethical handling of IFs and IRRs?

What should research protocols and consent forms say in advance about the likelihood of finding IFs and IRRs and how they will be handled? What should IRBs require? What should funders themselves require, and what funding is needed to support sound management of IFs and IRRs?

In our 2008 consensus recommendations for how to handle IFs, our project group concluded that investigators do shoulder duties to anticipate and manage IFs in their research. (1) We urged that they create a pathway for handling them, and offered a flowchart as well as description of that pathway. We suggested that researchers should address their plan for management of IFs in their proposed protocol and in the consent process, and obtain IRB approval. IRBs and funders should oversee fulfillment of these duties, assure the needed budget, and provide guidance.

In developing criteria for return, we distinguished three categories: (1) findings that should be returned, (2) findings that may be returned, and (3) those that should not be returned. This the 3-way division (which Reilly's 1980 article anticipated (6)) has proven durable, with a number of subsequent recommendations (including those from Fabsitz et al. (42) and Berg et al.[44]) also distinguishing should return, may return, and (often) do not return. In our paper, we sorted findings into these three categories based on whether return potentially offered strong net benefit to the participant (should return), possible net benefit (may return), or unlikely net benefit (do not return). Thus, we made the ethical judgment that returnability should hinge on the importance of return from the perspective of the research participant. In "should return," we included both findings of high clinical significance and those of high reproductive significance.

While the 3-way division has endured as well as the inclusion of findings of high clinical significance in the "should return" category, other features of our proposal have sparked more debate. A subsequent consensus paper by Fabsitz et al. stripped findings of

reproductive significance out of "should return." (42) That paper restricted "should return" to findings with important health implications, revealing established and substantial risks, when the findings were actionable, defined as having the potential to change the disease course. In addition, findings in this category had to be analytically valid, their disclosure had to comport with law (such as any applicable CLIA requirements), and the participant had to consent to receipt of the findings.

This was a more clinician-centered delineation of the "should return" category. The "actionability" requirement and definition meant that investigators had to conclude that clinicians could potentially use the returned finding to make a positive difference in the individual's clinical course. This was a different ethical perspective that the one taken in our 2008 paper, which was instead guided by what information participants themselves would likely find valuable. This debate over whether to tether return to what clinicians can use *versus* what participants can use remains unresolved. It echoes a long-standing debate (the subject of seminal court cases such as *Canterbury v. Spence*[45] as well as legislation) over whether informed consent in clinical care calls for disclosure of information whose scope is determined by professional custom or determined by what information patients are likely to find material.

Both our 2008 recommendations and those from Fabsitz et al. address return of individual findings in the context of research. Consequently, both have drawn objections from those who argue for maintaining a strict divide between research and clinical care. Key objections have been that return of IFs and IRRs requires time and resources, diverting personnel and funds from research.[46] Another core concern has been that offering IFs and IRRs to participants may invite them to confuse research for clinical care. A third objection has been that guidelines recommending return of some IFs and IRRs may invite liability for failure to return.[47]

There are, as yet, few studies analyzing the cost of return, which is likely to vary considerably depending on study design, the types and frequency of IFs and IRRs identified, the size of the sample population, and the determination of what IFs and IRRs to actually return. A common recommendation, which our own consensus papers include, is that funders need to add to research budgets in order to support addressing IFs and IRRs. The reality is that ethics takes time and costs money, including basic informed consent.[48]

The possibility that research participants may mistake research for clinical care is a long-recognized problem that significantly predates the return-of-results debate. Researchers and IRBs now routinely address the "therapeutic misconception" and take steps to minimize this confusion. Addressing possible return of IFs and IRRs with research participants might actually be an opportunity to emphasize the distinction between research and clinical care, as participants need to understand the option of receiving findings generated in research that will then need to be pursued and clarified through clinical work-up.

Finally, concern over potential liability seems at least premature, if not misplaced.[49] There have been no court cases as yet over return of results. However, guidelines that help move the research community toward a shared sense of what is owed to research participants may

actually help avert potential liability, by articulating flexible standards. Without those, a research participant who is not offered a particular IF or IRR and arguably suffers harm caused by not receiving that finding will be freer to argue that lack of return was a compensable harm. With flexible guidelines in place, investigators can instead point to their reasonable use of those guidelines. None of the guidelines published to date state that investigators should return all possible IFs and IRRs. Instead, the guidelines customarily restrict "should return" to a small subset.

Despite the concerns articulated over return of IFs and IRRs, it is now difficult to find commentators who argue that absolutely no IFs and IRRs should be returned. The reality that some IFs and IRRs are clinically urgent is widely recognized. Indeed, consensus approaches to IFs in imaging research clearly recognize that some IFs are clinically urgent and categorize them this way.[50]

The progress that has been made on return of results in primary research is the necessary backdrop for the more complex debate over return of IFs and IRRs in research that involves biobanks. I turn next to that debate.

Recommendations for Biobanks & Secondary Research

Because biobanks are increasingly the engines of large-scale genomic research, determining how to handle return of IFs and IRRs in the simpler model of primary research is not enough. It is essential to grapple with how to manage IFs and IRRs as data and specimens move through all three stages of a biobank research system.

However, the conventional view has been that once data and specimens move beyond the primary research site to biobanks and then to secondary research sites (Stages 2 and 3 in the biobank research system), either no IFs and IRRs should be returned at all, or the biobank and secondary researchers should convey any IFs and IRRs to the primary site to determine whether any return should be undertaken. ([51] 19) This view minimizes or eliminates biobank and secondary researcher responsibilities to manage IFs and IRRs.

There is a growing recognition, however, that there are problems with this conventional view. (19, 50) First, some findings are so clinically urgent that failing to return them poses serious ethical challenges for biobanks. An example is biobank discovery in processing newly acquired tumor specimens that the pathology and diagnosis noted at the primary collection site (Stage 1) appears to be incorrect. This problem of "discrepant diagnosis" has led to a literature on how to manage and return what may be an IF of urgent clinical importance.[52]

A second set of problems with confining responsibility for addressing IFs and IRRs to primary research and collection sites is that they may lack the capacity to address the finding. In some scenarios, the primary site has merely supplied specimens and data collected in clinical care, and my not have the expertise to analyze the returnability of the genetic or genomic findings that the biobank and secondary researchers generate. Even if the primary site collected the data and specimens in research, the relevant investigator may now be gone and the investigator's research project concluded.

More fundamentally, there is a strong argument for a systemic approach to the problem of how to manage IFs and IRRs that arise as data and specimens flow through a biobank research system. The flow of data and specimens is controlled by policies and documents such as MTAs and DAAs. (19) Those policies and agreements should address the responsibilities of primary research and collection sites, biobanks, and secondary researchers to manage IFs and IRRs. Only this kind of systemic approach will lead to harmonized expectations and clear notice to all of the actors as to their responsibilities.

Our 2012 consensus paper was the first to offer this kind of systemic analysis of how to approach the return of results problem in a biobank research system. We readily acknowledged that biobanks are varied. Some are population-based while others are diseased-based. They vary by source population, size, age of the collection, the range of data and specimens collected. They may aggregate data and specimens collected for clinical purposes and now deidentified, so that research on that material falls beyond the scope of "research on human subjects" under the Common Rule. (22, 23) On the other hand, data and specimens may have been collected for research or carry identifiers, so that this fundamental regulation of human subjects research applies.

Despite this variety, all biobanks and biobank research systems have the potential to discover IFs and IRRs. There is a need for guidance, especially guidance that offers the flexibility to tailor approaches to the realities of a given biobank research system. While some commentators have suggested that the sheer variety of biobanks counsels against general guidelines (30, 45), the virtue of offering guidance to biobanks is already recognized by publication of the influential *Best Practices for Biorepositories* issued by the National Cancer Institute's Office of Biospecimen and Biorepository Research. (51) In addition to this, a substantial literature has emerged on the ethical responsibilities of biobanks, including duties of responsible custodianship. (29, [535455]) Leaving each biobank to grapple alone with the return of results problem, without even general guidelines, invites inefficiency, unnecessary cost, and unwarranted inconsistencies.

Biobanks are already beginning to address return of results issues, so the time is ripe for offering guidance and inviting debate over proposed policy. The eMERGE Network of biobank research sites has a network-level Return of Results Oversight Committee to offer general guidance, which individual sites can then tailor to their circumstances and needs.[56] The Coriell Personalized Medicine Collaborative has an Informed Cohort Oversight Board (ICOB), a model suggested by Kohane et al. (23 [57]) The NIH Gene Environment Association (GENEVA) Studies use a Committee on Incidental Findings.[58] Not all biobank research systems can return results; Vanderbilt's BioVU is an example of a biobank that irretrievably strips identifiers, so that reidentification, and thus return, cannot be accomplished.[59] However, this remains an unusual practice. More common is to retain a key code that allows reidentification. Indeed, in some research designs participants are fully identified and followed prospectively.

Our project offered consensus recommendations for return of results from biobank research systems. (19) The most fundamental recommendation we offered was to approach the issue of return of results systemically, by considering how IFs and IRRs can arise as data and

specimens move through the entire system and by allocating among the key players within that system the responsibilities for dealing with return issues. We recognized that the biobank itself sits at the center of the 3-stage system, with relationships (including written agreements) extending both to primary research and collection sites and to secondary researchers. This puts biobanks in an important position to help ensure that the biobank research system as a whole addresses return of results issues.

To allocate responsibilities across the system, we identified four general steps involved in dealing with return of results: (i) Clarifying general criteria for what should be returned, may be returned, and should not be returned; (ii) Analyzing a particular finding in light of these criteria; (iii) Reidentifying the source individual; and (iv) Recontacting the individual to offer the finding. We summarized these four steps using the acronym CARR. We then offered specific recommendations for each step.

To clarify general criteria for return, we recommended that biobanks have a multidisciplinary committee such as an ICOB to work with an IRB on these return issues. As Fabsitz et al. also recommended (34), a nation-wide or central advisory committee would be helpful, to offer recommendations on the criteria for return and a periodically updated list of returnable variants. A given biobank research system might decide to deviate from those central recommendations, but at least would have a place to start.

To aid in formulating criteria for return, we offered a set of criteria similar to those for return in primary research, but with key caveats. Thus, we suggested that biobank research systems should return IFs and IRRs that reveal an established and substantial risk of a serious health condition, are actionable (offering a significant potential to alter the onset, course, or treatment of disease), are analytically valid and whose return complies with legal requirements (such as applicable CLIA requirements), and only if the source individual has consented to return. We went on to suggest that a biobank research system may return additional IFs and IRRs if they reveal an established and substantial risk of likely health or reproductive importance, or personal utility to the source and return is likely to provide net benefit from that person's perspective.

However, among the caveats we offered was that, "The greater difficulty and cost of biobank return, the lower likelihood of benefit with lapse of time, and the reality that some contributors will not have consented to research, justify more restrictive criteria for return in biobank research than primary research." Thus, although our 2008 consensus paper included some findings of reproductive importance in the "should return" category, the 2012 paper focusing on biobanks did not. We also noted that biobanks may hold data and specimens for so long that relocating and contacting the source individual may be challenging and the utility of return for that individual may be diminished. We also addressed the special challenges facing preexisting biobanks (as opposed to new biobanks that can consider return of results issues in their design). Older biobanks may hold data and specimens collected with consent forms that failed to address and seek consent for return or that stated there would be no return. We addressed options for recontacting source individuals for consent to return, but the need otherwise to respect the prior explicit agreement that there would be no return.

To analyze individual findings for potential return, we made a distinction. We urged that when IFs or IRRs arise in primary research, the primary researcher and institution should be responsible for handling them, working with their IRB. However, when IFs and IRRs arise later in the flow of data and samples through the biobank research system, the biobank itself has a crucial role to play. Thus, when IFs and IRRs arise in the biobank's own collection of data or specimens (when these are collected by the biobank directly rather than through separate primary research and collection sites); when they arise in biobank quality control, processing, or research; or when they arise in seconday research on data and specimens supplied by the biobank, we urged that the biobank bear primary responsibility for analyzing whether a particular IF or IRR should be offered back to the source individual.

To reidentify the source individual, again a distinction is necessary. When only the primary researcher holds the key code to reidentify individuals, reidentification will need to occur at the primary research site. However, we urged that biobanks consider holding the key code or using a "trusted intermediary" to hold the code. (53, [60]) This avoids relying entirely on the primary research site to maintain capacity for reidentification over the extended period of time during which biobank and secondary research is continuing. Planning for how to handle the return of results issue within a biobank research system thus requires planning how deidentification (if undertaken) will occur, how the key code allowing reidentification will be held, and thus what entity has the capacity to reidentify individuals as needed over time.

To recontact the individual to offer the finding, we suggested considering that in many cases the primary research or collection site may be best situated to perform recontact. The Stage 1 site may be the only site in the biobank research system that has had direct contact with the source individual (although in some biobank research systems, the biobank itself may collect data and specimens directly from these individuals and thus have direct contact). That history of direct contact may mean that the source individual is most directly familiar with the primary research or collection site, so the primary site would be the best entity to perform recontact. Thus, even if the biobank or a "trusted intermediary" performs reidentification, it may be the primary research or collection site that instead performs recontact.

This allocation of CARR responsibilities to different entities within the biobank research system demonstrates the importance of analyzing return of results systemically in genetic and genomic research involving biobanks. Our recommendations are sometimes misunderstood as thrusting all CARR responsibilities on biobanks themselves. (46) But that overlooks the systemic thrust of our analysis, distributing duties across the biobank research system, of which biobanks themselves are only one part.

Since we offered these recommendations, debate and research have continued. Bledsoe et al. have argued that the cost of return has the potential to be excessive. (46) Yet there is little work to date costing out return of results. (48) Getting a rigorous estimate of costs will be challenging, as cost will depend on the number of variants to be analyzed for potential return and the number to be returned, the method of sorting those variants to be returned, the size of the research populations, the method of return, and other variables. Indeed, the first of

these – the number of variants to be analyzed for potential return and returned – itself remains a subject of research and debate.[61626364] However, the fact that return of results requires expenditure of effort and funds is not itself an argument to avoid the practice. The reality is that ethics costs, including informed consent, IRB review, and the like. (48) If ethics calls for return, the key question will be how to scale return and develop procedures that make it feasible and compatible with achieving research objectives. ([6566] 62)

Normative guidance on return of results will and should evolve as research contributes further to the evidence base. What we recommended was a middle course. There are some commentators and researchers who would be much more restrictive, and would offer little or even no return. (46, 47) There are others who would be far more generous, and offer considerably more than our criteria suggest, up to the possibility of offering a source individual their full data set. (34, [67]) Thus, commentators from both sides can debate our proposals. We take an intermediate position.

Research continues on what findings source individuals wish to receive, what means of return are effective, and what consequences return has for those individuals, for their subsequent utilization of medical care, and for their health outcomes. Further research considers what genetics professionals consider to be returnable results and why. A good deal of effort is going into identifying a roster of returnable results with underlying criteria to justify the list. And researchers continue to debate how best to minimize false positives and create a process to restrict return to those findings whose meaning is adequately established. Of course, work is still required to reach consensus on what constitutes “adequately established” and how to best reconcile the effort to protect source individuals from false positives and data whose meaning is currently uncertain with the reality that some of these individuals want their data with accompanying indications of what is known and not, so that the individual can await further research to improve interpretation.

Further research addresses implementation of return of results, including the protocols, systems, informatics, consent processes, and costs involved. Getting a grip on these specifics and different models for return will be crucial to making progress.

Frontier issues prompting further research include how to approach return of results in pediatric populations.[686970] Issues include how to integrate return issues into pediatric assent and parent or guardian permission, to whom to offer pediatric IFs and IRRs, whether some findings (such as an IF of adolescent pregnancy) should be offered only to the adolescent, and how to handle disagreement between the pediatric proband and the parents or guardians on return of results issues. As WES and WGS move into research application to children and even newborns, the question arises whether to refrain from offering even to parents or guardians those findings that lack clinical utility in childhood.[71] This would be in keeping with long-established guidelines urging that children only be tested for genetic variants with established clinical utility in childhood, preserving for the child the option to choose or refuse testing for other variants once the child achieves the age of majority.[72]

Another pressing issue is under what circumstances (if any) to offer return of IFs and IRRs to the participant’s or source individual’s kin or family. Kin or family may already receive a

proband's IFs and IRRs if the proband is a child or an adult without decision-making capacity. In these cases, the kin or family member receives results in his or her capacity as a source of permission for the child to participate in the research or as a source of consent for the adult without capacity. The further issue, however, is whether IFs or IRRs should ever be offered to kin or family members because of the potential implications for their own health or reproductive decision-making. Our research group is examining this issue collaboratively with investigators at the Mayo Clinic in the context of research based in a pancreatic cancer biobank.[73] Because median life expectancy for probands diagnosed with pancreatic cancer remains short, the question arises whether to offer IFs and IRRs of significance to kin or family before or after death of the proband, whether proband consent is needed in order to share these findings, and what the utility and impact of sharing these findings are.[74] Recent debate on returning results to kin and family after the proband's death focuses on whether the shared familial nature of genetics makes a proband's genetic findings a resource that should be available to kin and family[7576] and how this comports with the ethics and law that have traditionally protected individual privacy and confidentiality, including after death.[7778]

Moving Into Clinical Care

The debate over return of IFs and IRRs that I have analyzed so far is a debate over the proper conduct of research. However, with the emergence of WES and WGS and their increasing integration into clinical care, concern has emerged over what to report to patients from the resulting flood of findings. This has led to the emergence of a literature that resembles the literature on return of research results and is often mistaken for guidance on return of research results, but actually addresses the question of what to return in a clinical context.

Thus, Berg et al. offer a schema for sorting WGS results into 3 "bins," which correspond with a requirement to report; an option to report, depending on shared decision-making involving both patient and provider; and an imperative not to report. (44) However, this is all in the context of clinical deployment of WGS. Their Bin 1 ("should report") covers results that are "known to cause disease or strongly predicted to disrupt function," "medically actionable," and have "direct clinical utility based on the current literature." Their Bin 2 ("may report") covers results that are "clinically valid but not directly actionable" in light of the recognition that some patients may want this information. They further subdivide Bin 2 into results of low risk and doubtful current utility (Bin 2A), medium risk but doubtful utility and may cause distress (Bin 2B), and may cause high distress (Bin 2C). Their Bin 3 ("should not report") covers variants of no or unknown significance.

Although this proposal addresses return in the context of clinical use of WGS, there is an active debate over where WGS sits in the translational pipeline, whether WGS is ready for clinical use, and if so, for what indications. In 2012 the ACMG "recognize[d] that genomic sequencing approaches can be of great value in the clinical evaluation of individuals with suspected germ-line genetic disorders. Although this is an area that will continue to evolve with further research…, there are already instances in which genomic sequencing

approaches can and should contribute to clinical care."[79] Yet a committee of the American Congress of Obstetricians and Gynecologists (ACOG) cautioned the same year that when personalized genomic tests are used to assess predictive risk, they "should be viewed as investigational at this time," as there is need to assess their validity and utility.[80] Writing in *Science*, Drmanac opined that WGS "is already a powerful research tool" and though doctors may "also use WGS for some of their patients (mostly with idiopathic disease or refractory cancers)…[but] usually as part of a clinical study."[81] Clearly, WGS is in transition into clinical use and for broadening indications.[82]

The ACMG 2012 policy statement in part addresses IFs in WGS and WES. The statement acknowledges that when WGS or WES is used for any purpose, IFs "are highly likely, if not inevitable." (81) It goes on to say that labs and clinics need policies on disclosure of IFs, and should share that policy with patients. Before testing, individuals should be counseled on what "will or will not be disclosed." The standards for disclosure should be sensitive to whether asymptomatic or affected individuals are undergoing testing. When screening asymptomatic individuals, standards for return should be high to avoid reporting multiple false-positives. However, when considering "diagnostic results that are clearly related to a patient's phenotype or clinical condition…a lower threshold for reporting is appropriate." Patients should be allowed to opt-out of receiving some IFs, although "exceptional" cases may arise.

As noted above, an ACMG Workgroup is now focusing on developing a "minimum list of variants/conditions that labs should look for and return," though labs may return more. A preliminary report from that Workgroup in March 2012 indicated that they are focusing on findings of high penetrance and high positive predictive value, that are not detected in newborn screening, and for which an effective intervention is available. (15)

The Translational Future of Return of IRRs & IFs

The fact that recommendations emerging for return of results in clinical WGS/WES are so close to recommendations for return of IFs and IRRs in research suggests a way forward for the translational future of genetics and genomics. Recognizing that genetic and genomic analytic tools (including WES/WGS) move through time from research use into clinical care, we may be able to identify a core set of criteria that should distinguish findings to be considered for return. However, we should not underestimate the challenge. We will need to remain sensitive to differences between the research and clinical contexts, even as we transition from viewing them as separate domains to recognizing their translational linkage.

In refining criteria for return, we will need to identify how established and substantial the risk should be, how useful the return, whether that usefulness is best judged from the standpoint of what the clinician can offer (clinical actionability) or from the standpoint of what source individuals find useful (which is likely to be a broader set of findings, including some with reproductive and even personal utility). While work on returnability now customarily embraces actionability as a core criterion, it remains unclear exactly how actionability should be defined. Nor is it clear why actionability should be limited to findings with health implications, omitting findings with high and established reproductive

importance. From the standpoint of source individuals, such a reproductive finding may be highly actionable.

In confronting the challenge of return of results, we are facing the translational nature of genetics and genomics. What is in the domain of research today is fast moving into the clinic. And it is unavoidable that in the course of conducting research, we will discover information about source individuals of clinical significance and even urgency. Imaging researchers have already confronted this reality.

The return of results debate thus forces us to re-think the traditional dichotomy in ethics (as well as in law) between the domain of research and the domain of clinical care. This old, static dichotomy was built on premises that are increasingly outmoded. Research on human genetics and genomics is translational science yielding insights that can move into clinical care with speed. And in a host of scenarios, researchers seek genetic and genomic answers to burdensome disease and disability, while helping individuals and families end their diagnostic odyssey, or while shedding light on any remaining interventional options for otherwise terminal disease. Research and clinical care are connecting along a translational continuum. Instead of a wall between the two, we now have a permeable membrane. The return of results is a debate about how to structure the flow of information through that membrane.

Conclusion

At the end of the day, the return of results debate is about people. It is about the research participant who does not know that she has a variant associated with malignant hyperthermia or Lynch syndrome, or that she has a *BRCA* 2 variant. It is about the family enrolling their child with a puzzling and devastating developmental disorder in genomic research, hoping that research to aid others will also yield some clue to the puzzle.

The debate is also about the investigator chafing at the custom of offering no information to participants, no matter how significant and actionable – the researcher troubled by the tradition of silence.[83] Nearly 30 years ago Jay Katz published his classic study of the tradition of silence in the doctor-patient relationship.[84] His most famous example was that of a physician, who finds himself disturbed shortly before performing a mastectomy on a young woman, troubled by information he had withheld from her. He went to her bedside to reveal what he had withheld, and it changed her choice of treatment. Katz was tracing the roots of a sea change in clinical care, the change that yielded a duty to share information with patients, to treat them as individual decision-makers entitled to material information about their condition.

We stand now at the brink of a change as profound in research. Research is not the same as clinical care. It seeks generalizable knowledge, in order to later yield diagnostics and treatments to benefit the many. But the only way to generate that knowledge is to earn and keep the trust of those people generous enough to participate in research. Even when research is conducted on data and specimens left over from clinical care, the trend increasingly is to recognize that these crucial materials derive from real people, who may

continue to incur a privacy risk even if the materials are deidentified, who retain a stake in the responsible use of their materials, and who may benefit greatly in some cases from return of results.

Return of results is the next frontier in the challenge of treating the people whose data and specimens make research possible as partners. Much work remains to be done, to develop appropriate criteria for return, efficient and sustainable processes, the evidence base to shape model protocols, and approaches that make sense for individual research projects and biobank research systems. But the silence is broken. The effort has begun to treat research participants and source individuals as indispensible partners in the research enterprise and people with a real stake in learning individual findings of significance.

Acknowledgments

Preparation of this article was supported by National Institutes of Health (NIH), National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI) grant #1-R01-CA154517 on "Disclosing Genomic Incidental Findings in a Cancer Biobank: An ELSI Experiment" (G. Petersen, B. Koenig, S.M. Wolf, PIs); Robert Wood Johnson Foundation (RWJF) Investigator Award # 69763 (S.M. Wolf, PI); and a Robina LaPPS Fund award from the University of Minnesota (S.M. Wolf, PI). The views expressed in this article are those of the author and not necessarily the views of NIH, NCI, NHGRI, RWJF, or the University of Minnesota. Thanks to Rebecca Boxhorn, J.D., Elliot Ferrel, J.D. candidate, and Elizabeth Oji, J.D., for research assistance. Any errors are my own.

Literature Cited

1. Wolf SM, et al. Managing incidental findings in human subjects research: analysis and recommendations. J Law Med & Ethics. 2008; 36:219–48. [PubMed: 18547191]
2. Stedman's Medical Dictionary. 27. Philadelphia: Lippincott Williams & Wilkins; 2000. incidentaloma
3. Grumbach MM, et al. Management of the clinically inapparent adrenal mass ("incidentaloma"). Ann Intern Med. 2003; 138:424–29. [PubMed: 12614096]
4. Friedman Ross L. Disclosing misattributed paternity. Bioethics. 1996; 10(2):115–30.
5. National Bioethics Advisory Commission. Research Involving Human Biological Materials: Ethical Issues and Policy Guidance. Vol. I. Rockville, MD: National Bioethics Advisory Commission; 1999. p. vi-vii.p. 71-72.Available at: http://bioethics.georgetown.edu/nbac/pubs.html
6. Reilly P. When should an investigator share raw data with the subjects? IRB. 1980; 2(9):4–5. 12. [PubMed: 11661886]
7. Yue NC, et al. Clinically serious abnormalities found incidentally at MR imaging of the brain: data from the Cardiovascular Health Study. Radiol. 1997; 202:41–46.
8. Katzman GL, Dagher AP, Patronas NJ. Incidental findings on brain magnetic resonance imaging from 1000 asymptomatic volunteers. JAMA. 1999; 282:36–39. [PubMed: 10404909]
9. Illes J, et al. Incidental findings in brain imaging research. Science. 2006; 311:783–84. [PubMed: 16469905]
10. Zalis ME, et al. CT colonography reporting and data system: a consensus proposal. Radiol. 2005; 236:3–9.
11. Mjoseth, J. NHGRI Funds Return of Results Studies. Forms Expert Consortium. Available at: http://www.genome.gov/27545526
12. Couzin-Frankel J. What would you do? Science. 2011; 331:662–65. [PubMed: 21310980]
13. Kolata G. Genes now tell doctors secrets they can't utter. New York Times. 2012;2012(Aug 25):A1.
14. Presidential Commission for the Study of Bioethical Issues. Privacy and Progress in Whole Genome Sequencing. Vol. 8–9. Washington, DC: 2012. p. 94-99.

15. Green, R. Preliminary report of the Secondary Findings in Clinical Sequencing Workgroup. 2012 Mar 28. Available at: http://www.slideshare.net/erikanature/acmg-secondary-findings-open-forum-3-2812-final
16. Zawati MH, Knoppers BM. International normative perspectives on the return of individual research results and incidental findings in genomic biobanks. Genet Med. 2012; 14:484–89. [PubMed: 22344229]
17. Knoppers BM, et al. Population studies: return of research results and incidental findings policy statement. Eur J Hum Genet. 201210.1038/ejhg.2012.152
18. Johnston C, Kaye J. Does the UK Biobank have a legal obligation to feedback individual findings to participants? Med Law Rev. 2008; 12:239–67.
19. Wolf SM, et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genet Med. 2012; 14:361–84. [PubMed: 22436882]
20. Beskow LM, et al. Offering aggregate results to participants in genomic research: opportunities and challenges. Genet Med. 2012; 14:490–96. [PubMed: 22261761]
21. 45 C.F.R. § 46.102(f) (2012)
22. Office for Human Research Protection. Guidance on Research Involving Coded Private Information or Biological Specimens. 2008. Available at: http://www.hhs.gov/ohrp/policy/cdebiol.html
23. Brothers KB, Clayton EW. "Human non-subjects research": privacy and compliance. Am J Bioethics. 2010; 10(9):15–17.
24. US Department of Health and Human Services. . Human subjects research protections: enhancing protections for research subjects and reducing burden, delay, and ambiguity for investigators. Federal Register. 2011; 76:44512–31. Available at: http://www.gpo.gov/fdsys/pkg/FR-2011-07-26/html/2011-18792.htm.
25. Organisation for Economic Co-Operation and Development. OECD Guidelines on Human Biobanks and Genetic Research Databases. 2009. p. 1Available at: http://www.oecd.org/dataoecd/41/47/44054609.pdf
26. Murphy J, et al. Public expectations for return of results from large-cohort genetic research. Am J Bioethics. 2008; 8(11):36–43.
27. Fernandez CV, et al. The return of research results to participants: pilot questionnaire of adolescents and parents of children with cancer. Pediatr Blood Cancer. 2007; 48:441–46. [PubMed: 16425279]
28. Wendler D, Emanuel E. The debate over research on stored biological samples: what do sources think? Arch Intern Med. 2002; 162:1457–62. [PubMed: 12090881]
29. Beskow LM, Smolek SJ. Prospective biorepository participants' perspectives on access to research results. J Empir Res Hum Res Ethics. 2009; 4:99–111. [PubMed: 19754239]
30. Facio FM, et al. Intentions to receive individual results from whole-genome sequencing among participants in the ClinSeq study. Eur J Hum Genet. 2012 1038/ejhg.2012.179.
31. Bollinger JM, et al. Public preferences regarding the return of individual genetic research results: findings from a qualitative focus group study. Genet Med. 2012; 14:451–57. [PubMed: 22402755]
32. Kaufman D, et al. Subjects matter: a survey of public opinions about a large genetic cohort study. Genet Med. 2008; 10:831–39. [PubMed: 19011407]
33. Trinidad SB, et al. Research practice and participant preferences: the growing gulf. Science. 2011; 331:287–88. [PubMed: 21252333]
34. Kohane IS, et al. Reestablishing the researcher-patient compact. Science. 2007; 316:836–37. [PubMed: 17495156]
35. Illes J, et al. Incidental findings in brain imaging research. Science. 2006; 311:783–84. [PubMed: 16469905]
36. Richardson HS, Belsky L. The ancillary-care responsibilities of medical researchers. an ethical framework for thinking about the clinical care that researchers owe their subjects. Hastings Cent Rep. 2004; 34(1):25–33. [PubMed: 15098404]
37. Richardson HS. Incidental findings and ancillary-care obligations. J Law Med Ethics. 2008; 36:256–70. [PubMed: 18547193]

38. Richardson, HS. Moral Entanglements: The Ancillary Care Obligations of Medical Researchers. New York: Oxford University Press; 2012.
39. Beskow LM, Burke W. Offering individual genetic research results: context matters. Sci Transl Med. 2010:2.10.1126/scitranslmed.3000952
40. Greely HT. The uneasy ethical and legal underpinnings of large-scale genomic biobanks. Ann Rev Genomics Hum Genet. 2007; 8:343–64. [PubMed: 17550341]
41. Ossorio P. Taking aims seriously: repository research and the limits on the duty to return individual research findings. Genet Med. 2012; 14:461–66. [PubMed: 22402758]
42. Wolf, SM. Incidental findings in neuroscience research: a fundamental challenge to the structure of bioethics and health law. In: Illes, J.; Sahakian, B., editors. Oxford Handbook of Neuroethics. New York: Oxford University Press; 2011.
43. Fabsitz RR, et al. Ethical and practical guidelines for reporting genetic research results to study participants: updated guidelines from a National Heart, Lung and Blood Institute working group. Circulation: Cardiovascular Genet. 2010; 3:574–80.
44. Berg JS, Khoury MJ, Evans JP. Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. Genet Med. 2011; 13:499–504. [PubMed: 21558861]
45. Canterbury v. Spence, 464 F.2d 772 (D.C. Cir. 1972)
46. Bledsoe, et al. Return of results from genomic biobanks: cost matters. Genet Med. 2012. Available at: http://www.nature.com/gim/journal/vaop/ncurrent/full/gim2012105a.html
47. Clayton EW, McGuire AL. The legal risks of returning results of genomic research. Genet Med. 2012; 14:473–77. [PubMed: 22323070]
48. Wolf SM. Return of results in genomic biobanks: ethics matters. Genet Med Letter. In press.
49. Wolf SM. The role of law in the debate over return of research results and incidental findings: the challenge of developing law for translational science. Minn J Law Sci Technol. 2012; 13:435–48.
50. Kim B, et al. Incidental findings on pediatric MR images of the brain. AJNR Am J Neuroradiol. 2002; 23:1674–77. [PubMed: 12427622]
51. National Cancer Institute, Office of Biorepositories and Biospecimen Research. Workshop Summary, 4 March 2011; Workshop on Release of Research Results to Participants in Biospecimen Studies; Bethesda, Maryland. 8–9 July 2010; 2011. Available at: http://biospecimens.cancer.gov/global/pdfs/NCI_Return_Research_Results_Summary_Final-508.pdf
52. Lockhart NC, et al. Intersection of biobanking and clinical care: should discrepant diagnoses and pathological findings be returned to research participants? Genet Med. 2012; 14:471–23.
53. International Society for Biological and Environmental Repositories. . best practices for repositories, collection, storage, retrieval and distribution of biological materials for research. Cell Preserv Technol. 2008; 6:3–58.
54. Chadwick R, Berg K. Solidarity and equity: new ethical framework for genetic databases. Nature Rev Genet. 2001; 2:318–21. [PubMed: 11283704]
55. Winickoff DE, Winickoff RN. The charitable trust as a model for genomic biobanks. N Engl J Med. 2003; 349:1180–84. [PubMed: 13679534]
56. Fullerton SM, et al. Return of individual research results from genome-wide association studies: experience of the Electronic Medical Records and Genomics (eMERGE) Network. Genet Med. 2012; 14:424–31. [PubMed: 22361898]
57. Holm IA, Taylor PL. The Informed Cohort Oversight Board: from values to architecture. Minn J Law Sci & Technol. 2012; 13:669–90. [PubMed: 24371432]
58. GENEVA Study. GENEVA Statement on Incidental Findings. Available at: https://genevastudy.org/Incidental_Findings_Files
59. Pulley J, et al. Principles of human subjects protections applied in an opt-out, de-identified biobank. Clin Transl Sci. 2010; 3:42–48. [PubMed: 20443953]
60. Yassin R, et al. Custodianship as an ethical framework for biospecimen-based research. Cancer Epidemiol Biomarkers Prev. 2010; 19:1012–15. [PubMed: 20332272]
61. Cassa CA, et al. Disclosing pathogenetic genetic variants to research participants: quantifying an emerging ethical responsibility. Genome Res. 2012; 22:421–28. [PubMed: 22147367]

62. Kohane IS, Hsing M, Kong SW. Taxonomizing, sizing, and overcoming the incidentalome. Genet Med. 2012; 14:399–404. [PubMed: 22323072]
63. Johnston JJ, et al. Secondary variants in individuals undergoing exome sequencing: screening of 572 individuals identifies high-penetrance mutations in cancer-susceptibility genes. Am J Hum Genet. 2012; 91:97–108. [PubMed: 22703879]
64. Westbrook, MJ., et al. Mapping the incidentalome: estimating incidental findings generated through clinical pharmacogenomics testing. Genet Med. 2012. Available at: http://www.nature.com/gim/journal/vaop/ncurrent/pdf/gim2012147a.pdf
65. Berg, JS., et al. An informatics approach to analyzing the incidentalome. Genet Med. 2012. Available at: http://www.nature.com/gim/journal/vaop/ncurrent/full/gim2012112a.html
66. Ball MP, et al. A public resource facilitating clinical use of genomes. PNAS. 2012; 109:11920–27. [PubMed: 22797899]
67. Thakuria, J. Managing IFs and IRRs in genomic biobanks and archives. Presentation at working group meeting, Managing Incidental Findings and Research Results in Genomic Biobanks & Archives; Washington, DC. 2010 Jun.
68. Wilfond BS, Diekema DS. Engaging children in genomics research: decoding the meaning of assent in research. Genet Med. 2012; 14:437–43. [PubMed: 22323071]
69. Jenkins MM, et al. Ethical issues raised by incorporation of genetics into the National Birth Defects Prevention Study. Am J Med Genet Part C: Semin Med Genet. 2008; 148C:40–46. [PubMed: 18189287]
70. Kaufman D, et al. Ethical implications of including children in a large biobank for genetic-epidemiologic research: a qualitative study of public opinion. Am J Med Genet Part C: Semin Med Genet. 2008; 148C:31–39. [PubMed: 18189289]
71. Hens K, et al. Children and biobanks: a review of the ethical and legal discussion. Hum Genet. 2011; 130:403–13. [PubMed: 21660506]
72. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. . Points to consider: ethical, legal, and psychological implications of genetic testing in children and adolescents. Am J Hum Genet. 1995; 57:1233–41. [PubMed: 7485175]
73. Disclosing genomic incidental findings in a cancer biobank: an ELSI experiment. 2011–16. NIH/NCI/NHGRI #1-R01-CA154517 (Petersen G, Koenig B, Wolf SM, PIs)
74. Ormondroyd E, et al. Disclosure of genetics research results after the death of the patient participant: a qualitative study of the impact on relatives. J Genet Counsel. 2007; 16:527–38.
75. Chan B, et al. Genomic inheritances: disclosing individual research results from whole-exome sequencing to deceased participants' relatives. Am J Bioethics. 2012; 12(10):1–8.
76. Black L, McClellan KA. Familial communication of research results: a need to know? J Law Med Ethics. 2011; 39:605–13. [PubMed: 22084846]
77. Rothstein MA. Disclosing decedents' research results to relatives violates the HIPAA privacy rule. Am J Bioethics. 2012; 12(1):16–17.
78. Tassé AM. Biobanking and deceased persons. Hum Genet. 2011; 130:415–23. [PubMed: 21706182]
79. American College of Medical Genetics and Genomics. Policy statement: points to consider in the clinical application of genomic sequencing. 2012. Available at: http://www.acmg.net/AM/Template.cfm?Section=Policy_Statements&Template=/CM/HTMLDisplay.cfm&ContentID=6979
80. American College of Obstetricians and Gynecologists, Committee on Genetics. . Committee opinion, number 527. Personalized genomic testing for disease risk. Obstet Gynecol. 2012; 119:1318–19. [PubMed: 22617616]
81. Drmanac R. The ultimate genetic test. Science. 2012; 336:1110–12. [PubMed: 22654043]
82. Biesecker LG. Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: lessons from the ClinSeq project. Genet Med. 2012; 14:393–98. [PubMed: 22344227]
83. Biesecker L. Genet Med Letter. In press.
84. Katz, J. The Silent World of Doctor and Patient. New York: Free Press; 1984.

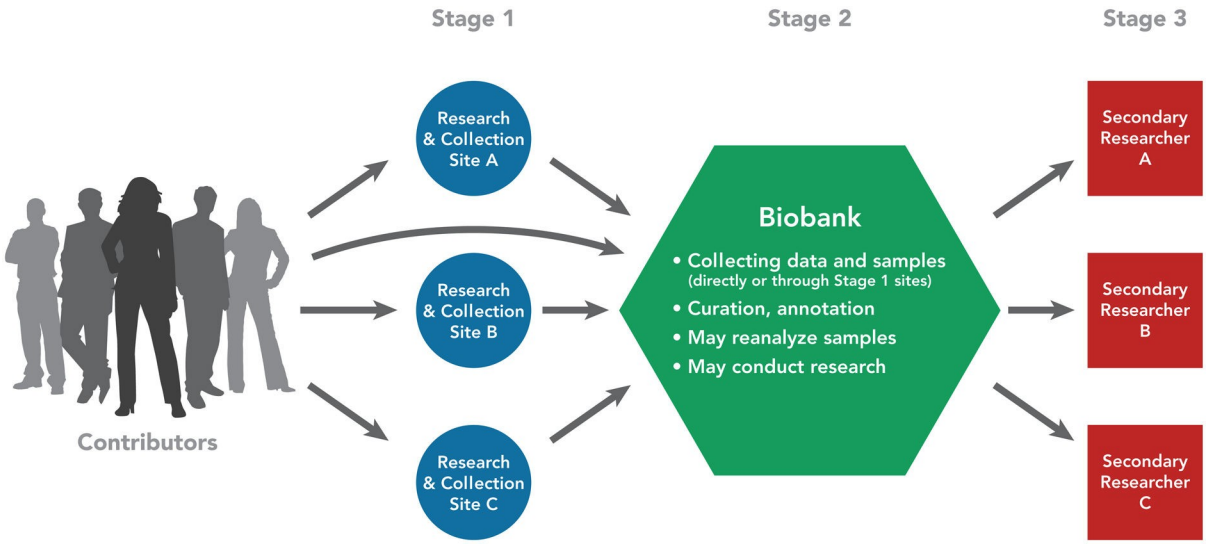


Figure 1.
A biobank research system. (Reprinted with permission from Wolf et al. 2012 (19))

Ethics and Stem Cell Research

Jeremy Sugarman

Required Reading

Jeremy Sugarman, Human Stem Cell Ethics: Beyond the Embryo, Cell Stem Cell 2(6) (2008 Jun 5):529-33. doi: 10.1016/j.stem.2008.05.005.

Douglas Sipp, et al., "Marketing of unproven stem cell–based interventions: A call to action," Science Translational Medicine 9(397) (2017 Jul 5): ii: eaag0426. doi: 10.1126/scitranslmed.aag0426.

George Q. Daley, et al. "Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines." Stem cell reports 6,6: 787-797. doi:10.1016/j.stemcr.2016.05.001 et al

Cell Stem Cell
Forum

Human Stem Cell Ethics: Beyond the Embryo

Jeremy Sugarman[1,2,3,*]
[1]Berman Institute of Bioethics
[2]Department of Medicine
[3]Department of Health Policy and Management
Johns Hopkins University, Baltimore, MD 21205, USA
*Correspondence: jsugarm1@jhmi.edu
DOI 10.1016/j.stem.2008.05.005

Human embryonic stem cell research has elicited powerful debates about the morality of destroying human embryos. However, there are important ethical issues related to stem cell research that are unrelated to embryo destruction. These include particular issues involving different types of cells used, the procurement of such cells, in vivo use of stem cells, intellectual property, and conflicts of interest.

Research with human embryonic stem cells has been inextricably associated with ethical, social, and political debates across the globe. Although some of these debates relate to the integrity of research, arguably the most vociferous and strident debates have involved moral questions regarding the destruction of human embryos to derive stem cells. Amidst this continuing controversy, recent reports by different teams of scientists regarding the possibility of reprogramming cells to create induced pluripotent stem cells (iPSCs) (Holden and Vogel, 2008) have captured the imaginations of scientists and society. Although some accounts in the popular media suggest that the ethical issues associated with stem cell research will be resolved based on these results, because their derivation does not involve destroying embryos, such suggestions neglect scientific arguments for continuing stem cell research with embryos. Setting aside for a moment the particular issues related to research and iPSCs, the recent reports and discussion surrounding them make it at least plausible to imagine a day when there isn't a compelling scientific call to create stem cells from human embryos. If and when that occurs, will all the relevant ethical debates and considerations regarding research and treatment with stem cells be resolved? Unfortunately, they will not. In fact, there is a set of more subtle, yet serious, ethical concerns that are embedded in stem cell research. Accordingly, in this paper, I describe some of the ethical issues that are relevant to stem cell research and treatment that are not related to concerns about the embryo. It is important to acknowledge that, although many of these issues have been raised elsewhere, previous discussions have tended to deal with them in isolation. My hope is that by highlighting the range and nature of these issues, those engaged in stem cell research and its oversight may be better prepared to examine and navigate them in the context of basic and translational research. Such an approach should enhance the likelihood that some of the promises of stem cell research will be realized into safe and effective therapies. I also encourage individuals engaged in stem cell research to continue to develop and adhere to ethical guidelines that reflect the nature of this rapidly moving field.

Types of Cells

There are particular considerations depending on the types of cells collected and used for stem cell research and treatment, including umbilical cord blood, bone marrow, and other somatic cells. Many of these considerations have been described in different literatures, but reviewing them in aggregate suggests some crosscutting concerns regarding the use of human tissue for stem cell research. Further, awareness of the concerns and how they have been managed with respect to particular cell types may provide useful lessons and analogies for other cell types.

Umbilical Cord Blood

An assumption by some involved with cord blood collection is that the placenta would be considered waste save for the use of placental and cord blood. Although this may be true for a majority of persons in some parts of the globe, this may not be true in others (Jenkins and Sugarman, 2005). Indeed, there are wide variety of beliefs and practices regarding the proper treatment and disposition of the placenta that can have profound implications for those being asked to have cord blood collected. For example, in some cultures, the placenta may be ingested by the mother after delivery or it may be used in a variety of ceremonial practices that can include burial or desiccation. In addition to such cultural concerns, there are additional implications for pregnant women and donors (Kurtzberg et al., 2005). First are a set of questions regarding the appropriate timing of consent. Obviously, labor and delivery are not ideal times for deliberation and careful decision making! Ideally then, parents would provide consent for collection in advance of labor and delivery. However, this may not be feasible due to when and where some women access prenatal care. In some cord blood banking centers, clinicians obtain "mini-consent" solely for the collection of cord blood at the time of delivery. Then, subsequent consent is obtained for testing and banking. Second, if cord blood will be banked for potential use, it is typically necessary to quarantine collected units to ensure that they are free from transmissible disease, such as HIV and hepatitis, so that they do not cause harm to recipients. Nevertheless, the testing of a newborn's blood for transmissible diseases may create unanticipated and inadvertent harms related to privacy. Similarly, suppose researchers tested banked cord blood for adult onset disorders. What should be done with the results of such testing? Should parents have access to

such test results even if nothing can be done in childhood to avert the onset of the disorder later in life? Would parents somehow treat differently the child with such a result? Third, many parents have the option of either private cord blood banking, in which cord blood is stored for use in their families and at their expense, and public banking, in which cord blood is donated and stored as a public resource at no cost to the parents. Concerns that have been raised about private banking include whether it is acceptable to market banking services if it is currently unlikely that the material will be used, whether marketing of units of cord blood is acceptable, and the disposition of cord blood should storage fees go unpaid.

Bone Marrow

The harvesting of bone marrow poses obvious pain and risks to the donor. Risks include those related to anesthesia and physical damage coincident to harvesting. Further, a range of cases have been encountered involving the harvesting of bone marrow for use in transplantation that raises important ethical questions. For example, consider the relative who is asked to donate but doesn't feel comfortable doing so or who knows about some medical contraindication to donation (such as being HIV positive) that she does not wish to share with her family. Although such a person would not be eligible to be a donor, how this private information is handled can be difficult for the person believed to be a potential donor as well as for clinicians. Consider also the now famous Ayala case, in which a child was conceived with the hope that she would be a suitable donor for her sibling who stood to benefit from a bone marrow transplant. Ultimately, she was and a transplant was successful (Boyle and Savulescu, 2001). However, this case and those similar to it raise important issues related to the appropriate use of sibling donors who are children. Furthermore, the systems used to identify bone marrow donors are associated with a set of issues related to justice or fairness, especially in regard to the ability to provide suitable donors for patients who are members of racial and ethnic minority communities.

Other Somatic Cells

The collection of other somatic cells (such as adipocytes, hepatocytes, and skin cells) from adults raises some discrete but, at least to date, manageable issues. To be sure the collection of adipocytes and hepatocytes incurs certain discomfort and some discernable physical risk; yet most adults should be capable of providing meaningful informed consent for such collections. Nevertheless, informed consent for such collections, as well as the collection of skin cells by means of a punch biopsy intended for use in developing iPSCs for research, needs to ensure that patients who are asked to provide specimens for the creation of stem cell lines not harbor unrealistic expectations regarding the likelihood that a cell line will certainly be produced and, if so, that it will ultimately redound in personal benefit to them (Hyun, 2008). In addition, when there is intent to create iPSCs, using as an analogy the accepted provisions that have emerged regarding the use of human embryos to create stem cells (Committee on Guidelines for Embryonic Stem Cell Research, National Research Council, 2005; Human Embryonic Stem Cell Research Advisory Committee, National Research Council, 2007; see also the International Society for Stem Cell Research [ISSCR] guidelines), it is essential that the informed consent process include similar information. For example, donors must understand that their cells may be used to create immortalized cell lines with future uses that may be unclear and include the possibility of in vivo experimentation, genetic manipulation, transfer to other institutions, and commercial potential. The lingering concerns of the family members of the person from whom the HeLa cell line was created underscores this point (Gold, 1986; Washington, 1994). In addition, once cell lines have been created, it may be impossible for donors to meaningfully withdraw consent for use. Further, the extent to which identifiable information about the donor will be maintained should be clarified.

Additionally, it appears that it is far easier to derive iPSCs than to develop hESC lines, given in part to that fact that obtaining the necessary cellular materials does not require access to human embryos or oocytes. Although this may prove to be beneficial because easier derivation may make diversity and relative scarcity of stem cells less of an issue, concerns have been raised about their ready use for types of science that raise additional sets of ethical questions (Cyranoski, 2008). For instance, such cells may be used in an effort to derive embryonic germ cells with a hope of ultimately using gametes derived from them for the treatment of infertility. As part of this endeavor, attempts would likely be made to create embryos in the research and treatment process, again raising ethical questions about the embryo. Of course, these questions could arise with other types of stem cells from different sources, provided it is technically possible to derive germ cells from them, but the ready availability of skin cells from those with infertility may make the iPSC approach seem advantageous.

Procurement

Given that informed consent is now expected for most medical research and treatment, it is not surprising that informed consent would be expected for procuring cells used for stem cell research and treatment (see ISSCR guidelines). Regardless of the setting, at a very basic level informed consent requires that the person being asked to provide this consent be capable of engaging in the consent process, both in terms of their decision-making capacity and ability to make a voluntary decision. If so, they must be given relevant information about what is being asked in a manner in which they can understand it. So, as described earlier, labor and delivery can potentially compromise the ability to provide informed consent due to decision-making capacity at that time, or being a graduate student or lab worker may undermine the ability to make a voluntary choice. It is beyond the scope of this paper to outline all the relevant information to be disclosed during the informed consent process for each type of procurement. However, in addition to information regarding the procedures for procurement and the associated risks (physical and social), issues related to future uses, intellectual property, ownership, and control over cell lines and their derivatives should be incorporated into the consent process.

Privacy is another crosscutting issue coupled to cell procurement because it is generally important to keep identifiers when there is a hope to use the cells or their derivatives in clinical settings. After all, there are legitimate concerns

regarding the privacy of this information for those who provide cells. For example, data that might be disclosed include information about current illnesses, genetic predispositions to future diseases, and the like, which may pose social or economic risks to the individual. Accordingly, where possible, protections of privacy should be incorporated into the procurement process.

Finally, selecting the sources for stem cell procurement may ultimately redound into questions of justice. For example, if stem cell lines are developed only among those of a certain ethnic background, and those lines are the ones banked and used to develop cell-based interventions, it is conceivable that the lines might only be suitable for use in those of a similar background. As a result, such therapies may not be available to those of other ethnic groups (Bok et al., 2004). Despite the relative ease of creating iPSCs compared to deriving stem cell lines from embryos, at this point it seems premature to conclude that it will be a simple matter to create autologous iPSCs for transplantation or regenerative medicine (assuming of course that at some point they are demonstrated to be safe and effective for doing so) in such a way that will resolve matters of justice. This is due in large part to the current inefficiencies in the process that translate into substantial cost, making personal iPSCs unaffordable to many who might stand to benefit from a future cellular intervention (Cyranoski, 2008). In addition, depending on the proposed intervention, there may be a substantial time lag between the creation of a cell line and its availability for regenerative purposes. This limitation also adds to the likelihood that individualized iPSC therapies will be largely impractical for widespread clinical use.

In Vivo Use

The in vivo use of stem cells or their derivatives, whether during experimentation with nonhuman animals or humans or by using untested interventions in an attempt to treat patients, can each raise ethical questions, regardless of the cell source.

Nonhuman Animals

In addition to the ethical issues associated with research involving nonhuman animals in general, particular attention in stem cell research has focused on the creation of chimeras. Although chimeras don't seem to raise substantial ethical issues in some settings, for example in allogeneic bone marrow transplantation, the creation of nonhuman-human chimeras has animated popular concern. Of special relevance are studies involving the use of neural stem cells and the possibility of creating human-like characteristics in primates. Taken to an extreme is Michael Crichton's fictionalized account of chimeras in the novel *Next*. Despite the implausibility of Crichton's account, it presents a set of serious issues that are relevant to this sort of science. For example, will the engraftment of stem cells into the brains of nonhuman primates alter the mental capacity of the recipient? As such, it is essential that these sorts of experiments receive close scrutiny (Greene et al., 2005).

First-in-Human Use

First-in-human experiments with cell-based interventions also raise important ethical questions. These include obligations to have adequate preclinical evidence regarding the safety of proposed interventions, that there be reasonable plausibility about benefit, that the scientific design of the first human trials be sound, and that there be robust attention to obtaining meaningful informed consent (Sugarman, 1999). It is arguably only acceptable to move to a first-in-human trial with a cell-based intervention if there is scientific agreement about safety. Determining safety may be particularly complex for stem cell research (Scott, 2008). In addition, early findings regarding iPSCs, although exciting, still face a set of obstacles that must be overcome prior to their possible use in treating human disease. In particular, based upon how they are currently generated, there are concerns about the use of viruses to transmit the reprogramming factors, their undetermined developmental potential after transplantation, and the possibility of tumor formation (Cyranoski, 2008; Holden and Vogel, 2008; Hyun, 2008; Kuehn, 2008). To the extent possible, these sorts of issues need to be resolved in preclinical testing before assessing them again during first-in-human trials.

Once such scientific questions about safety have been addressed, focus must shift toward assessing the likelihood that patients will benefit at some point in the future, even before first-in-human trials are conducted to assess the safety of this approach. That is, future benefit should be plausible based on such factors as determining the mechanisms of disease and the characteristics of the proposed cell-based intervention. This is especially important when the intervention will pose certain harms with unknown benefits, for instance when ablative regimens are used to prevent the rejection of a cell-based intervention.

If there is ample suggestion for the possibility of benefit, at least to the level of "clinical equipoise," meaning that a community of relevant experts is at least divided about the potential for improvement, the next step is the careful design of a particular trial. Essential points for consideration include such issues as dose, route of administration, whether ablative regimens will be employed, choice of monitoring procedures, and the selection of appropriate outcome measures. In addition to these issues, the selection of particular subjects to participate in first-in-human trials also raises important ethical questions. For example, how should the extent of illness affect the appropriateness of participation? Although those who are sickest may have the least to lose, the scientific usefulness of the results of first-in-human trials might be compromised if such patients have a range of comorbidities that confound the results. Alternatively, if healthier patients participate, and the cell-based intervention proves to be harmful, the subjects may have shortened their lives or incurred additional morbidity as a result of participating.

Further, given the hype that can be associated with exciting emerging technologies, especially if they provide hope for treating an otherwise untreatable condition, it can be particularly difficult to obtain consent. In short, the combination of hype and desperation may make it difficult to convey that first-in-human trials are conducted primarily to assess safety, not efficacy. As efforts are taken to translate research findings into clinical practice, it seems prudent to use appropriate terms to describe the state of the field when seeking funding, describing results, and obtaining consent. For instance, at this point a term such as "cell-based intervention" rather than "cell-based therapy" would be more precise because we lack information to substantiate a claim that these interventions will indeed be

therapeutic. Similar issues were encountered in describing ''gene-transfer research'' as ''gene therapy'' (King, 1999).

Using Untested Cell-Based Interventions

Complicating the usual process of carefully staged clinical trials has been the availability of so-called ''stem cell therapies'' in different parts of the world, prior to rigorous demonstrations of safety and efficacy (see report by C. Bodeen and A. Zagier). Such programs are rarely only local and may also attract ''stem cell tourists'' who travel across international borders to receive these untested interventions. Whether iPSCs will be associated with an upswing in these practices due to their relative ease of derivation in comparison to stem cells from embryos (but far more complicated than using cord blood or bone marrow) is unclear. However, transplantation of iPSCs may be especially treacherous, given their propensity to give rise to tumors in animal models. Regardless, the use of cell-based interventions of any type may violate clinicians' fiduciary responsibilities to patients because of the distinct possibility of harming patients as a result of using untested and unproven approaches. Moreover, such approaches may also deprive the scientific and medical communities of any data, whether positive or negative, that might enhance current understanding about these interventions. As the history of medicine makes clear, adopting untested interventions without studying them systematically can be fraught with peril and should be avoided.

Intellectual Property

It would be a mistake to suggest that the ethical issues related to intellectual property and conflicts of interest are unique to stem cell research. Nevertheless, because these conflicts can have profound effects at every stage of the research enterprise and the intellectual, financial, and moral stakes in stem cell research are so high, they warrant mention. A central tension in acknowledging legitimate intellectual property rights is the potential effect such acknowledgments can have on advancing research in general. Obviously, this involves a balance of reward for effort and the desire to enhance scientific understanding regarding stem cell biology. Such questions about intellectual property may also arise in international collaboration as well as when working with commercial entities. The ISSCR urges negotiation among collaborating parties regarding these issues so as to conform to local policies while striving for maximal availability of materials to noncommercial entities in the hopes of advancing science and public benefit (see ISSCR guidelines).Whether such recommendations are achievable in all settings remains unclear, yet explicitly discussing such issues seems to be an important first step.

Continuing legal debates about patented stem cell lines also deserve close attention (Holden, 2008; Scott, 2008). Of note, at a more fundamental level, there is a related debate focusing on the moral acceptability of patenting human tissue, which is reflected in different approaches to patenting across the globe (Plomer et al., 2008).

Conflicts of Interest

Both nonfinancial and financial conflicts of interest may adversely affect good judgment regarding stem cell research. Although this issue is also not unique to stem cell science, substantial concerns have been raised about what could be considered nonfinancial conflicts of interests in stem cell research as scientists rush to publish their findings, sometimes resulting in error. Indeed, recently an editorial in a high-impact journal went so far as to suggest that, ''Competition is good. . .Nonetheless, the fast-moving fields of science are showing some unpleasant tendencies. Researchers are cutting corners and making mistakes. They are making over-hyped promises that will probably be broken.'' (Editorial, 2008) Although at times difficult to assess and manage, it is essential that those engaged in stem cell research be alert to the possibilities of such nonfinancial conflicts in order to maximize the possibility of good science and good medicine.

In contrast, financial conflicts of interest in research may be easier to identify, simply because financial interests can be measured and more easily described than those associated with nonfinancial interests, such as the advancement of scientific and professional concerns. Although having financial interest in research is understandable, financial conflicts of interest have the potential to threaten the integrity of a research effort, and the welfare of research participants, and so raise serious concerns that must be managed. Considerable attention has been directed at these issues in the research enterprise more broadly. Elevated awareness in this area was instigated in part by the death of Jesse Gelsinger during a gene transfer experiment. The principal investigator and the University of Pennsylvania, where the research was conducted, were alleged to have financial interests dependent on the study outcome (see reports from the American Association of Medical Colleges, the American Association of Universities, and the United States General Accounting Office). Current guidelines for stem cell research touch only briefly on issues of conflict of interest (Committee on Guidelines for Embryonic Stem Cell Research, National Research Council, 2005; see also ISSCR guidelines) and thus should be expanded to accommodate these important concerns.

Navigating Ethical Issues in Stem Cell Research

As should be clear, stem cell research and treatment are immersed in ethical issues that go far beyond questions that are related to the destruction of the embryo. Nevertheless, it is essential that individuals involved in stem cell research and treatment be alert to these less polarizing issues so that this incredibly exciting path of research can be pursued in an ethically appropriate fashion. Guidelines issued by the National Academies of Science and the ISSCR address many of the important ethical issues in stem cell research (Committee on Guidelines for Embryonic Stem Cell Research, National Research Council, 2005; Human Embryonic Stem Cell Research Advisory Committee, National Research Council, 2007; see also ISSCR guidelines). Experience using such approaches is now being garnered, and the particular approaches taken are rightly expected to change in step with scientific progress (Zettler et al., 2007). Although guidelines and oversight mechanisms should not be expected to resolve the full range of ethical issues associated with stem cell research, they provide a useful starting point and a process for sorting through the challenges at hand. As such, it is incumbent on those engaged in stem cell research to become familiar with the available guidelines and to help

to improve them as needed to remain in step with scientific advances in the field. Overall, it is imperative that guidelines written to optimize the ethical design and conduct of stem cell research are sensitive to the realities of the enterprise and to its inherent moral concerns.

ACKNOWLEDGMENTS

John Gearhart, PhD, and Andrew Siegel, PhD, JD, provided important comments on an earlier version of this paper.

WEB RESOURCES

American Association of Medical Colleges, Task Force on Financial Conflicts of Interest in Clinical Research. (2001) Protecting subjects, preserving trust, promoting progress-policy and guidelines for the oversight of individual financial interests in human subjects research. http://www.aamc.org/research/coi/firstreport.pdf.

American Association of Universities, Task Force on Research Accountability. (2001) Report on individual and institutional financial conflict of interest. http://www.aau.edu/research/COI.01.pdf.

Bodeen. C., and Zagier, A.S. (2008). China offers unproven medical treatments. Associated Press. http://www.thescizone.com/news/articles/1496/1/China-Offers-Unproven-Medical-Treatments/1.html.

International Society for Stem Cell Research. (2007). Guidelines for the conduct of human embryonic stem cell research. http://www.isscr.org/guidelines/index.htm.

United States General Accounting Office. (2001). HHS direction needed to address financial conflicts of interest. http://www.aau.edu/research/gao.pdf.

REFERENCES

Bok, H., Schill, K.E., and Faden, R.R. (2004). Lancet *364*, 118–121.

Boyle, R.J., and Savulescu, J. (2001). BMJ *323*, 1240–1243.

Committee on Guidelines for Embryonic Stem Cell Research, National Research Council (2005). Guidelines for human embryonic stem cell research (Washington, DC: National Academies Press).

Cyranoski, D. (2008). Nature *452*, 406–408.

Editorial (2008). Nature *452*, 388.

Gold, M. (1986). A conspiracy of cells: one woman's immortal legacy and the medical scandal it caused (Albany, NY: SUNY Press).

Greene, M., Schill, K., Takahashi, S., Bateman-House, A., Beauchamp, T., Bok, H., Cheney, D., Coyle, J., Deacon, T., Dennett, D., Donovan, P., et al. (2005). Science *309*, 385–386.

Holden, C. (2008). Science *319*, 1602–1603.

Holden, C., and Vogel, G. (2008). Science *319*, 560–563.

Human Embryonic Stem Cell Research Advisory Committee, National Research Council (2007). 2007 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research (Washington, DC: National Academies Press).

Hyun, I. (2008). Stem cells from skin cells. Hastings Cent. Rep. *38*, 20–22.

Jenkins, G.L., and Sugarman, J. (2005). J. Lab. Clin. Med. *145*, 118–124.

King, N.M.P. (1999). Hum. Gene Ther. *10*, 133–139.

Kuehn, B.M. (2008). JAMA *299*, 26.

Kurtzberg, J., Lyerly, A.D., and Sugarman, J. (2005). J. Clin. Invest. *115*, 2592–2597.

Plomer, A., Taymor, K.S., and Scott, C.T. (2008). Cell Stem Cell *2*, 13–17.

Scott, C.T. (2008). Neurosurg. Focus *24*, 1–4.

Sugarman, J. (1999). Science *285*, 2071–2072.

Washington, H.A. (1994). Emerge *6*, 29.

Zettler, P., Wolf, L.E., and Lo, B. (2007). Acad. Med. *82*, 6–10.

STEM CELLS

Marketing of unproven stem cell–based interventions: A call to action

Douglas Sipp,[1,2,3,4]* Timothy Caulfield,[5,6] Jane Kaye,[7] Jan Barfoot,[8] Clare Blackburn,[8] Sarah Chan,[9] Michele De Luca,[10] Alastair Kent,[11] Christopher McCabe,[12] Megan Munsie,[13,14] Margaret Sleeboom-Faulkner,[15] Jeremy Sugarman,[16] Esther van Zimmeren,[17] Amy Zarzeczny,[18] John E. J. Rasko[19,20,21]*

The global industry engaged in marketing and delivering unproven stem cell–based interventions through direct-to-consumer advertising continues to grow. Compelling evidence supporting the efficacy of stem cell–based interventions in treating most conditions for which they are currently being marketed is lacking. Moreover, providers often acknowledge neither this deficit nor the potential harms to patients who receive them. Such practices first emerged in the peripheries of international biomedical research and development, but providers have been making inroads in some leading global markets, including Japan, Australia, and the United States. More than a decade of critical commentary by scientific organizations and scholars and enforcement efforts by regulatory authorities have curtailed such practices in some jurisdictions. However, an international consensus on acceptable standards and implementation has yet to be reached. The recent resolution of the Stamina Foundation controversy in Italy, in which scientists and regulatory officials successfully pushed back against a highly publicized provider of unproven stem cell treatments, represents a rare victory in the fight to ensure that unsupported therapeutic claims about stem cells do not go unchallenged.

INTRODUCTION

The growth of the industry engaged in direct-to-consumer online marketing of unproven stem cell interventions has become impossible to ignore (1, 2). Effective measures for regulating this sector both nationally and internationally are urgently needed. Despite the lack of compelling evidence from well-designed studies to support their efficacy (3), or even in some cases in the absence of a plausible biological rationale, providers aggressively promote the use of stem cells for a wide range of indications. Such practices first emerged in the peripheries of international biomedical research and development (4), but providers have been making inroads in some leading global markets, including Japan (5), Australia (2, 6), and the United States (1, 7). Public warnings by scientific and medical groups (8, 9), government organizations (10), and the media (11) have not slowed the global expansion of an industry based on inappropriate marketing of unproven stem cell treatments. The success of this industry has adverse implications for patients' health and the integrity of health care markets, as well as potential repercussions for legitimate biomedical endeavors. It also provides an unsettling glimpse of what may lie ahead for other emerging biomedical technologies, such as mitochondrial replacement therapy and gene editing (12).

Efforts to ensure that stem cell–based interventions rest on a foundation of scientific evidence have not all been in vain. Authorities in Germany were successful in closing a private clinic that marketed stem cell treatments primarily to overseas patients, but only after several reports of serious adverse events, including the death of an infant (13). The Chinese Ministry of Health has made significant strides in curtailing an industry in which hundreds of clinics promoted purported stem cell therapeutics over the Internet (14). More recently, the resolution of the Stamina Foundation controversy in Italy provides an excellent example of academic researchers and regulatory officials successfully pushing back against a highly publicized provider of unproven stem cell treatments (15). In this case, a private foundation aggressively promoted purported therapeutic uses of mesenchymal stem cells, and gained national attention by rallying support from some media and advocacy groups around a narrative of patients' rights and demands for accelerated testing and approval. Following a several-year public debate and scientific review, the "Stamina method" was unanimously rejected and deemed unworthy of further study by a Ministry of Health expert panel. This was an important victory in the fight to ensure that unsupported therapeutic claims about stem cell–based interventions do not go unchallenged. The Stamina Foundation case, in particular,

[1]Riken Center for Developmental Biology, 2-2-3 Minatojima Minamimachi, Kobe 650-0047, Japan. [2]Department of Physiology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. [3]Global Initiatives, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. [4]Riken Center for Advanced Intelligence Project, 1-4-1 Nihonbashi, Chuo-ku, Tokyo 103-0027, Japan. [5]Health Law Institute, 461 Law Centre, University of Alberta, Edmonton, Alberta T6G 2H5, Canada. [6]Faculty of Law and School of Public Health, 461 Law Centre, University of Alberta, Edmonton, Alberta T6G 2H5, Canada. [7]Department of Public Health, University of Oxford, Oxford, UK. [8]Medical Research Council Centre for Regenerative Medicine, School of Biological Sciences, University of Edinburgh, 5 Little France Drive, Edinburgh EH16 4UU, UK. [9]Usher Institute for Population Health Sciences and Informatics, University of Edinburgh, Nine Bioquarter, 9 Little France Road, Edinburgh EH16 4UX, UK. [10]Center for Regenerative Medicine "Stefano Ferrari," Department of Life Sciences, University of Modena and Reggio Emilia, Via G. Gottardi 100, 41125 Modena, Italy. [11]Genetic Alliance UK, Level 3 Barclay House, 37 Queen Square, London WC1N 3BH, UK. [12]Department of Emergency Medicine, University of Alberta, Edmonton, Canada. [13]Centre for Stem Cell Systems, Department of Anatomy and Neuroscience, School of Biomedical Science, Faculty of Medicine, Dentistry and Health Science, University of Melbourne, Level 2, Kenneth Myer Building, 30 Royal Parade Parkville, 3010 Victoria, Australia. [14]Education, Ethics, Law and Community Awareness Unit, Stem Cells Australia, University of Melbourne, Level 2, Kenneth Myer Building, 30 Royal Parade Parkville, 3010 Victoria, Australia. [15]Department of Anthropology, University of Sussex, Brighton BN1 9SJ, UK. [16]Berman Institute of Bioethics and Department of Medicine, Johns Hopkins University, Baltimore, MD 21205, USA. [17]University of Antwerp, Faculty of Law, Research Group Government and Law, Venusstraat 23, 2000 Antwerp, Belgium. [18]Johnson Shoyama Graduate School of Public Policy, University of Regina, 110-2 Research Drive, Regina, Saskatchewan S4S 7H1, Canada. [19]Sydney Medical School, University of Sydney, Sydney, Australia. [20]Gene and Stem Cell Therapy Program, Centenary Institute, Sydney, Australia. [21]Department of Cell and Molecular Therapies, Royal Prince Alfred Hospital, Level 2, Building 89, Missenden Road, Camperdown, New South Wales 2050, Australia.
*Corresponding author. Email: sipp@cdb.riken.jp (D.S.); j.rasko@centenary.org.au (J.E.J.R.)

provides critical insights into how promoters of unproven stem cell treatments harness and manipulate popular sentiments and misconceptions and how scientists and physicians can help to inform both representations by the media and public policy (16). By mobilizing support from international scientific organizations and engaging with the public through traditional and social media, scientists were able to exert a positive influence on national policies that initially appeared to be veering toward state support for pseudomedicine (17).

In this perspective, we draw on the mounting body of literature describing the growth and characteristics of direct-to-consumer marketing of stem cell–based therapies (1, 2, 18, 19) to highlight a number of key features and challenges for broad-based efforts to regulate this industry. We also examine how past successes in countering the premature commercialization of stem cell–based therapies in medicine can inform coordinated responses to this phenomenon nationally and internationally (Fig. 1).

DEFINING THE PROBLEM

The online marketing of stem cells takes place within a context of heightened direct-to-consumer marketing activity in the health sector. Direct-to-consumer advertising of medical products and services reflects the increasingly commercialized and consumer-oriented nature of the health sector. The growth of the Internet and social media has provided new outlets for the marketing of both licensed and unlicensed therapeutics and offers sellers the ability to reach worldwide audiences, amplifying the difficulties of enforcing national laws in a global marketplace (20). Critics have cautioned that such unmediated forms of drug advertising may evade regulatory oversight and provide unreliable or incomplete information regarding risks, efficacy, and treatment alternatives (21).

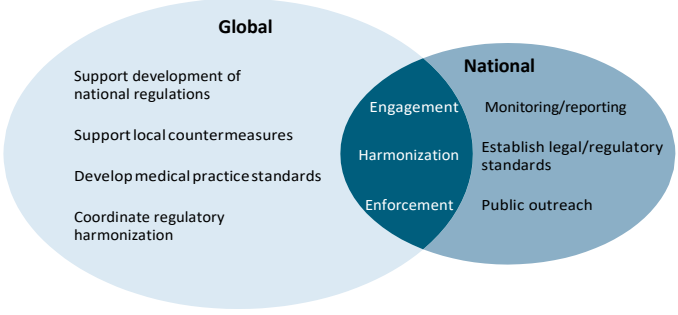
Many professional organizations, including the largest international academic societies in cell therapy (3) and stem cell research (9), have adopted a staged approach to determining what constitutes sufficient evidence of efficacy to justify routine clinical uses of stem cells. These approaches hold that such decisions should typically be based on results from independent, randomized, controlled clinical trials, a view broadly consistent with the norms of evidence-based medicine. Nevertheless, it is important to recognize that study designs and evidentiary standards continue to evolve, and there is a diversity of viewpoints on the nature and quality of evidence needed to support widespread clinical adoption. For this reason, there is inevitably a gray zone between the extremes of strong scientific support and quackery (22). Nonetheless, requiring new stem cell–based interventions to be carefully evaluated for safety and efficacy prior to entering widespread clinical use is consistent with best practices in biomedical research and development, for which there is substantial agreement across many jurisdictions. The steps involved in conventional clinical translation of new therapies include a compelling scientific rationale, well-defined and validated standards for ex vivo processing to achieve cellular product quality and potency, substantial evidence from rigorously designed independent clinical studies demonstrating safety and efficacy in the context of a specific medical indication, and the provision of information from such studies to inform clinical decision-making (23).

Stem cell–based interventions are classified under diverse and potentially incompatible national regulatory frameworks. Many countries have defined a wide spectrum of treatments using human cell and tissue as medical products, which require the oversight of the U.S. Food and Drug Administration (FDA) in the United States or an equivalent authority, such as the European Medicines Agency in the European Union. Other countries, including Australia and Japan, allow physicians' broad discretion in using autologous cells in the course of medical procedures (24). In the majority of nations, however, clear rules governing the clinical use of stem cell–based interventions are absent. Cell-based interventions may be categorized as "products," which are subject to oversight by national regulatory authorities, or as "procedures" conducted within the scope of medical practice. These distinct regulatory philosophies have direct implications for how stem cells can be advertised in different jurisdictions. Evidence standards in the context of commercial advertising, market authorization, and standard of care often vary considerably, as do the enforcement options available to national regulators.

INFLATED MESSAGES

Much of the coverage of stem cells in the popular press to date has been unjustifiably optimistic, both in terms of the potential clinical benefit and the time frame in which such treatments would reach routine clinical application (25). This positive messaging is leveraged by some providers to market unproven stem cell–based interventions. Indeed, the term "stem cell" has been used broadly in promises of youth, rejuvenation, and good health, as well as in the branding of cosmetics, dietary supplements, and sports products (26). Such hyperbole carries with it not only an increased risk of exploitation of vulnerable patients and their families desperate for a cure but also of significant damage to the health of those subjected to these unproven interventions. In the longer term, unfulfilled promises may bring regenerative medicine research and development into disrepute.

In parallel to the hyping of the clinical utility of stem cells, providers of unproven stem cell interventions often display tokens of scientific legitimacy in their marketing messages (Table 1). Such tokens of scientific legitimacy include publications in journals with weak or nonexistent peer review and the registration of pay-to-participate clinical trials on public databases. It can be difficult even for professionals, let alone patients, to determine whether these tokens demonstrate true compliance with the evidentiary



CREDIT: A. KITTERMAN/*SCIENCE TRANSLATIONAL MEDICINE*

Fig. 1. Ways to counter the premature commercialization and deregulation of unproven stem cell therapies. Approaches will require both national and global action by the scientific, medical, and regulatory communities. Advocacy, monitoring, public outreach, rule-making, and enforcement at the national level are necessary activities. These can be complemented by international standard setting, coordination, engagement, and harmonization, which may benefit from support by authoritative international bodies such as the World Health Organization.

standards for developing and testing stem cell therapies.

Misrepresentations of the safety and efficacy of stem cell interventions by providers may build on exaggerated accounts of the state of the science in the popular media and research publications. Media accounts may uncritically report statements about the efficacy of stem cell–based treatments. Such articles are then re-posted on clinic websites, cited in social media, and used in crowd-funding efforts, which may further consolidate public expectations and arouse the curiosity of patients. However, the presumption of the efficacy of stem cell–based interventions is not simply a media issue. The pressure to publish, patent, promote, and commercialize research results, as well as to secure funding for future research, are all contributors to the hyping of stem cell science (27).

REGULATORY TURMOIL

National regulatory authorities have been challenged in recent decades by calls for faster access to medical products, even in advance of the completion of rigorous clinical trials. This may reduce the willingness or ability of policy makers, patient groups, and regulators to take a stand against the commercial promotion of unproven stem cell interventions. In the United States, for example, in the face of a strong push for deregulation by providers and patient activists, the FDA is reviewing its regulations on human cell and tissue products. This comes at a time when so-called "right to try" laws designed to weaken federal oversight of the sale of products to terminally ill patients have been passed in the majority of U.S. states (28), and the newly enacted federal 21st Century Cures Act has included provisions for accelerating approvals of cell biologics (29). New laws passed in Japan to stimulate the regenerative medicine industry through the introduction of conditional approvals (effectively shifting efficacy testing to a postmarket context) (30) have also had a major impact on discussions of how new stem cell–based products should be regulated.

Current trends toward ever greater acceleration of medical approvals are a cause for concern given the limits they inevitably impose on premarket testing and the new ethical and legal questions they raise. Whereas medical product deregulation may promote access to interventions via a market model, there are accompanying risks to the health and economic well-being of patients. In under-regulated markets or those in which direct-to-consumer marketing goes unchecked, patients are obliged to make health care decisions without access to reliable information. Furthermore, providers may not be held accountable for the validity of their therapeutic claims, thereby increasing physical, emotional, and financial risks to patients and their families. When individuals spend their limited resources on ineffective therapies, such expenditure come at the cost of alternative effective therapies and other activities that could improve their quality of life; thus, patients purchasing inefficacious treatments might forego effective care. Further, under-regulated markets make it difficult for experts and non-experts to seek and evaluate information about competing claims. Even within regulated markets, health care is characterized by a high degree of information asymmetry, in which consumers must rely on providers' expert knowledge. Under-regulated health markets, in contrast, permit a lack of reliable information on both sides of the equation that can be profitable to sellers without conferring utility to buyers. Such deficits severely limit both the opportunity for patients to make informed decisions and the incentives for investment in the development of definitive clinical evidence. Deregulation exacerbates these problems and thus increases the likelihood of the wasteful allocation of limited health care resources.

Table 1. Co-opted tokens of scientific legitimacy.

Accreditations and awards	Asserting certification of products or practices by international standards organizations or claiming training certification
Boards and advisers	Convening scientific or medical advisory boards featuring prominent business leaders and academic faculty members
Clinical study registration	Registering trials whose apparent purpose is solely to attract patients willing to pay to participate in them
Ethics review	Marketers may use the imprimatur of "ethics review" to convey a sense of legitimacy to their products or procedures
Location	Renting of laboratory or business space within a legitimate scientific or government institution
Membership	Joining established academic or professional societies to suggest legitimacy by association
Outcome registries	Publication of open-ended voluntary monitoring data sets rather than undertaking controlled clinical trials
Patenting	Suggesting that patent applications or grants indicate clinical utility rather than initiation of an application process or recognition of novelty and inventiveness
Publication	Publishing research and commentary in journals with limited anonymous peer review
Rationales	Citing preclinical and other research findings to justify clinical application without sufficient efficacy testing in humans
Self-regulation	Forming organizations to self-regulate in ways that support premature commercialization
Technical language	Using scientific-sounding words that imply academic rigor
Testimonials and endorsements	Providing expert opinions or celebrity comments on unsupported clinical uses or standing of the provider

TIME TO ACT

What, then, is to be done? Clearly, mutual engagement across a broad range of stakeholders is needed to foster regulatory frameworks that facilitate progress in medical research and ultimately affordable clinical benefit. Uncontrolled advertising and delivery of stem cell interventions for which no evidence or proven rationale exists risks stem cell medicine becoming identified as just another instance of commercialization outpacing evidence. The situation is further complicated by jurisdictional limits on the ability to control cross-border trade in health services (31). If the enormous public investment into stem cell research and development, and indeed its real therapeutic potential, is not to be squandered, it is important that health care systems are structured in ways that incentivize scientifically grounded,

clinically meaningful and valuable innovation while curtailing exploitative practices.

Recent history provides several examples of successful responses against direct-to-consumer stem cell marketers. Journalistic pressure has in some cases been effective in exposing predatory stem cell clinics, leading to the closure of clinics in the United States (32) and Germany (13). Medical specialties, such as plastic surgery (33) and respiratory medicine (34), have issued position statements highlighting the lack of sufficient evidence to justify routine use of stem cells in these fields, and state licensing boards have taken action in a small number of instances (35). The Stamina Foundation incident is a case in point where scientific experts worked with, and sometimes confronted, the media to get the facts straight on the actual state of the science with respect to the cells purportedly used by the clinic in question.

National efforts, while critically important, cannot alone succeed in countering the activities of a transnational industry. The effectively borderless nature of the Internet, the ease of international travel, and the jurisdictional limits on extraterritorial enforcement all create windows of opportunity for clinics targeting patients across national borders. International research and medical organizations can play vital roles in supporting the work of local colleagues but also in setting consensus regulatory and practice standards, driving evidence development, and facilitating the exchange of information among stakeholder groups (Fig. 1). To date, organizations dedicated to stem cell and cell therapy research have taken the lead in global coordination, but recent surveys of the global stem cell marketing industry suggest that much work remains to be done. Proactive efforts should now be implemented by organizations with broad constituencies, such as the World Health Organization.

We propose a cooperative model in which stakeholder groups at the national and international levels work together. In their respective national contexts, stakeholder organizations can contribute by advocating for appropriate regulations and accurate media representations and by supporting regulatory agencies through monitoring and outreach efforts. They can also play a role in developing national guidelines to protect patients and human research subjects. This latter function is particularly important in countries that have yet to formalize rules governing clinical research and use of human stem cell–based products. Similarly, advice from international stem cell research and medical organizations on the development of regulations appropriate to individual nations' specific circumstances could make a significant impact on efforts to harmonize the current patchwork of national regulatory systems.

Approaches for international regulation not only need to develop consistent rules over the commercialization of medical practices and products but also need to give them teeth by developing cross-border partnerships for compliance. Consensus building may best be facilitated by global agencies with the breadth of perspective and authority to coordinate and reconcile divergent interests. We note that international harmonization by professional, industry, and other stakeholder groups has been broadly effective in the regulation of small-molecule drugs and biotechnologies, but this remains underdeveloped with respect to cellular therapeutics, which could similarly benefit from consensus medical practice standards, harmonization of market approval pathways, and resource-building for the development and enforcement of local regulations. In the pharmaceuticals arena, the International Council for Harmonization has been successful in developing and promulgating global drug quality standards. A similar international effort in the field of stem cells and regenerative medicine could help to reduce the heterogeneity and incompatibility of the various national systems governing stem cell products. Additionally, for medical practice, the World Health Organization could contribute through developing guidelines on the responsible clinical use of human cells and tissues and could advise countries seeking to develop local practice standards. Importantly, the success of this model depends on cooperation among relevant national and international organizations around public engagement, harmonization, and enforcement activities (Fig. 1). However, the need for global conformity should not preclude local action where the opportunity arises. Given the time it takes to achieve consensus on policy issues, this would allow local jurisdictions to provide protections while subsequently bringing them into line with a more globally harmonized framework. The globalization of health markets and the specific tensions surrounding stem cell research and its applications have made this a difficult challenge. However, the stakes are too high not to take a united stance.

REFERENCES AND NOTES

1. L. Turner, P. Knoepfler, Selling stem cells in the USA: Assessing the direct-to-consumer industry. *Cell Stem Cell* 19, 154–157 (2016).
2. I. Berger, A. Ahmad, A. Bansal, T. Kapoor, D. Sipp, J. E. J. Rasko, Global distribution of businesses marketing stem cell-based interventions. *Cell Stem Cell* 19, 158–162 (2016).
3. A. Srivastava, C. Mason, E. Wagena, N. Cuende, D. J. Weiss, E. M. Horwitz, M. Dominici, Part 1: Defining unproven cellular therapies. *Cytotherapy* 18, 117–119 (2016).
4. D. Lau, U. Ogbogu, B. Taylor, T. Stafinski, D. Menon, T. Caulfield, Stem cell clinics online: The direct-to-consumer portrayal of stem cell medicine. *Cell Stem Cell* 3, 591–594 (2008).
5. M. Fujita, T. Hatta, R. Ozeki, A. Akabayashi, The current status of clinics providing private practice cell therapy in Japan. *Regen. Med.* 11, 23–32 (2016).
6. A. K. McLean, C. Stewart, I. Kerridge, Untested, unproven, and unethical: The promotion and provision of autologous stem cell therapies in Australia. *Stem Cell Res. Ther.* 6, 33 (2015).
7. H. Taylor-Weiner, J. Graff Zivin, Medicine's wildwest—Unlicensed stem-cell clinics in the United States. *N. Engl. J. Med.* 373, 985–987 (2015).
8. M. Dominici, K. Nichols, A. Srivastava, D. J. Weiss, P. Eldridge, N. Cuende, R. J. Deans, J. E. Rasko, A. D. Levine, L. Turner, D. L. Griffin, L. O'Donnell, M. Forte, C. Mason, E. Wagena, W. Janssen, R. Nordon, D. Wall, H. N. Ho, M. A. Ruiz, S. Wilton, E. M. Horwitz, K. C. Gunter; 2013–2015 ISCT Presidential Task Force on Unproven Cellular Therapy, Positioning a scientific community on unproven cellular therapies: The 2015 International Society for Cellular Therapy Perspective. *Cytotherapy* 17, 1663–1666 (2015).
9. G. Q. Daley, I. Hyun, J. F. Apperley, R. A. Barker, N. Benvenisty, A. L. Bredenoord, C. K. Breuer, T. Caulfield, M. I. Cedars, J. Frey-Vasconcells, H. E. Heslop, Y. Jin, R. T. Lee, C. McCabe, M. Munsie, C. E. Murry, S. Piantadosi, M. Rao, H. M. Rooke, D. Sipp, L. Studer, J. Sugarman, M. Takahashi, M. Zimmerman, J. Kimmelman, Setting global standards for stem cell research and clinical translation: The 2016 ISSCR Guidelines. *Stem Cell Reports* 6, 787–797 (2016).
10. Food and Drug Administration, FDA warns about stem cell claims (2012); www.fda.gov/forconsumers/consumerupdates/ucm286155.htm#Regulation.
11. G. Kolata, "A cautionary tale of 'Stem Cell Tourism'," 22 June 2016, p. A19; www.nytimes.com/2016/06/23/health/a-cautionary-tale-of-stem-cell-tourism.html.
12. R. A. Charo, On the road (to a cure?)—Stem-cell tourism and lessons for gene editing. *N. Engl. J. Med.* 374, 901–903 (2016).
13. R. Mendick, A. Hall, "Europe's largest stem cell clinic shut down after death of baby," 8 May 2011; www.telegraph.co.uk/news/worldnews/europe/germany/8500233/Europes-largest-stem-cell-clinic-shut-down-after-death-of-baby.html.
14. A. Rosemann, M. Sleeboom-Faulkner, New regulation for clinical stem cell research in China: Expected impact and challenges for implementation. *Regen. Med.* 11, 5–9 (2016).
15. L. Margottini, "Final chapter in Italian stem cell controversy?," *Science*, 7 October 2014; www.sciencemag.org/news/2014/10/final-chapter-italian-stem-cell-controversy.
16. E. Cattaneo, G. Corbellini, Stem cells: Taking a stand against pseudoscience. *Nature* 510, 333–335 (2014).
17. P. Bianco, R. Barker, O. Brüstle, E. Cattaneo, H. Clevers, G. Q. Daley, M. De Luca, L. Goldstein, O. Lindvall, C. Mummery, P. G. Robey, Clara S. de Sousa e Brito, A. Smith, Regulation of stem cell therapies under attack in Europe: For whom the bell tolls. *EMBO J.* 32, 1489–1495 (2013).
18. B. A. Liang, T. K. Mackey, Stem cells, dot-com. *Sci. Transl. Med.* 4, 151cm9 (2012).
19. R. Connolly, T. O'Brien, G. Flaherty, Stem cell tourism—A web-based analysis of clinical services available to

international travellers. *Travel Med. Infect. Dis.* 12, 695–701 (2014).
20. T. K. Mackey, R. E. Cuomo, B. A. Liang, The rise of digital direct-to-consumer advertising?: Comparison of direct-to-consumer advertising expenditure trends from publicly available data sources and global policy implications. *BMC Health Serv. Res.* 15, 236 (2015).
21. K. C. Stange, Time to ban direct-to-consumer prescription drug marketing. *Ann. Fam. Med.* 5, 101–104 (2007).
22. M. E. Sleeboom-Faulkner, The large grey area between 'bona fide' and 'rogue' stem cell interventions—Ethical acceptability and the need to include local variability. *Technol. Forecast. Soc. Change* 109, 76–86 (2016).
23. J. Sugarman, D. Sipp, in *Translational Stem Cell Research*, K. Hug, G. Hermerén, Eds. (Humana Press, 2011), pp. 125–135.
24. A. Rosemann, G. Bortz, F. Vasen, M. Sleeboom-Faulkner, Global regulatory developments for clinical stem cell research: Diversification and challenges to collaborations. *Regen. Med.* 11, 647–657 (2016).
25. A. Zarzeczny, C. Rachul, M. Nisbet, T. Caulfield, Stem cell clinics in the news. *Nat. Biotechnol.* 28, 1243–1246 (2010).
26. D. Sipp, Stem cell stratagems in alternative medicine. *Regen. Med.* 6, 407–414 (2011).
27. T. Caulfield, D. Sipp, C. E. Murry, G. Q. Daley, J. Kimmelman, Confronting stem cell hype. *Science* 352, 776–777 (2016).
28. M. J. Rubin, K. R. W. Matthews, The impact of right to try laws on medical access in the United States. *Baker Institute Policy Report* (2016); www.bakerinstitute.org/media/files/files/8c781c33/CHB-pub-PolicyReport66.pdf.
29. K. Servick, Under 21st century cures legislation, stem cell advocates expect regulatory shortcuts. *Science* 10.1126/science.aal0500 (2016).
30. D. Sipp, Conditional approval: Japan lowers the bar for regenerative medicine products. *Cell Stem Cell* 16, 353–356 (2015).
31. I. G. Cohen, *Patients with Passports: Medical Tourism, Law, and Ethics* (Oxford Univ. Press, 2015).
32. J. Forsyth, "Three arrested for peddling miracle stem cell cure," *Reuters*, 2 January 2012; www.reuters.com/article/usstem-cell-arrest-idUSTRE8010RP20120102.
33. F. F. Eaves III, P. C. Haeck, R. J. Rohrich, ASAPS/ASPS position statement on stem cells and fat grafting. *Aesthet. Surg. J.* 31, 716–717 (2011).
34. L. Ikonomou, R. J. Freishtat, D. E. Wagner, A. Panoskaltsis-Mortari, D. J. Weiss, The global emergence of unregulated stem cell treatments for respiratory diseases. Professional societies need to act. *Ann. Am. Thorac. Soc.* 13, 1205–1207 (2016).
35. R. Miller, "Flouting warning, Florida stem-cell cardiologist has license suspended," *Medscape*, 8 March 2012; www.medscape.com/viewarticle/791172.

Funding: We received funding from the Brocher Foundation for a 3-day residential workshop in Hermance, Switzerland, on the subject of marketing unproven stem cell therapies.
Competing interests: D.S. is a member of the Ethics and Public Policy Committees of the International Society for Stem Cell Research. T.C. is a member of the Ethics Committee of the International Society for Stem Cell Research. M.D.L. is a Board Member and Scientific Director of Holostem Terapie Avanzate, Modena, Italy. C.B. is a Coordinator of the EuroStemCell public engagement project, which receives funding from the European Union's Horizon 2020 research and innovation program under grant agreement no. 652796. M.M. is a member of the advisory committee of the Australasian Society for Stem Cell Research, International Society for Stem Cell Research, and International Society for Cellular Therapy. J.S. serves on the Merck KGaA Bioethics Advisory Panel and Stem Cell Research Oversight Committee and on the Quintiles Ethics Advisory Panel and is a member of the Ethics and Public Policy Committees of the International Society for Stem Cell Research. J.E.J.R. is a Director of Pathology at Genea, an IVF company, is a Scientific Patron of FSHD Global Research Foundation, is a committee member of New Directions in Leukemia, is a Director of Cure The Future Foundation, and is President-elect of the International Society for Cellular Therapy. J.E.J.R. is also chair of the Royal Prince Alfred Hospital Institutional Biosafety Committee and Gene Technology Technical Advisory Committee of the Office of the Gene Technology Regulator, Australian Government.

10.1126/scitranslmed.aag0426

Citation: D. Sipp, T. Caulfield, J. Kaye, J. Barfoot, C. Blackburn, S. Chan, M. De Luca, A. Kent, C. McCabe, M. Munsie, M. Sleeboom-Faulkner, J. Sugarman, E. van Zimmeren, A. Zarzeczny, J. E. J. Rasko, Marketing of unproven stem cell–based interventions: A call to action. *Sci. Transl. Med.* 9, eaag0426 (2017).

Abstract

One-sentence summary: Commercial promotion of unsupported therapeutic uses of stem cells is a global problem that should be addressed by coordinated approaches at the national and international levels.

Please cite this article in press as: Daley et al., Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines, Stem Cell Reports (2016), http://dx.doi.org/10.1016/j.stemcr.2016.05.001

Stem Cell Reports
Commentary
OPEN ACCESS

Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines

George Q. Daley,[1,*] Insoo Hyun,[2] Jane F. Apperley,[3] Roger A. Barker,[4] Nissim Benvenisty,[5] Annelien L. Bredenoord,[6] Christopher K. Breuer,[7] Timothy Caulfield,[8] Marcelle I. Cedars,[9] Joyce Frey-Vasconcells,[10] Helen E. Heslop,[11] Ying Jin,[12] Richard T. Lee,[13] Christopher McCabe,[14] Megan Munsie,[15] Charles E. Murry,[16] Steven Piantadosi,[17] Mahendra Rao,[18,19] Heather M. Rooke,[20] Douglas Sipp,[21,22] Lorenz Studer,[23] Jeremy Sugarman,[24] Masayo Takahashi,[25] Mark Zimmerman,[26] and Jonathan Kimmelman[27,*]

[1]Division of Hematology/Oncology, Boston Children's Hospital and Dana Farber Cancer Institute, Boston, MA 02115, USA
[2]Department of Bioethics, Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA
[3]Centre for Hematology, Imperial College, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK
[4]John van Geest Centre for Brain Repair, Department of Clinical Neuroscience, Cambridge CB2 0PY, UK
[5]Department of Genetics, The Azrieli Center for Stem Cells and Genetic Research, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
[6]Department of Medical Humanities, Julius Center, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands
[7]Center for Cardiovascular Research, Nationwide Children's Hospital, Columbus, OH 43215, USA
[8]Health Law Institute, University of Alberta, Edmonton, AB T6G 2H5, Canada
[9]University of California San Francisco School of Medicine, San Francisco, CA 94158, USA
[10]Frey-Vasconcells Consulting, Sykesville, MD 21784, USA
[11]Center for Cell & Gene Therapy, Baylor College of Medicine, Houston Methodist Hospital and Texas Children's Hospital, Houston, TX 77030, USA
[12]Institute of Health Science, Shanghai JiaoTong University School of Medicine/Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, Shanghai, 200025, China
[13]Harvard Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge MA 02138, USA
[14]Department of Emergency Medicine, University of Alberta, Edmonton, AB T6G 2B7, Canada
[15]Education, Ethics, Law & Community Awareness Unit, Stem Cells Australia, Department of Anatomy and Neuroscience, University of Melbourne, Melbourne, Parkville, VIC 3010, Australia
[16]Departments of Pathology, Bioengineering and Medicine/Cardiology, Institute for Stem Cell and Regenerative Medicine, Center for Cardiovascular Biology, University of Washington, Seattle, WA 98109, USA
[17]Samuel Oschin Comprehensive Cancer Institute at Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA
[18]The New York Stem Cell Foundation Research Institute, New York, NY 10023, USA
[19]Q Therapeutics, Salt Lake City, UT 84108, USA
[20]International Society for Stem Cell Research, Skokie, IL 60077, USA
[21]RIKEN Center for Developmental Biology, Kobe, 650-0047 Japan
[22]Keio University School of Medicine, Tokyo, 160-8582 Japan
[23]Center for Stem Cell Biology, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
[24]Johns Hopkins Berman Institute of Bioethics, Baltimore, MD 21205, USA
[25]Center for Developmental Biology, RIKEN, Kobe, Hyogo 650-0047, Japan
[26]ViaCyte, San Diego, CA 92121, USA
[27]Biomedical Ethics Unit, McGill University, Montreal, QC H3A 1X1, Canada
*Correspondence: george.daley@childrens.harvard.edu (G.Q.D.), jonathan.kimmelman@mcgill.ca (J.K.)
http://dx.doi.org/10.1016/j.stemcr.2016.05.001

The International Society for Stem Cell Research (ISSCR) presents its 2016 Guidelines for Stem Cell Research and Clinical Translation (ISSCR, 2016). The 2016 guidelines reflect the revision and extension of two past sets of guidelines (ISSCR, 2006; ISSCR, 2008) to address new and emerging areas of stem cell discovery and application and evolving ethical, social, and policy challenges. These guidelines provide an integrated set of principles and best practices to drive progress in basic, translational, and clinical research. The guidelines demand rigor, oversight, and transparency in all aspects of practice, providing confidence to practitioners and public alike that stem cell science can proceed efficiently and remain responsive to public and patient interests. Here, we highlight key elements and recommendations in the guidelines and summarize the recommendations and deliberations behind them.

As the largest international professional organization engaged with stem cell research, the International Society for Stem Cell Research (ISSCR) has promoted both rigorous scientific inquiry and careful ethical deliberations regarding stem cell science and regenerative medicine. Through its Guidelines for the Conduct of Human Embryonic Stem Cell Research (ISSCR, 2006) and Guidelines for the Clinical Translation of Stem Cells (ISSCR, 2008), the ISSCR has set high standards, offering concrete mechanisms for review and conduct of research and clinical development. These guidelines were designed to promote rapid yet responsible advances in fundamental knowledge and the clinical application of stem cell science. However, in the decade since the release of the first ISSCR guidelines, stem cell science has made remarkable advances but has also encountered numerous new ethical, social, and policy challenges. For example, new discoveries and techniques such as gene editing or mitochondrial replacement offer bold possibilities while also posing ethical conundrums. Moreover, stem cell science and clinical application are increasingly

Stem Cell Reports Vol. 6, 1–11, June 14, 2016 ª 2016 The Author(s) 1

Please cite this article in press as: Daley et al., Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines, Stem Cell Reports (2016), http://dx.doi.org/10.1016/j.stemcr.2016.05.001

pursued across geographical and boundaries, necessitating the need for policies that can be applied internationally. In an effort to keep pace with these many new developments and future prospects, the ISSCR has undertaken a comprehensive revision of its guidelines to account for scientific progress, policy developments, globalization of stem cell activities, and evolving ethics scholarship.

Below, we highlight what has been preserved and what is new in the 2016 ISSCR Guidelines for Stem Cell Research and Clinical Translation. We also provide a window into our deliberations and describe key elements of the process from which these revised guidelines emerged. Specific recommendations embodied in the document are presented in Table 1, giving the reader a synopsis of core principles.

Core Tenets Preserved

The revised guidelines reassert many of the bedrock tenets of the ISSCR's 2006 and 2008 guidelines. At their core, the 2016 guidelines preserve the general imperative that ethically sensitive stem cell research projects should undergo a specialized oversight process. This oversight process, which earlier ISSCR guidelines labeled Stem Cell Research Oversight (SCRO), enlists stem cell-specific expertise and ethical review that acknowledge the uniquely sensitive aspects of research involving human embryos. The 2016 guidelines retain the original three categories of research that guide the oversight process. Category 1 allows routine aspects of research to be conducted under a streamlined process of administrative approval (for example, work with existing human embryonic stem cell or hESC lines). Category 2 defines research projects warranting special scrutiny (for example, derivation of new hESC lines). Category 3 describes impermissible research (for example, reproductive cloning and extended in vitro culture of human embryos beyond 14 days or formation of the primitive streak). Also retained is the requirement for review of certain human-animal chimera experiments, when high degrees of central nervous system or germ lineage chimerism are anticipated. The requirement for explicit consent from donors is emphasized for use of their biomaterials in sensitive aspects of stem cell research, such as the derivation of new hESC lines, generation of embryos via somatic cell nuclear transfer, or future use in commercial development. To facilitate widespread adoption of the informed consent principles embodied in these guidelines, the ISSCR is providing template informed consent documents that can be downloaded and customized to specific protocols (http://www.isscr.org). In the realm of clinical translation, the 2016 guidelines retain stringent standards of preclinical evidence and high aspirations for understanding the mechanism of action of stem cell-based interventions prior to clinical trials. The updated guidelines restate a strong condemnation of the now widespread marketing and delivery of unproven stem cell-based interventions, practices that free-ride on the excitement of stem cell science but have little scientific basis and exploit the hopes of patients and their families.

New Format, Principles, and Formulations

The 2016 guidelines break new ground in several areas. They encompass a broader and more expansive scope of research and clinical endeavor and speak assertively to contentious issues of regulatory practice, the cost of regenerative medicine products, and public communication. The 2016 guidelines are now presented as a single document, with a preamble that articulates core ethical principles for guiding both basic and clinical stem cell research: the integrity of the research enterprise, the primacy of patient welfare, respect for research subjects, transparency, and social justice. These principles provide a foundation for the recommendations that follow in the guidelines and inform their interpretation.

Among the most significant changes is the scope of research that warrants specialized review. Given that human induced pluripotent stem cells (iPSCs) do not engender the same sensitivities as derivation of new hESC lines, the new guidelines exclude the derivation of iPSCs from specialized review, instead calling upon committees that oversee human subjects to scrutinize donor cell procurement. Protocols that employ human iPSCs to achieve human-animal chimerism of the central nervous system or the admixture of human iPSCs with human embryos will, however, still trigger specialized review.

Acknowledging that stem cell researchers engage in many forms of human embryo research that do not explicitly involve derivation or use of hESC lines, the guidelines broaden the scope of specialized review beyond the SCRO function to encompass all forms of human embryo research. The 2016 guidelines specify a process of embryo research oversight (EMRO), which encompasses both embryonic stem cell research and any human embryo research that may not explicitly pertain to stem cells or stem cell lines, such as single cell analyses, genome modification, and embryo chimerism. At present, the guidelines for EMRO review represent the most comprehensive set of principles to inform oversight of the emerging technologies being applied to human embryo research and are consistent with embryo research policy statements by the American College of Obstetricians and Gynecologists (2006), the American Society for Reproductive Medicine (Ethics Committee of American Society for Reproductive Medicine, 2013), the European Society for Human Reproduction and Reproductive Endocrinology (ESHRE Taskforce on Ethics and Law, 2001), and the Human Fertilisation and Embryology Authority (HFEA) of the United Kingdom.

Please cite this article in press as: Daley et al., Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines, Stem Cell Reports (2016), http://dx.doi.org/10.1016/j.stemcr.2016.05.001

Table 1. Summary of Recommendations from the ISSCR Guidelines for Stem Cell Research and Clinical Translation

Section	Recommendation
2.1.1	All research that (a) involves preimplantation stages of human development, human embryos, or embryo-derived cells or (b) entails the production of human gametes in vitro when such gametes are tested by fertilization or used for the creation of embryos shall be subject to review, approval, and ongoing monitoring by a specialized human embryo research oversight (EMRO) process capable of evaluating the unique aspects of the science. The derivation of human pluripotent stem cells from somatic cells via genetic or chemical means of reprogramming (for example, induced pluripotent stem cells or iPSCs) requires human subjects review but does not require specialized EMRO as long as the research does not generate human embryos or entail sensitive aspects of the research use of human totipotent or pluripotent stem cells as outlined in this section.
2.1.2	The EMRO process should be conducted by qualified scientists, ethicists, and community members who are not directly engaged in the research under consideration.
2.1.3	To ensure that human embryo and embryonic stem cell research is proceeding with due consideration, to ensure consistency of research practices among scientists globally, and to specify the nature of scientific projects that should be subject to review, research review and oversight should use the three categories of review described in this section.
2.1.4	The ISSCR supports laboratory-based research that entails modifying the nuclear genomes of gametes, zygotes and/or preimplantation human embryos, performed under a rigorous EMRO process. Such research will enhance fundamental knowledge and is essential to inform any thoughtful deliberations about the potential safety and use of nuclear genome modification in strategies aimed at preventing the transmission of genetic disorders. Until further clarity emerges on both scientific and ethical fronts, the ISSCR holds that any attempt to modify the nuclear genome of human embryos for the purpose of human reproduction is premature and should be prohibited at this time.
2.1.5	Research that entails incorporating human totipotent or pluripotent cells into animal hosts to achieve chimerism of either the central nervous system or germline requires specialized research oversight. Such oversight should utilize available baseline animal data grounded in rigorous scientific knowledge or reasonable inferences and involve a diligent application of animal welfare principles.
2.2.1	Rigorous review must be performed prior to the procurement of all gametes, embryos, or somatic cells that are destined for use in human embryo and stem cell research.
2.2.2	Explicit and contemporaneous informed consent for the provision of all biomaterials for embryo and embryonic stem cell research is necessary, including from all gamete donors. Informed consent should be obtained at the time of proposed transfer of any biomaterials to the research team or during the time that biomaterials are collected and stored for future research use.
2.2.3	Review of procurement protocols must ensure that biomaterials donors are adequately informed about the specific aspects of their voluntary research participation.
2.2.4	Research oversight bodies must authorize all proposals to reimburse, compensate, or provide valuable considerations of any kind to providers of embryos, gametes, or somatic cells.
2.2.5	For provision of oocytes for research, when oocytes are collected outside the course of clinical treatment, compensation for nonfinancial burdens should not constitute an undue inducement.
2.2.6	Informed consent for research donation must be kept distinct from informed consent for clinical treatment.
2.2.7	The informed consent process and study design of human biomaterials procurement should be robust.
2.3.1	Proposals for derivations of new human embryonic stem cell lines should be scientifically justified and executed by scientists with appropriate expertise. Hand-in-hand with the privilege to perform these derivations is the obligation to distribute the cell lines to the research community.
2.3.2	A clear, detailed outline for banking and open access to the new lines should be incorporated into derivation proposals. New pluripotent stem cell lines should be made generally available as soon as possible following derivation and first publication.
2.3.3	Researchers and repositories should develop a policy that states whether and how incidental findings will be returned to research subjects. This policy must be explained during the informed consent process and potential subjects should be able to choose which types of incidental findings they wish to receive, if any. Reporting findings with relevance to public health may be required by law in certain jurisdictions.
2.3.4	The ISSCR encourages the establishment of national and international repositories that are expected to accept deposits of newly derived stem cell lines and to distribute them on an international scale.

(*Continued on next page*)

Please cite this article in press as: Daley et al., Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines, Stem Cell Reports (2016), http://dx.doi.org/10.1016/j.stemcr.2016.05.001

Table 1. *Continued*

Section	Recommendation
2.3.5	Documentation of the provenance of stem cell lines is critical if the cell lines are to be widely employed in the research community. Provenance must be easily verifiable by access to relevant informed consent documents and raw primary data regarding genomic and functional characterization.
2.3.6	Institutions engaged in human stem cell research, whether public or private, academic or nonacademic, should develop procedures whereby research scientists are granted, without undue financial constraints or bureaucratic impediment, unhindered access to research materials for scientifically sound and ethical purposes, as determined under these guidelines and applicable laws.
2.4.1	These ISSCR guidelines should be upheld and enforced through standards of academic, professional, and institutional self-regulation.
3.1.1.1	In the case of donation of cells for allogeneic use, the donor should give written and legally valid informed consent that covers, where applicable, terms for potential research and therapeutic uses, return of incidental findings, potential for commercial application, and other issues.
3.1.1.2	Donors should be screened for infectious diseases and other risk factors, as is done for blood and solid organ donation, and for genetic diseases as appropriate.
3.1.2.1	All reagents and processes should be subject to quality control systems and standard operating procedures to ensure the quality of the reagents and consistency of protocols used in manufacturing. For extensively manipulated stem cells intended for clinical application, good manufacturing practice (GMP) should be followed.
3.1.2.2	The degree of oversight and review of cell processing and manufacturing protocols should be proportionate to the risk induced by manipulation of the cells, their source and intended use, the nature of the clinical trial, and the number of research subjects who will be exposed to them.
3.1.2.3	Components of animal origin used in the culture or preservation of cells should be replaced with human or chemically defined components whenever possible.
3.1.2.4	Criteria for release of cells for use in humans must be designed to minimize risk from culture-acquired abnormalities. Final product as well as in-process testing may be necessary for product release and should be specified during the review process.
3.1.2.5	Funding bodies, industry, and regulators should work to establish a public database of clinically useful lines that contains adequate information to determine the lines' utility for a particular disease therapy.
3.2.1.1	Given that preclinical research into stem cell-based therapeutics makes heavy use of animal models, researchers should adhere to the principles of the three Rs: reduce numbers, refine protocols, and replace animals with in vitro or nonanimal experimental platforms whenever possible.
3.2.1.2	Early phase human studies should be preceded by rigorous demonstration of safety and efficacy in preclinical studies. The strength of preclinical evidence demanded for trial launch should be proportionate with the risks, burdens, and ethical sensitivities of the anticipated trial.
3.2.1.3	All preclinical studies testing safety and efficacy should be designed in ways that support precise, accurate, and unbiased measures of clinical promise. In particular, studies designed to inform trial initiation should have high internal validity; they should be representative of clinical scenarios they are intended to model and they should be replicated.
3.2.2.1	Cells to be employed in clinical trials must first be rigorously characterized to assess potential toxicities through studies in vitro and, where possible for the clinical condition and tissue physiology to be examined, in animals.
3.2.2.2	Risks for tumorigenicity must be rigorously assessed for any stem cell-based product, especially if extensively manipulated in culture, genetically modified, or when pluripotent.
3.2.2.3	For all cell-based products, whether injected locally or systemically, researchers should perform detailed and sensitive biodistribution studies of cells.
3.2.2.4	Before launching high-risk trials or studies with many components, researchers should establish the safety and optimality of other intervention components, like devices or co-interventions such as surgeries.
3.2.2.5	Preclinical researchers should adopt practices to address long-term risks and to detect new and unforeseen safety issues.
3.2.2.6	Researchers, regulators, and reviewers should exploit the potential for using stem cell-based systems to enhance the predictive value of preclinical toxicology studies.

(*Continued on next page*)

Please cite this article in press as: Daley et al., Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines, Stem Cell Reports (2016), http://dx.doi.org/10.1016/j.stemcr.2016.05.001

Table 1. *Continued*

Section	Recommendation
3.2.3.1	Trials should generally be preceded by compelling preclinical evidence of clinical promise in well-designed studies. Animal models suited to the clinical condition and the tissue physiology should be used unless there is very strong evidence of efficacy using similar products against similar human diseases.
3.2.3.2	Small animal models should be used to assess the morphological and functional recovery caused by cell-based interventions, the biological mechanisms of activity, and to optimize implementation of an intervention.
3.2.3.3	Large animal models should be used for stem cell research when they are believed to better emulate human anatomy or pathology than small animal models and where risks to human subjects in anticipated clinical trials are high.
3.2.4.1	Sponsors, researchers, and clinical investigators should publish preclinical studies in full and in ways that enable an independent observer to interpret the strength of the evidence supporting the conclusions.
3.3.1.1	All research involving clinical applications of stem cell-based interventions must be subject to prospective review, approval, and ongoing monitoring by independent human subjects review committees.
3.3.1.2	The review process for stem cell-based clinical research should ensure that protocols are vetted by independent experts who are competent to evaluate (a) the in vitro and in vivo preclinical studies that form the basis for proceeding to a trial and (b) the design of the trial, including the adequacy of the planned endpoints of analysis, statistical considerations, and disease-specific issues related to human subjects protection.
3.3.2.1	Launch of clinical trials should be supported by a systematic appraisal of evidence supporting the intervention.
3.3.2.2	Risks should be identified and minimized, unknown risks acknowledged, and potential benefits to subjects and society estimated. Studies must anticipate a favorable balance of risks and benefits.
3.3.2.3	When testing interventions in human subjects that lack capacity to provide valid informed consent, risks from study procedures should be limited to no greater than minor increase over minimal risk unless the risks associated with the intervention are exceeded by the prospect of therapeutic benefit.
3.3.2.4	A stem cell-based intervention must aim at ultimately being clinically competitive with or superior to existing therapies or meet a unique therapeutic demand. Being clinically competitive necessitates having reasonable evidence that the nature of existing treatments poses some type of burden related to it that would likely be overcome should the stem cell-based intervention prove to be safe and effective.
3.3.2.5	Individuals who participate in clinical stem cell research should be recruited from populations that are in a position to benefit from the results of this research. Groups or individuals must not be excluded from the opportunity to participate in clinical stem cell research without rational justification. Unless scientifically inappropriate, trials should strive to include women as well as men and members of racial and/or ethnic minorities.
3.3.2.6	Informed consent must be obtained from potential human subjects or their legally authorized representatives. Reconsent of subjects must be obtained if substantial changes in risks or benefits of a study intervention or alternative treatments emerge over the course of the research.
3.3.2.7	Prior to obtaining consent from potential adult subjects who have diseases or conditions that are known to affect cognition, their capacity to consent should be assessed formally.
3.3.2.8	Research teams must protect the privacy of human subjects.
3.3.2.9	Patient-sponsored and pay-to-participate trials pose challenges for ensuring scientific merit, integrity, and priority as well as fairness. Accordingly, these financial mechanisms should be used only if they are approved and supervised by a rigorous independent review body that espouses the principles outlined in these guidelines regarding integrity of the research enterprise, transparency, and patient welfare.
3.3.3.1	Consent procedures in any prelicensure phase, but especially early phase trials of stem cell-based interventions, should work to dispel potential research subjects' overestimation of benefit and therapeutic misconception.
3.3.3.2	In general, initial tests of a novel strategy should be tested under lower risk conditions before escalating to higher risk study conditions even if they are more likely to confer therapeutic benefit.
3.3.3.3	Researchers should take measures to maximize the scientific value of early phase trials.
3.3.4.1	Clinical research should compare new stem cell-based interventions against the best therapeutic approaches that are currently or could be made reasonably available to the local population.

(*Continued on next page*)

Please cite this article in press as: Daley et al., Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines, Stem Cell Reports (2016), http://dx.doi.org/10.1016/j.stemcr.2016.05.001

Table 1. *Continued*

Section	Recommendation
3.3.4.2	Where there are no proven effective treatments for a medical condition and stem cell-based interventions involve invasive delivery, it may be appropriate to test them against placebo or sham comparators, assuming early experience has demonstrated feasibility and safety of the particular intervention.
3.3.5.1	An independent data-monitoring plan is required for clinical studies. When deemed appropriate, aggregate updates should be provided at predetermined times or on demand. Such updates should include adverse event reporting and ongoing statistical analyses if appropriate. Data monitoring personnel and committees should be independent from the research team.
3.3.5.2	Given the potential for transplanted cellular products to persist, and depending on the nature of the experimental stem cell-based intervention, subjects should be advised to undergo long-term health monitoring. Additional safeguards for ongoing research subject privacy should be provided. Subject withdrawal from the research should be done in an orderly fashion to promote physical and psychological welfare.
3.3.5.3	To maximize the opportunities for scientific advance, research subjects in stem cell-based intervention studies should be asked for consent to a partial or complete autopsy in the event of death to obtain information about cellular implantation and functional consequences. Requests for an autopsy must consider cultural and familial sensitivities. Researchers should strive to incorporate a budget for autopsies in their trials and develop a mechanism to ensure that these funds remain available over long time horizons if necessary.
3.3.6.1	All trials should be prospectively registered in public databases.
3.3.6.2	Investigators should report adverse events including their severity and their potential causal relationship with the experimental intervention.
3.3.6.3	Researchers should promptly publish aggregate results regardless of whether they are positive, negative or inconclusive. Studies should be published in full and according to international reporting guidelines.
3.4.1	Clinician-scientists may provide unproven stem cell-based interventions to at most a very small number of patients outside the context of a formal clinical trial and according to the highly restrictive provisions outlined in this section.
3.5.1.1	The introduction of novel products into routine clinical use should be dependent on the demonstration of an acceptable balance of risk and clinical benefit appropriate to the medical condition and patient population for which new treatments are designed.
3.5.1.2	Developers, manufacturers, providers, and regulators of stem cell-based interventions should continue to systematically collect and report data on safety, efficacy, and utility after they enter clinical use.
3.5.1.3	Registries of specific patient populations can provide valuable data on safety and outcomes of stem cell-based interventions within defined populations but should not substitute for stringent evaluation through clinical trials prior to introduction into standard care.
3.5.1.4	Off-label uses of stem cell-based interventions should be employed with particular care, given uncertainties associated with stem cell-based interventions.
3.5.2.1	Stem cell-based interventions should be developed with an eye toward delivering economic value to patients, payers, and healthcare systems.
3.5.2.2	Developers, funders, providers, and payers should work to ensure that cost of treatment does not prevent patients from accessing stem cell-based interventions for life-threatening or seriously debilitating medical conditions.
4.1	The stem cell research community should promote accurate, balanced, and responsive public representations of stem cell research.
4.2	When describing clinical trials in the media or in medical communications, investigators, sponsors, and institutions should provide balance and not emphasize statistically significant secondary results when pre-specified primary efficacy results are not statistically significant. They should also emphasize that research is primarily aimed at generating systematic knowledge on safety and efficacy, not therapeutic care.
4.3	The provision of information to patients on stem cell-based interventions must be consistent with the primacy of patient welfare and scientific integrity.
5.1	Researchers, industry, and regulators should work toward developing and implementing standards on design, conduct, interpretation, and reporting of research in stem cell science and medicine.
5.2	These guidelines should be periodically revised to accommodate scientific advances, new challenges, and evolving social priorities.

Please cite this article in press as: Daley et al., Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines, Stem Cell Reports (2016), http://dx.doi.org/10.1016/j.stemcr.2016.05.001

In concordance with recent deliberations in the United Kingdom, the United States, and elsewhere, the 2016 guidelines articulate principles for evaluating both basic and clinically applied research on mitochondrial replacement in embryos aimed at preventing transmission of diseases that are caused by mutations in the mitochondrial genome. In addition, the 2016 guidelines consider basic research on editing of the nuclear genomes of embryos in the permissible category, subject to a rigorous EMRO process. However, given current uncertainties about the safety of nuclear genome editing and a lack of societal consensus on whether any form of heritable nuclear genome editing should be allowed, the guidelines consider uterine transfer of human embryos that have undergone modification of their nuclear genome impermissible at this time. Nonetheless, we recognize that the potential benefits and harms of such technologies remain poorly understood and that more scientific research and ethical inquiry are needed to inform future policy.

Another aspect of the guidelines that has evolved over time is the permissibility of compensating women who provide oocytes for research. Based on a white paper from the ISSCR Ethics and Public Policy Committee (Haimes et al., 2013), the new recommendations reflect an evolving consensus that compensating women who provide oocytes can be ethically permissible. The 2016 guidelines specify a review to determine appropriate compensation for oocyte providers' nonfinancial burdens, so long as such payments do not constitute an undue financial inducement to participate.

Researchers are developing novel methods to probe human development, including the formation of complex organoids and embryo-like structures that manifest potential for self-organization. Experiments wherein tissue aggregates manifest markers of the human primitive streak (for example, Warmflash et al., 2014) or in which human embryos are cultured to reveal post-implantation stages of development (for example, Deglincerti et al., 2016 and Shahbazi et al., 2016) challenge the time-honored limitations of human embryo culture, widely known as the ''14 day rule.'' Embodied in the 1984 Warnock commission report issued in the wake of the first practice of in vitro fertilization (Warnock, 1985), the 14 day rule precludes culture of intact preimplantation human embryos beyond the point of streak formation or 14 days. Applying the standard of primitive streak formation requires judgment and in light of advances in organoid biology, synthetic biology, chimera research, tissue engineering, and recent experiments that have extended embryo culture, there have been recent calls for its reassessment (Hyun et al., 2016). Still more challenging, the task force has provided principles of review for experiments in which human cells might self-organize into embryo-like structures with the realistic potential to become a living organism. The task force concluded that human embryo-like structures at any stage of development should not be maintained in culture for more than the minimal period of time necessary for the study, with the scientific merit of the experiments evaluated in a rigorous EMRO process. Here again, the ISSCR guidelines articulate a core principle to be interpreted by local review, subject to local customs, mores, and legal restrictions. For this emerging area of research on human development, specific elements of review and the distinctions between permissible and impermissible experiments must be re-evaluated over time in light of scientific advances and continued deliberations.

New Stipulations for Preclinical Research, Clinical Translation, and Practice

Despite the relatively immature state of our scientific understanding of mechanisms of stem cell differentiation, transplantation, and tissue integration, clinical testing of stem cell applications has proceeded rapidly, and as judged by the task force, prematurely in many cases. Against calls for relaxed standards for autologous use of cell products, the guidelines retain an emphasis on high standards of cell processing and manufacture. Recent revelations that fungal contamination of drugs prepared by a United States pharmacy caused infections and dozens of deaths (Smith et al., 2013) serve as a reminder that injection into patients of any material, whether chemical or cellular, irrespective of the degree of ex vivo processing, carries the risk of devastating complications. The 2016 guidelines retain the high standard of good manufacturing practice (GMP) in the preparation of cell-based therapeutics.

The guidelines recognize the many opportunities for improving the conduct and reporting of preclinical studies in stem cell research. They recommend that human studies proceed only after rigorous demonstration of safety and efficacy in adequately powered preclinical studies and that clinical trial protocols be subject to rigorous peer review that scrutinizes the weight of preclinical evidence, and balances risk with opportunity, as appropriate to the stage of the trial. The guidelines have sought further to address the problem of irreproducibility of research, articulating high standards for preclinical design, study reporting, and an imperative to publish negative as well as positive results.

Guidance is provided regarding clinical trials involving subjects with diminished capacity. The guidelines also address the use of placebo and sham surgical controls, which have been criticized in the past in the context of studies of surgically implanted cell transplants for Parkinson's disease (Macklin, 1999). Patient funding of clinical trials and direct payments by patients to participate in clinical trials is a trend that, while making some research

Please cite this article in press as: Daley et al., Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines, Stem Cell Reports (2016), http://dx.doi.org/10.1016/j.stemcr.2016.05.001

possible, also raises concerns for the integrity of the research enterprise, objectivity, and patient welfare. The 2016 guidelines articulate a highly limited set of circumstances under which patients may provide funding for trials in which they enroll. New recommendations stipulate that protocols that involve patient funding undergo independent review for scientific rationale, priority, and design and be conducted with independent oversight.

New sections in the 2016 guidelines articulate high standards for transparency in the conduct and reporting of clinical trials, prospective registration in public databases (for example, https://clinicaltrials.gov), reporting of adverse events, and an imperative to publish both negative and equivocal results. Guidelines for the provision of innovative care outside of formal clinical trials have been strengthened and extended, as have admonitions against off-label use of approved cell-based therapies, given the uncertainties associated with heterologous applications of stem cells. A commentary devoted to aspects of clinical translation in the new guidelines appears elsewhere (Kimmelman et al., 2016a).

Social Justice

The 2016 guidelines encourage developers of stem cell-based medicines to aspire to social justice and fairness in their pricing of new products, stipulating that new therapies should provide economic value to patients, payers, and health care systems and that costs should not prevent patients from accessing stem cell interventions for life-threatening or seriously debilitating medical conditions. Developers are encouraged to engage in studies intended to assess comparative effectiveness, as legally mandated in some countries.

With rising commercial interest in stem cell-based medicines, some countries have adopted or are considering streamlined regulatory pathways that grant conditional marketing approval for regenerative medicine products after early stage trials that establish only a baseline of safety and some promise of efficacy. The task force vigorously debated the advantages and potential risks of regulatory changes in the standards of safety and efficacy required for marketed products. The deliberations of the task force and the recommendations embodied in the guidelines emphasize considerations of patient welfare and concerns for patient safety, equity, and the financial sustainability of health care systems. Fewer than one in ten drugs that enter early phase clinical testing gain regulatory approval, while roughly two-thirds of drugs that progress from phase I to more advanced stages ultimately fail for reasons of either safety or ineffectiveness (Waring et al., 2015). Striking the right balance between facilitating patient access to new therapies and rigorous evaluation of new therapies continues to present a challenge for drug regulation. Unless thoughtful choices are made regarding which products are afforded expedited review and conditional marketing approval, regenerative medicine products approved based on early stage trial results could prove either unsafe or ineffective when tested more widely and rigorously. Noting examples where interventions entered clinical practice based on promising pilot clinical data that were ultimately not substantiated in randomized clinical trials (for example, high-dose chemotherapy and autologous bone marrow transplantation for advanced breast cancer; Rettig, 2007), the task force was wary that premature market authorization and clinical practice of unproven intervention strategies can slow their rigorous evaluation in formal trials and erode confidence in the scientific standards of the field. Moreover, there is concern that asking patients, insurance providers, and health care systems to bear the cost of therapies that might not be safe or effective would further stress health care systems and patients already burdened by rising costs.

A Call for Responsible Communication

The guidelines task force took special note of the rising visibility of stem cell research and the exuberance for clinical translation over the past decade. The new guidelines strengthen calls for responsible communication by scientists, clinicians, science communications professionals, industry spokespersons, and members of the media. Exaggeration of potential benefits or understatement of challenges and risks can have tangible impacts on the expectations of the general public, patient communities, and physicians and on the setting of health and science policies (Caulfield et al., 2016).

The Process

The process of revising and updating the ISSCR guidelines began at the 2014 annual ISSCR meeting in Vancouver, Canada, when the ISSCR board of directors empaneled a special task force. The task force of 25 scientists, ethicists, and experts in health care policy, with representatives from nine countries, was chaired by bioethicist Jonathan Kimmelman (McGill University). George Daley (Boston Children's Hospital) and Insoo Hyun (Case Western Reserve University), chairs of the guidelines task forces of 2006 and 2008, respectively, provided continuity and thematic consistency across the three ISSCR guidelines efforts. The work of revisions fell mostheavily upon a core steering committee comprised of Nissim Benvenisty, Timothy Caulfield, Helen Heslop, Charles Murry, Douglas Sipp, Lorenz Studer, and Jeremy Sugarman, who alongside Hyun, Daley, and Kimmelman served as co-chairs of working subgroups of the larger task force. Deliberations began in August 2014 with biweekly conference calls and face-to-face meetings in Boston and at the ISSCR Annual Meeting in June 2015 in Stockholm, when a draft version of the revised guidelines

Please cite this article in press as: Daley et al., Setting Global Standards for Stem Cell Research and Clinical Translation: The 2016 ISSCR Guidelines, Stem Cell Reports (2016), http://dx.doi.org/10.1016/j.stemcr.2016.05.001

Table 2. Number and Sources of Comments Received by the ISSCR on Draft Guidelines

Countries (Number of Comments Received)			
Argentina (1)	Australia (3)	Austria (1)	Brazil (1)
Canada (2)	China (1)	France (1)	Germany (5)
India (1)	Iran (1)	Italy (1)	Israel (1)
Japan (6)	Korea (1)	Netherlands (2)	Norway (1)
Singapore (1)	Spain (2)	Sweden (4)	Turkey (1)
United Kingdom (9)	United States (32)	Regional/International (7)	

Many comments represent the input from multiple individuals or entities.

Consortia, Societies/Networks, Organizations	
American Society for Reproductive Medicine	American Society for Transplantation
American Society of Transplant Surgeons	Associação Brasileira de Terapia Celular (Brazilian Association for Cell Therapy)
Australian Therapeutic Goods Administration	Austrian Society for Regenerative Medicine
California Institute for Regenerative Medicine	Canadian Institutes of Health Research
Catholic Organizations New York	Centre of Genomics and Policy at McGill University
Coriell Institute for Medical Research	European Medicines Agency
German Stem Cell Network	Health Research Authority, United Kingdom
Human Fertilization and Embryology Authority, United Kingdom	International Alliance of Patients' Organizations
International Society for Experimental Hematology	International Stem Cell Forum Ethics Working Party
International Society for Cell Therapy	Japanese Society for Regenerative Medicine
Korean Society for Stem Cell Research	Miltenyi Biotech
Nature Magazine/NPG	Organization for Economic Co-operation and Development
RUCDR Infinite Biologics	Secretariat on Responsible Conduct of Research, Canada
Spanish Agency on Medicines and Medical Devices	Stem Cell Network North Rhine-Westphalia
StemBANCC	

Publication of the draft guidelines was announced widely and request for comment was made to 110 individuals/entities. Comments on the draft guidelines were received from a wide range of individual and organizational stakeholders from around the world. Comments were thoughtfully reviewed by the ISSCR task force. Listing does not constitute endorsement of the ISSCR Guidelines for Stem Cell Research and Clinical Translation.

was released. A three-month period of public comment followed, and targeted inquiries were made to a large number of individuals and organizations for feedback. The task force made particular efforts to solicit perspectives from diverse and underrepresented stakeholders. The taskforce also sought perspectives from individuals within regulatory authorities, funding agencies, industry, patient advocacy organizations, and professional societies. Ultimately, comments and critiques were received from 85 individuals and organizations, reflecting the seriousness with which the global community responded to the issuance of the draft guidelines (Table 2). All responses, including many in exhaustive detail, were cataloged, reviewed, and considered by multiple members of the steering committee, with consultation from working group members on select issues. For the critical last phase of revision, the steering committee was supported by Sally Temple, ISSCR president-elect, who fostered additional communication with the society's executive committee and board of directors. In this final phase, issues flagged in review as contentious were weighed, debated, and reassessed by the working sub-groups and steering committee. After revising the draft released in Stockholm, a penultimate version of the guidelines document was then presented to the ISSCR board of directors at its meeting in December 2015. Following discussion and debate, the ISSCR board of directors voted unanimously to approve the revised

guidelines, which were then subject to extensive reformatting, referencing, and assembly of appendices into a final document, which we now release (ISSCR, 2016).

While we believe the 2016 ISSCR guidelines represent a considerably broader as well as more integrated set of principles and best practices to direct the review of both basic and clinical research protocols, we acknowledge that no guidelines can represent the final word. We appreciate that just as stem cell science and medicine have evolved over the last decade, new challenges will surface that necessitate an ongoing process of reflection, review, reinterpretation, and future revision. Such a contemplative and iterative process is healthy and essential to maintain a culture of adherence to sound ethical principles of research conduct. The 2016 ISSCR guidelines give confidence to practitioners and public alike that stem cell science can proceed efficiently and remain responsive to public and patient interests (Kimmelman et al., 2016b).

Finally, Paolo Bianco, a member of our task force who passed away suddenly and unexpectedly in November 2015, was a stalwart advocate for rigor in science and evidence-based clinical application. He was also a passionate and vocal critic of practitioners who violated the standards embodied in our guidelines. In recognition of Paolo's legacy, the task force has dedicated the 2016 ISSCR guidelines to his memory.

ACKNOWLEDGMENTS

The authors thank the many individuals and organizations who reviewed the draft guidelines and provided comments or otherwise contributed to our deliberations. Despite earnest efforts to digest and consider all feedback, we apologize for the errors that persist in the document, and invite ongoing comment. As a scientific advisor to the following companies, G.Q.D. receives consulting fees or holds equity in MPM Capital, Epizyme, True North, Solasia, Verastem, Raze, and 28/7. J.F.A. acknowledges the support of the Imperial NIHR-BRC. R.A.B. is an advisor to Living Cell Technologies for a New Zealand-based clinical trial. C.K.B. is the founder of LYST Therapeutics, received grant support from Gunze Limited, and is on the scientific advisory board for Cook Biomedical. H.E.H. is founder of Viracyte and holds a licensing agreement with Cell Medica and a collaborative research agreement with Celgene and Bluebird Bio. M.R. works as a consultant in the field of regenerative medicine and serves on the board and SAB of several companies. The opinions expressed by the author are solely his own and do not reflect the policy or work of the companies he is affiliated with. L.S. is a member of the Scientific Advisory Board of Neurona Therapeutics. J.S. is a member of the Bioethics Advisory Committee and Stem Cell Research Oversight Committee for Merck KGaA, for which he receives consulting income and reimbursement for travel expenses. M.T. has research funds from Healios and Sumitomo Dainippon Pharma. M.Z is an employee of Viacyte, Inc.

REFERENCES

American College of Obstetricians and Gynecologists. (2006). ACOG committee opinion no. 347, November 2006: using preimplantation embryos for research. Obstet. Gynecol. *108*, 1305–1317.

Caulfield, T., Sipp, D., Murry, C.E., Daley, G.Q., and Kimmelman, J. (2016). Confronting stem cell hype. Science. http://dx.doi.org/10.1126/science.aaf4620.

Deglincerti, A., Croft, G.F., Pietila, L.N., Zernicka-Goetz, M., Siggia, E.D., and Brivanlou, A.H. (2016). Self-organization of the in vitro attached human embryo. Nature. http://dx.doi.org/10.1038/nature17948.

ESHRE Taskforce on Ethics and Law. (2001). The moral status of the pre-implantation embryo. Hum. Reprod. *17*, 1409–1419.

Ethics Committee of American Society for Reproductive Medicine. (2013). Donating embryos for human embryonic stem cell (hESC) research: a committee opinion. Fertil. Steril. *100*, 935–939.

Haimes, E., Skene, L., Ballantyne, A.J., Caulfield, T., Goldstein, L.S., Hyun, I., Kimmelman, J., Robert, J.S., Roxland, B.E., Scott, C.T., et al. (2013). Position statement on the provision and procurement of human eggs for stem cell research. Cell Stem Cell *12*, 285–291.

Hyun, I., Wilkerson, A., and Johnston, J. (2016). Embryology policy: Revisit the 14-day rule. Nature *533*, 169–171.

International Society for Stem Cell Research (ISSCR). (2006). Guidelines for the conduct of human embryonic stem cell research. http://www.isscr.org/docs/default-source/hesc-guidelines/isscrhescguidelines2006.pdf.

International Society for Stem Cell Research (ISSCR). (2008). Guidelines for the clinical translation of stem cells. http://www.isscr.docs/default-source/clin-trans-guidelines/isscrglclinicaltrans.pdf.

International Society for Stem Cell Research (ISSCR). (2016). Guidelines for stem cell research and clinical translation. http://www.isscr.org/guidelines2016.

Kimmelman, J., Heslop, H.E., Sugarman, J., Studer, L., Benvenisty, N., Caulfield, T., Hyun, I., Murry, C.E., Sipp, D., and Daley, G.Q. (2016a). New ISSCR guidelines on the ethics of stem cell research. Lancet. Published online May 11, 2016. http://dx.doi.org/10.1016/S0140-6736(16)30390-7.

Kimmelman, J., Hyun, I., Benvenisty, N., Caulfield, T., Heslop, H.E., Murry, C.E., Sipp, D., Studer, L., Sugarman, J., and Daley, G.Q. (2016b). Global standards for stem-cell research. Nature. http://dx.doi.org/10.1038/533311a.

Macklin, R. (1999). The ethical problems with sham surgery in clinical research. N. Engl. J. Med. *341*, 992–996.

Rettig, R.A. (2007). False Hope: Bone Marrow Transplantation for Breast Cancer (Oxford, New York: Oxford University Press).

Shahbazi, M.N., Jedrusik, A., Vuoristo, S., Recher, G., Hupalowska, A., Bolton, V., Fogarty, N.M.E., Campbell, A., Devito, L.G., Ilic, D., et al. (2016). Self-organization of the human embryo in the absence of maternal tissues. Nat. Cell Biol. http://dx.doi.org/10.1038/ncb3347.

Smith, R.M., Schaefer, M.K., Kainer, M.A., Wise, M., Finks, J., Duwve, J., Fontaine, E., Chu, A., Carothers, B., Reilly, A., et al. (2013). Fungal infections associated with contaminated methylprednisolone injections. N. Engl. J. Med. *369*, 1598–1609.

Waring, M.J., Arrowsmith, J., Leach, A.R., Leeson, P.D., Mandrell, S., Owen, R.M., Pairaudeau, G., Pennie, W.D., Pickett, S.D., Wang, J., et al. (2015). An analysis of the attrition of drug candidates from four major pharmaceutical companies. Nat. Rev. Drug Discov. *14*, 475–486.

Warmflash, A., Sorre, B., Etoc, F., Siggia, E.D., and Brivanlou, A.H. (2014). A method to recapitulate early embryonic spatial patterning in human embryonic stem cells. Nat. Methods *11*, 847–854.

Warnock, M. (1985). The Warnock report. Br. Med. J. (Clin. Res. Ed.) *291*, 187–190.

Mitochondrial Replacement Techniques & CRISPR

Jeffrey Kahn and Jeremy Sugarman

Required Reading

Anne B. Claiborne, Rebecca A. English and Jeffrey P. Kahn, "Finding an ethical path forward for mitochondrial replacement," Science 351(6274) (2016): 668-670. doi: 10.1126/science.aaf3091.

Jeremy Sugarman, "Ethics and germline gene editing," EMBO reports 16(8) (2015): 879-80. doi:10.15252/embr.201540879

Suggested Further Reading

National Academies of Sciences, Engineering, and Medicine, Mitochondrial replacement techniques: Ethical, social, and policy considerations. (Washington, DC: The National Academies Press 2016).

Marni J. Falk, Alan Decherney, and Jeffrey P. Kahn, "Mitochondrial Replacement Techniques—Implications for the Clinical Community," New England Journal of Medicine 374(12) (2016): 1103-1106. doi: 10.1056/NEJMp1600893.

ETHICS OF NEW TECHNOLOGIES

Finding an ethical path forward for mitochondrial replacement

It is ethically permissible to initiate clinical investigations of mitochondrial replacement techniques in humans so long as significant conditions and restrictions are in place

Anne B. Claiborne[1]*†, Rebecca A. English[1]*, Jeffrey P. Kahn[2]*†

Mitochondria are organelles found in nearly all cells in the human body and are best known for their role in regulating cellular energy balance (sometimes described as the "energy factory" of the cell). Mitochondrial DNA (mtDNA) is the only source of DNA in human cells found outside of the nucleus. The mitochondrial genome contains 37 genes (as compared with the 20,000 to 30,000 found in the nuclear genome), but pathogenic mutations in mtDNA can lead to rare, serious diseases that tend to affect organs with the highest energy demand and can be severely debilitating, progressive, and sometimes fatal in childhood (*1, 2*). mtDNA diseases involve extensive clinical and genetic heterogeneity, creating a challenge for estimates of prevalence. Estimates range from 1 in 200 (*3*) to 1 in 5000 (*4*) people harboring a pathogenic mtDNA mutation that may result in disease.

Proposed mitochondrial replacement techniques (MRTs) would potentially prevent maternal transmission of pathogenic mtDNA by removing from the intended mothers' oocytes (eggs) or zygotes (fertilized eggs) the nuclear DNA (nDNA) and transferring that genetic material into another woman's oocyte or zygote from which the nDNA has been removed (*5*). If shown to be effective, MRT could satisfy the desire of some women to have a genetically related child (by maintaining a nuclear DNA connection), while mitigating the risk of passing on pathogenic mutations in their mtDNA.

[1]Institute of Medicine, U.S. National Academies of Sciences, Engineering, and Medicine, Washington, DC 20001, USA. [2]Johns Hopkins Berman Institute of Bioethics, Johns Hopkins University, Baltimore, MD 21205, USA. *Responsibility for the content of this article rests with the authors and does not necessarily represent the views of the Institute of Medicine (IOM), its committees, and its convening activities. †J.P. Kahn was chair of the IOM committee. ‡Corresponding author. E-mail: aclaiborne@nas.edu

In 2015, the United Kingdom approved MRT for clinical use (*6*) and remains, as of early 2016, the only country to have authorized the techniques. Remaining scientific reviews of MRT and procedures for licensing clinics and individual patients are being finalized. A U.S. Food and Drug Administration (FDA) Advisory Committee discussed MRT in 2014 and received public comments that reflected concern about certain ethical, social, and policy issues surrounding the techniques (*7*). The FDA requested that the Institute of Medicine (IOM) convene an expert committee to consider whether MRT clinical investigations could ethically be conducted. The committee's report was released on 3 February 2016, and we summarize its general findings and recommendations here (*8*).

> ***"The committee's recommendations—place a high priority on a cautious approach and reduction of risk."***

DO ETHICAL, SOCIAL, OR POLICY CONSIDERATIONS PRECLUDE MRT? *Parental desire to pursue MRT.* Women at risk for transmitting mtDNA disease to their offspring but who wish to become mothers currently have reproductive options that result in varying degrees of nuclear genetic connection with the resulting child. Options range from unassisted sexual reproduction (and variable but possibly high risk of disease transmission) or preimplantation genetic diagnosis (with limited ability to identify embryos that would not carry risk of mtDNA disease), to in vitro fertilization using an egg from an unrelated female or adoption or childlessness. The latter three avoid transmission of disease but lack genetic relatedness to offspring. The committee concluded that, from an ethical perspective, the desire of some women to pursue MRT in order to maintain an nDNA connection while significantly reducing the risk of passing on pathogenic mtDNA can justify proceeding with clinical investigations, subject to limits that focus on protecting the health and well-being of children who would be born as a result of MRT.

Genetic modification of germ cells and the germ line. Over the past few decades, there has been a growing international consensus supporting prohibition of genetic modification to germ cells where such genetic changes could be inherited by subsequent generations; in addition to those countries that would prohibit such modifications, a number of countries (including the United States) have laws or policies that would restrict if not fully prohibit it (*9, 10*). There has been much controversy about whether genetic modification of humans, whether inheritable by future generations or not, is ethically acceptable or constitutes inappropriate interference with the human genome (*11*).

It is the committee's view that MRT involves genetic modification, but it is only heritable genetic modification ("germline modification") "if used to produce female offspring because mtDNA is solely maternally inherited, and therefore any changes to mtDNA in male offspring would not be inherited by their descendants" (*8*) (see the figure). The committee considered a number of ethical, social, and policy concerns that have been raised about human genetic modification, whether heritable or not, and concluded that these concerns, in the context of MRT, warrant caution and the imposition of restrictions rather than a blanket prohibition.

Unintended downstream implications of MRT. In the U.S. regulatory context, social and market forces largely drive uptake of innovative reproductive technologies. The committee noted that, if MRT is approved by the FDA, its expanded use for scientifically unproven or potential enhancement purposes would be of concern. For example, expanding the use of MRT to female idiopathic or age-related infertility would considerably enlarge the pool of possible users of the technology. The committee concluded that federal regulations would be needed, and professional society guide-

Published by AAAS

lines interpreting the regulations would be helpful to limit the use of MRT and to prevent expansion into applications that raise other ethical issues. The committee recommended limiting initial clinical investigations to women at risk of transmitting a serious mtDNA disease (i.e., where "the mutation's pathogenicity is undisputed, and the clinical presentation of the disease is predicted to be characterized by early mortality or substantial impairment of basic function") (*8*).

Implications of the DNA contribution of two women. Combining mtDNA and nDNA from two women via MRT could blur traditional concepts of relatedness and undermine intergenerational connections and lineage that are traditionally measured by mtDNA. Some reviews have also suggested that introducing mtDNA from a second woman could have negative effects on the child's self-perception (*12*). In the committee's view, the contribution of genetic material from two women does not form a basis for prohibiting initial MRT investigations; rather, it is a "matter for reflection by families considering undertaking MRT and for societal discussions related to conceptions of identity, kinship, and ancestry" (*8*).

Distinguishing modification of mtDNA and nDNA. A central question for the committee was to consider whether the heritable modification of mtDNA resulting from MRT raises ethical, social, and policy issues comparable to those raised by heritable modification of the nuclear genome. Recent advances in gene-editing technologies such as CRISPR-Cas9, which has been used to modify nDNA and could also be used to modify mtDNA, have renewed international debate about the appropriate use of these technologies (*13*). The committee concluded that there are substantial and "important distinctions between modification of mtDNA and nDNA that matter for an analysis of the ethical, social, and policy issues" of MRT (*8*) and that could allow justification of MRT independent of considerations about heritable genetic modification of nDNA. MRT would involve wholesale replacement of the mtDNA genome. By design, the procedures lack precise editing capabilities that could target particular phenotypes, which helps circumscribe MRT's applications and places some natural limitations on the potential for its misuse. In addition, the committee found that traits encoded by nDNA constitute, in the public understanding, the "core of genetic relatedness" and most forms of disease and that modification of nDNA could be more susceptible to efforts to perform undesirable "genetic enhancement" than would modification of mtDNA. In the committee's judgment, the most germane ethical, social, and policy issues can be avoided through limitations on the use of MRT or are blunted by meaningful differences between the modification of mtDNA and nDNA. Therefore, the committee concluded that it is ethically permissible to conduct clinical investigations of MRT, although only under certain conditions and principles.

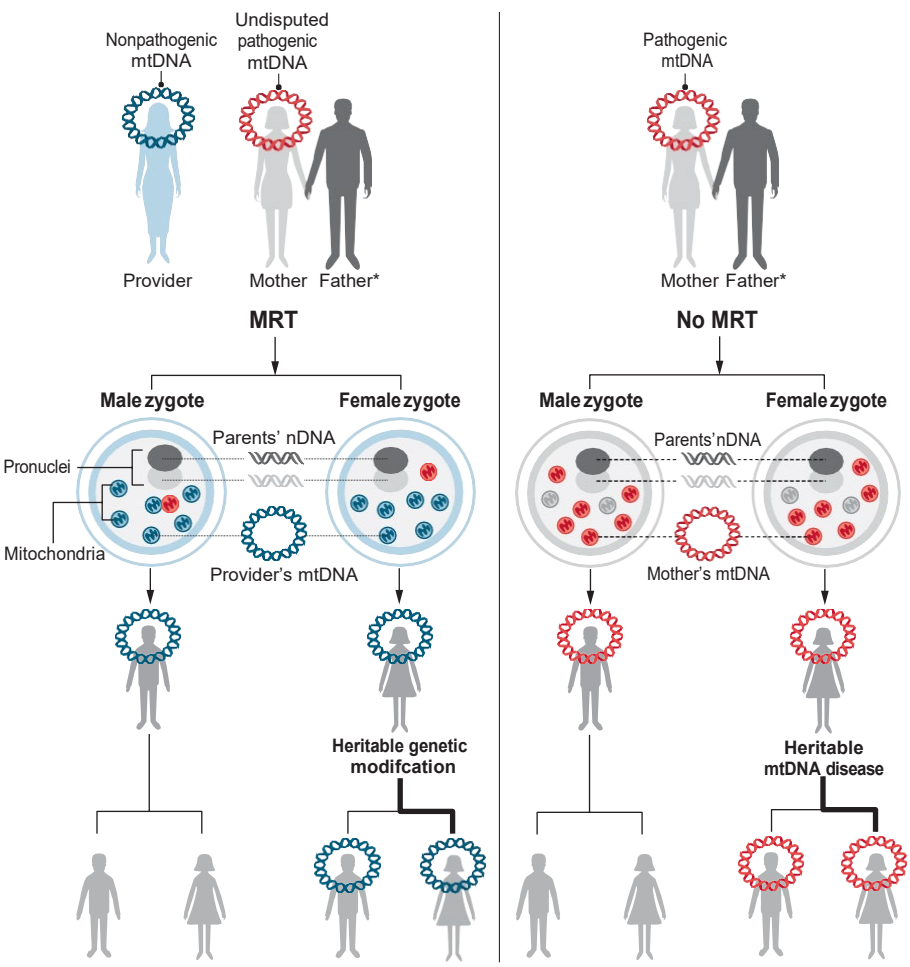


ILLUSTRATION: K. SUTLIFF/*SCIENCE*

Heritable genetic modification via MRT. MRT replaces pathogenic mtDNA from the intended mother with nonpathogenic mtDNA from an oocyte provider. For simplicity, reproductive partners are not shown and are assumed not to carry pathogenic mtDNA mutations. As shown, it is largely accepted that in transferring the nDNA there could be some carryover of pathogenic mtDNA, the level of which would be part of the evaluation of the zygotes suitable for transfer.

REGULATION AND OVERSIGHT OF MRT IN HUMANS. *Initial restriction to transfer of male embryos.* The committee's recommendations for the necessary conditions for any initial investigations of MRT place a high priority on a cautious approach and reduction of risk. The first such condition is that initial investigations be limited to transferring male embryos for gestation. Although there is ethical debate about whether sex selection is acceptable, this recommendation is not based on the preferential selection of one sex "but on the need to proceed slowly and to prevent potential adverse and uncertain consequences of MRT from being passed on to future generations" (*8*). Preclinical research to study intergenerational effects of MRT could continue while investigations proceed in which MRT is used to give some families the opportunity to have male children. Any births resulting from initial investigations would occur in an investigational context, and the initial limitation to males is a matter of responsible clinical investigation focused on minimizing risk. Although some research questions cannot be examined if initial MRT investigations are limited to male embryos, the committee believes that this is justified and necessary to effectively eliminate the risk of introducing adverse genetic modifications that are heritable by future generations. The restriction is also consistent with research staging and other design features used routinely in biomedical clinical investigations.

Before expanding MRT to include transfer of female embryos, robust evidence of

the safety and efficacy of the techniques in males—no matter how long it will take to collect it—would be needed. This evidence would come from experience with numerous male children followed at least through their early childhood years, as well as evidence from animal models that showed no adverse intergenerational effects when MRT was used to produce female offspring. This long-term follow-up is not unique to boys but, rather, is a feature of the necessity of monitoring the results of these initial investigations.

Should sufficiently compelling evidence of safety and efficacy (*8*) be obtained, ex- panding MRT to include transfer of female embryos would remain a controversial step as it would introduce a heritable ge- netic modification. A public discussion and international process is under way to create a shared framework to guide the circumstances of when, if ever, it would be acceptable to perform heritable genetic modification (*13, 14*).

Safeguards in the conduct of clinical investigations. Consideration of issues of safety and efficacy, and the ultimate deter- mination about whether the agency should move forward with evaluating applica- tions for MRT clinical investigations, rests with the FDA. The committee cautioned, however, that, with significant complexi- ties and unknowns remaining regarding the field of mitochondrial genetics, it will

"If shown to be effective, MRT could satisfy the desire of some women to have a genetically related child..."

be important for the scientific commu- nity and the agency to develop a thorough understanding of the state of the science related to mtDNA genetics and MRT to fur- ther inform, in an ongoing way, the benefit and risk assessment entailed in clinical in- vestigations. Although providing guidance to the FDA about what preclinical research would need to be conducted was outside the scope of the committee's charge, the committee noted that the FDA's Advi- sory Committee had suggested a need for animal studies across a variety of species designed to evaluate safety over the long term. If MRT were ever to be extended to transfer of female embryos, the committee noted, "animal studies of second, and per- haps third, generations would need to be performed" (*8*).

The primary value to be considered in assessing the ethics of the balance of benefits and risks in clinical investigations of MRT is the minimization of risk of harm to the resulting child. For initial clinical in- vestigations, the committee recommended, in addition to restricting transfer to male embryos, limiting clinical investigations to women who are otherwise at risk of transmitting a serious mtDNA disease (as defined above). Additional principles for all clinical investigations include attention to clinical issues specific to the technique, such as the health of the intended mother to carry a pregnancy, ensuring technical ex- pertise of MRT investigators and centers, and attention to the science relating to ad- dressing potential mtDNA–nDNA incom- patibilities. The design of protocols should include mechanisms for standardization, maximizing data quality, data sharing, and collection of long-term information. The report also emphasizes the need to pay close attention to best practices for con- sent in research and special attention to communicating the novel aspects of MRT research to potential participants. Trans- parency and partnership with prospective parents and the general public are crucial, and public engagement is vital. ■

REFERENCES AND NOTES

1. S. B. Vafai, V. K. Mootha, *Nature* 491, 374 (2012).
2. R. P. Saneto, M. M. Sedensky, *Neurotherapeutics* 10, 199 (2013).
3. H. R. Elliott, D. C. Samuels, J. A. Eden, C. L. Relton, P. F. Chinnery, *Am. J. Hum. Genet.* 83, 254 (2008).
4. G. S. Gorman *et al.*, *Ann. Neurol.* 77, 753 (2015).
5. D. P. Wolf, N. Mitalipov, S. Mitalipov, *Trends Mol. Med.* 21, 68 (2015).
6. U.K. Parliament, Lords discusses mitochondrial donation (29 October 2015); http://bit.ly/1KIxvfx.
7. FDA, 59th Meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee, Gaithersburg, MD, 25 February 2014 (FDA, 2014); http://1.usa.gov/1OSXrJ8.
8. National Academies of Sciences, Engineering, and Medicine, "Mitochondrial replacement techniques: Ethical, social, and policy considerations" (National Academies Press, Washington, DC, 2016).
9. M. Araki, T. Ishii, *Reprod. Biol. Endocrinol.* 12, 108 (2014).
10. R. Isasi, E. Kleiderman, B. M. Knoppers, *Science* 351, 337 (2016).
11. International Bioethics Committee, "Report of the IBC on updating its reflection on the human genome and human rights" (United Nations Educational, Scientific, and Cultural Organization, Paris, 2015).
12. Nuffield Council on Bioethics, *Novel Techniques for the Prevention of Mitochondrial DNA Disorders: An Ethical Review* (Nuffield Council on Bioethics, London, 2012); http://bit.ly/NuffieldPubs.
13. National Academy of Medicine, "International Summit on Human Gene-Editing: AGlobal Discussion," 1 to 3 December, 2015, Washington, DC (National Academies, Washington, DC, 2015); bit.ly/209qZKZ.
14. National Academies of Sciences, Engineering, and Medicine, Human Gene-Editing Initiative (2015); http:// bit.ly/20w0A75.

ACKNOWLEDGMENTS

R.E. and A.C. were supported by U.S. Department of Health and Human Services, Food and Drug Administration (contract no. 10002265). We would like to thank the members of the Committee and also M. Stathem and M. Berrios of the IOM.

Published online 3 February 2016

10.1126/science.aaf3091

Science

Finding an ethical path forward for mitochondrial replacement

Anne B. Claiborne, Rebecca A. English and Jeffrey P. Kahn

Science **351** (6274), 668-670.
DOI: 10.1126/science.aaf3091originally published online February 3, 2016

Published online: July 2, 2015

Opinion

EMBO reports

Ethics and germline gene editing

Jeremy Sugarman

The current kerfuffle around the use of CRISPR/Cas9 and other gene editing technologies in human germline research is the latest in a series of related controversies at the intersection of science, medicine, and ethics [1]. Soon after a promi- nent *ad hoc* group of scientists called for a moratorium on clinical applications of germ- line gene editing [2], a research group from China published an article that described the genetic modification of human embryos [3]. Although these experiments were performed in nonviable, triploid embryos that were neither intended nor suitable for clinical use, the work nonetheless demonstrates how the prospect of manipulating the human germline elicits hopes and fears and triggers moral debates. Are such concerns warranted? Should research be put on hold while ethical and legal debates take place? Similar tensions arose in the past with recombinant DNA technology, assisted reproductive technologies, gene-transfer research, human cloning, embryonic stem cell research, and mitochondrial replacement therapy. What, if anything, might be learned from these prior debates?

CRISPR/Cas9 is an efficient, inexpensive, and precise method to edit genes at the level of individual nucleotides, which enables the exploration of myriad scientific questions. Moreover, it promises potential new treatments for many human diseases: HIV infection has been targeted, for example, by editing the CCR5 receptor in somatic cells using TALEN (transcription activator-like effector nucleases) [4]. Of course, the prospect of altering the germline opens an even greater range of possibilities. For example, germline editing might be the only means of treating genetic diseases, which are otherwise fatal *in utero*. In addition, gene editing technologies could eventually supplant the need for assisted reproductive technologies in those who are affected by certain genetic diseases. Correcting the faulty gene in the embryo or in gametes could minimize the use of burdensome procedures such as oocyte stimulation and selective abortion following prenatal diagnosis. Moreover, the use of gene editing technologies in conjunction with stem cells, such as induced pluripotent stem cells, might make it possible to generate gametes for reproductive purposes and correct errors in their genome, thus precluding or minimizing the need for oocyte donation.

While such applications might at first glance be appealing and beneficial to those who are directly affected—and the clinicians caring for them—the potential hazards may be substantial. For instance, there are scientific concerns that CRISPR/Cas9, TALEN or Zinc Finger nucleases could inadvertently target other loci in the genome and that such unanticipated genetic manipulations could alter biological functions in problematic ways. In addition, the potential of using gene editing technologies in the human germline adds considerable moral complexity. After all, deliberately manipulating the human germline has generally been viewed as unacceptable, and it is prohibited in many parts of the world [5]. Furthermore, if gene editing technologies are combined with pluripotent stem cells for clinical purposes, the ethical territory is not well charted. Such considerations undoubtedly contributed to the proposed moratorium on clinical experimentation using gene editing technologies.

It is informative to review the global landscape of assisted reproductive technologies in understanding the need for a moratorium. First, although such technologies raise a series of important ethical and clinical challenges, their clinical use is regulated and overseen to variable degrees around the world [6], which results in differences in professional practice. Similarly, in some jurisdictions, including the USA, research related to human embryos and some assisted reproductive technologies can escape substantial oversight, despite the inherent ethical issues associated with it [7]. Arguably, there is currently no uniform, global approach to ensuring that novel clinical approaches using reproductive technologies are scientifically, medically and ethically sound. This stands in contrast to most therapeutic interventions which are expected to be carefully evaluated along with established oversight processes that rest on widely shared ethical principles as described, for example, in the Belmont Report.

Some of the scientific concerns about manipulating the human germline with gene editing technologies will likely be addressed through more research and development to increase safety and efficacy. Regarding the related ethical issues, it is helpful to be aware of prior discussions to better understand what is at stake. There are several arguments against manipulating the human germline. To name just a few, these include that it is unfeasible to provide intergenerational consent, that the consequences are impossible to predict, and that such manipulations pose a threat to human dignity [5,8,9]. Despite their appeal, however, these and other arguments alone are not necessarily sufficient to argue against human germline manipulation. For instance, while intergenerational consent is unfeasible, it has been argued that such a concern may be misplaced since "germline manipulations that effect [*sic*] future generations are not different ethically from any other human decisions that effect [*sic*] future generations" [10]. Similarly, arguments concerning the inability to predict consequences may not be relevant for well-intentioned research to improve the current state of affairs, but rather highlight the need for more data about the safety of proposed interventions. Finally, critical questions about human

Johns Hopkins Berman Institute of Bioethics, Baltimore, MD, USA. E-mail: jsugarman@jhu.edu
DOI 10.15252/embr.201540879 | Published online 2 July 2015

dignity cannot be readily answered in a uniform way owing to profoundly different notions of the concept of dignity. Yet, there are also non-irrefutable reasons for proceeding with germline interventions. These would include clinicians' professional responsibility to choose the optimal treatment for their patients and the right of individuals to have their reproductive autonomy respected [9].

These tensions have been addressed for other biotechnologies in the past. For instance, they were discussed in detail for the possibility of conducting *in utero* gene transfer, which has the potential to inadvertently affect the germline. In this case, a major conference was convened to discuss two pre-protocols for gene transfer in attempt to cure alpha-thalassemia (which is fatal *in utero*) and adenosine deaminase deficient-severe combined immunodeficiency (for which there are treatment alternatives). After considering these issues in depth, the Recombinant DNA Advisory Committee that is responsible for oversight of gene-transfer research in the USA, decided not to permit such research to move forward in 2002 [7].

In view of the unanswered scientific questions and inherent moral issues concerning germline gene editing in general, it is essential to conduct public discussion and deliberation about these emerging technologies. However, given the repetitive nature of these types of debates, it would be valuable to consider not only the issues raised by the technology du jour, but rather seek to articulate general principles so that they might be applied as new technologies with the ability to edit the germline are being developed. Discussions on gene editing in particular that are planned so far include efforts facilitated by academicians such as the Hinxton Group and entities with broad convening power such as the US National Academy of Medicine (formerly the Institute of Medicine). Such efforts can help to underscore the normative aspects of science, separate facts from fiction and provide frameworks to parse scientific practices that are acceptable from those which are unacceptable. Scientists, clinicians, and those affected by conditions that might be ameliorated by germline editing should engage in such efforts to help ensure the integrity of not only the processes, but also the outcomes.

Although it is impossible to forecast the results of such deliberations, given the historical precedents set by gene-transfer research and embryonic stem cell research, it is likely that there will be at least some calls for special oversight of research that could possibly lead to clinical applications. After all, translating gene editing from the bench to the bedside will necessitate overcoming a succession of scientific, technological, and ethical hurdles. Given the legitimate concerns about its safety, aligned with the lack of political and moral consensus about these technologies, especially in the germline, establishing an oversight mechanism seems prudent.

Such an approach to oversight should have representation from a broad range of stakeholders with legitimate interests and expertise to meaningfully engage in a fair process. While it is unlikely to foster global consensus around all of the inherent issues, having an oversight system in place should help to address and manage the most important concerns and might even lead to generating some globally accepted standards akin to most research with human subjects. Regardless, developing and implementing efficient oversight and policies will require resources and will inevitably raise questions about what, if anything, is exceptional about this sort of research. Unfortunately, existing mechanisms for similar types of oversight—research ethics committees, stem cell oversight committees—do not seem to be appropriately suited to perform review for germline editing, given their composition and operating guidelines. In view of the associated moral stakes, scientific promise and public interest, however, establishing widely accepted approaches toward the oversight of the science seems to be a prudent path forward.

References

1. Cyranoski D, Reardon S (2015) *Nature* doi: 10.1038/nature.2015.17378
2. Baltimore D, Berg P, Botchan M *et al* (2015) *Science* 348: 36 – 38
3. Liang P, Xu Y, Zhang X *et al* (2015) *Protein Cell* 6: 363 – 372
4. Tebas P, Stein D, Tang WW *et al* (2014) *N Engl J Med* 370: 901 – 910
5. Araki M, Ishii T (2014) *Reprod Biol Endocrinol* 12: 108
6. Levine AD (2011) *HEC Forum* 23: 15 – 30
7. Dresser R (2004) *Milbank Q* 82: 195 – 214
8. Lappé M (1991) *J Med Philos* 16: 621 – 639
9. Wivel NA, Walters L (1993) *Science* 262: 533 – 538
10. Moseley R (1991) *J Med Philos* 16: 641 – 647

Digital Health Information

Effy Vayena

Required Reading

Effy Vayena, et al., “Ethical challenges of big data in public health,” PLoS computational biology, 11 (2) (2015 Feb 9): e1003904. doi:10.1371/journal.pcbi.1003904

PLOS | COMPUTATIONAL BIOLOGY

EDITORIAL

Ethical Challenges of Big Data in Public Health

Effy Vayena[1]*, Marcel Salathé[2], Lawrence C. Madoff[3], John S. Brownstein[4]

1 Institute of Biomedical Ethics, University of Zurich, Zurich, Switzerland, 2 Center for Infectious Disease Dynamics, Department of Biology, Penn State University, University Park, Pennsylvania, United States of America, 3 ProMED (Program for Monitoring Emerging Diseases), International Society for Infectious Diseases and University of Massachusetts Medical School, Worcester, Massachusetts, United States of America, 4 Children's Hospital Informatics Program, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, United States of America

* vayena@ethik.uzh.ch

Citation: Vayena E, Salathé M, Madoff LC, Brownstein JS (2015) Ethical Challenges of Big Data in Public Health. PLoS Comput Biol 11(2): e1003904. doi:10.1371/journal.pcbi.1003904

Editor: Philip E. Bourne, National Institutes of Health, UNITED STATES

Published: February 9, 2015

Funding: The authors received no specific funding for this article.

Competing Interests: The authors have declared that no competing interests exist. Marcel Salathé is an Associated Editor for *PLOS Computational Biology*.

Introduction

Digital epidemiology, also referred to as digital disease detection (DDD), is motivated by the same objectives as traditional epidemiology. However, DDD focuses on electronic data sources that emerged with the advent of information technology [1–3]. It draws on developments such as the widespread availability of Internet access, the explosive growth in mobile devices, and online sharing platforms, which constantly generate vast amounts of data containing health-related information, even though they are not always collected with public health as an objective. Furthermore, this novel approach builds on the idea that information relevant to public health is now increasingly generated directly by the population through their use of online services, without their necessarily having engaged with the health care system [4, 5]. By utilizing global real-time data, DDD promises accelerated disease outbreak detection, and examples of this enhanced timeliness in detection have already been reported in the literature. The most recent example is the 2014 Ebola virus outbreak in West Africa [6]. Reports of the emerging outbreak were detected by digital surveillance channels in advance of official reports. Furthermore, information gleaned by the various datasets can be used for several epidemiological purposes beyond early detection of disease outbreaks [7, 8], such as the assessment of health behavior and attitudes [4] and pharmacovigilance [9].

This is a nascent field that is developing rapidly [10]. While changes in the ways in which epidemiologic information is obtained, analyzed, and disseminated are likely to result in great social benefits, it is important to recognize and anticipate potential risks and unintended consequences. In this article we identify some of the key ethical challenges associated with DDD activities and outline a framework for addressing them. We argue that it is important to engage with these questions while the field is at an early stage of evolution in order to make ethical awareness integral to its development.

The Context in Which DDD Operates

DDD operates at the intersection of personal information, public health, and information technologies, and increasingly within the so-called *big data* environment. *Big data* lacks a widely accepted definition. The term has, nevertheless, acquired substantial rhetorical power. We use it here in the sense of very large, complex, and versatile sets of data that are constantly evolving in terms of format and velocity [11]. This dynamic environment generates various ethical challenges that relate not only to the value of health for individuals and societies, but also to

individual rights and other moral requirements. In order to spell out these challenges and possible ways of meeting them, it is necessary to take into account the distinctive nature of DDD and the broader context in which it operates. Generally, these distinct features are linked to the methods by which data are generated, the purposes for which they are collected and stored, the kind of information that is inferred by their analysis, and eventually how that information is translated into practice [12]. More specifically, some of these relevant features include those outlined below—namely, the steady growth of digital data, the multifaceted character of big data, and ethical oversight and governance.

The steady growth of digital data

The amount of data that is generated from activities facilitated by the Internet and mobile technologies is unprecedented. The global number of mobile-cellular subscriptions is close to the world's population figures, with a total penetration rate of 96%. The mobile-cellular penetration rate in developing countries is 89%, and about 40% of the world's population is connected to the internet [13]. 82% of the world's online population uses social media and networks. [14]. More than 40,000 health apps are available, and a new higher-level Internet domain name "health" is about to be released [15, 16]. Not surprisingly, personal data have recently been described as a new asset class with the potential to, among other things, transform health care and global public health [17].

The multifaceted character of big data

Big data cannot be readily grouped into clearly demarcated functional categories. Depending on how they are queried and combined with other datasets, a given dataset can traverse categories in unpredictable ways. For example, health data can now be extracted from our purchases of everyday goods, our social media exchanges, and our web searches. New data analytics constantly change the kinds of outcomes that become possible. They go beyond early identification of outbreaks and disease patterns to include predictions of the event's trajectory or likelihood of reoccurrence [18, 19]. These new possibilities render good data governance, which ensures their ethical use, all the more complex.

Ethical oversight and governance

Public health surveillance and public health research are governed by national and international legislation and guidelines. However, many of these norms were developed in response to very different historical conditions, including technologies that have now been superseded [20]. Such mechanisms may not be appropriate or effective in addressing the new ethical challenges posed by DDD, nor the questions that will be raised if DDD is effectively integrated into standard public health systems. Health research utilizing social media data and other online datasets has already exerted pressure on existing research governance procedures [21].

Ethical Challenges

Against this background we have identified three clusters of ethical challenges facing DDD that require consideration (Table 1).

A. Context sensitivity

At the crux of the debate on the ethics of big data lies a familiar, but formidably complex, question: how can big data be utilized for the common good whilst respecting individual rights and liberties, such as the right to privacy? What are the acceptable trade-offs between

Table 1. Mapping the ethical issues in digital disease detection.

Categories	Ethical Challenges	Specific Examples	Values
Context sensitivity	Differentiating between commercial versus public health uses of data	Is identification permitted? Is consent required for DDD uses? If so, has consent been obtained? Can it be revoked?	Privacy and contextual integrity
	User agreements, terms of service, participatory epidemiology	Are users protected in all contexts irrespective of privacy laws that differ according to jurisdiction?	Transparency
	Global health issues	Are privately collected data open to global public health uses?	Global justice
Nexus of ethics and methodology	Robust methodology: algorithm validation, algorithm recalibration, noise filtering, and feedback mechanisms	False identification of outbreaks and inaccurate predictions of outbreak trajectory	Risk of harm
		Pressure to mobilize public health resources in light of rapidly spreading unvalidated predictions	Fair use of resources
	Data provenance	Awareness about public health uses of personal data (in aggregated form)	Trust, transparency, accountability
Legitimacy requirements	Best practice standards	Is there a shared code of practice amongst all those working on DDD?	Trustworthiness
	Monitoring bodies (policies for ongoing monitoring and action plans for correction of false results)	Is there a mechanism for quick response to inaccuracies about outbreaks?	Trust, transparency, accountability
	Paced integration of DDD to standard surveillance systems	Are there mechanisms for redressing harms caused by DDD activities?	Justice
	Communication to the public (prevent hype)	Management of expectations	Common good

doi:10.1371/journal.pcbi.1003904.t001

individual rights and the common good, and how do we determine the thresholds for such trade-offs? These ethical concerns and the tensions between them are not new to public health research and practice, but now they must be addressed in a new context, with the result that appropriate standards may vary according to the type of big data activity in question.

It is clear that the context of DDD differs in significant ways from other types of big data activity concerned with health. DDD has a public health function, aiming ultimately to improve health at the population level. Public health is a common good from which all individuals benefit and one that is essential to human development and prosperity. There is a clear contrast here with forms of corporate activity that may use the exact same data (i.e., social networking data), but for other purposes, such as advertising. The former aims at fostering a public good (health); the latter at generating a corporate profit. Such differences have important ethical implications. A context-sensitive understanding of ethical obligations may reveal that some data uses that may not be acceptable within corporate activity (e.g., user profiling and data sharing with third parties) may be permissible for public health purposes. Furthermore, societal obligations to foster the common good of public health may generate duties on corporate data collectors to make data available for use in DDD.

Pursuing this line of thought, it is arguable that privacy considerations that apply in standard public health practice will have to be creatively extended and adapted to the case of DDD. This will result in new standards that relate to data from a diverse range of sources, e.g., self-tracking, citizen scientists, social networks, volunteers, or other participatory contexts [22, 23]. Such new standards are urgently needed, especially as greater convergence of datasets becomes possible. An illustration of global activity on this front is the United Nations Global Pulse project [24]. This project explores the concept of data philanthropy whereby public−private partnerships are formed to share data for the public good. Such so-called *data commons*, operating on the basis of clear rules about privacy and codes of conduct, can profoundly affect disease surveillance and public health research more generally.

Another dimension of context relates to global justice. Historically, new health tools have been predominantly used to improve the health of inhabitants of the better-off parts of the world. DDD projects that access global data are often less costly than traditional public health approaches. They could thus offer a potential breakthrough in early disease detection that would benefit communities throughout the world [25, 26]. However, this potential brings moral obligations in its train. This requires not only efforts to detect diseases in poorer parts of the world but also measures to ensure that the way data are collected and processed respect the rights and interests of people from these diverse regions and communities. This raises difficult questions of cultural relativity, such as whether standards of privacy can take different forms in relation to different cultures or whether some minimal core of uniform standards is also justified.

B. Nexus of ethics and methodology

Robust scientific methodology involves the validation of algorithms, an understanding of confounding, filtering systems for noisy data, managing biases, the selection of appropriate data streams, and so on. Some have expressed skepticism about the role that DDD can play in public health practice given its early state of development [27]. In 2013, when Google Flu Trends overestimated flu prevalence levels in the US, further concerns were raised about the sensitivity of this methodology to the digital environments created by users' behavior—for example, different uses of search terms [28] from those used to develop the initial algorithm or the distorting influence of searches arising from media coverage of the flu [29, 30].

Methodological robustness is an ethical, not just a scientific, requirement. This is not only because limited resources are wasted on producing defective results or because trust in scientific findings is undermined by misleading or inaccurate findings. There is a further risk of harm to individuals, businesses, or communities if they are falsely identified as affected by an infectious disease. The harm can take many forms, including financial losses, such as a tourist region being falsely identified as the location of a disease outbreak; stigmatization of particular communities, which may adversely affect individual members; and even the infringement of individual freedoms, such as the freedom of movement of an individual falsely identified as a carrier of a particular disease.

The issue of data provenance comes within the remit of ethically sound methodology. Currently published DDD studies and other initiatives have mostly used data that are in the public domain (e.g., Twitter) or that have been contributed by individuals with their explicit consent for use in disease surveillance (flunearyou.org). While in principle data in the public domain are open to being used for public health purposes, what constitutes public domain on the Internet is the subject of lively debate [31]. Especially in the context of data derived from social network interactions, it remains unclear whether users understand in what ways their data can be used and who may access them [32]. Any DDD project will inevitably have to navigate this uncertain environment and so must exercise diligence about data provenance and exhibit transparency about its uses.

C. Bootstrapping legitimacy

Legitimacy concerns the extent to which DDD is actually ethically justified in imposing the compliance burdens that it does and also the extent to which it is perceived to be ethically justified. In recent years the concept of "global health security" has been mobilized by international organizations, nongovernmental organizations, and national governments to strengthen the legitimacy of systems of disease surveillance both nationally and globally. The idea of human security has been expanded to include health (protection from infectious diseases and other health hazards), augmenting state responsibilities to provide appropriate safeguards. The

revised International Health Regulations [33], which set out a global legal framework for disease detection and response, are premised on the understanding that in our globalized world diseases spread rapidly and therefore on the need for the timely notification of any public health threat of potentially international significance. They also recognize the importance of information gathering from various sources, including unofficial or informal ones, whilst also requiring that the validity of such information be verified [34]. This creates a legitimate space for DDD activities because they are precisely responses to both the accelerated detection and the global nature of the spread of disease.

However, even if ethical arguments already justify the DDD enterprise, they only serve as a starting point. DDD will have to build its own legitimacy over time as an integral part of its approach. This means that the issues under categories A and B have to be constantly engaged with thorough processes that bootstrap DDD's legitimacy, so it is continuously self-generating and enhanced over time. So, for example, it is not enough simply to appeal to the great contribution that DDD stands to make to the common good of public health. It is important that this contribution is made in certain ways rather than others, through transparent procedures that are worthy of engendering trust among those individuals whose data are used in DDD.

Current regulatory and ethical oversight mechanisms are ill-equipped to address the entire spectrum of DDD-type activities. The distinction between public health and public health research has long been considered a problematic one, and this is even more evident in the DDD context. Consider an analogy with participant-led biomedical research—a growing movement of people collecting data about themselves and conducting various forms of research in large groups. Either such activities fall through the cracks of the existing oversight mechanisms or else, if they do not, those mechanisms impose inappropriate burdens upon them [35, 36]. Participatory approaches to disease surveillance confront similar challenges. Individuals report on disease symptoms on online platforms, (e.g., flunearyou.org) which enables them to contribute to the common good of disease surveillance and often to receive feedback about disease prevalence in their area [37]. This active participation potentially empowers individuals and democratizes the process of scientific discovery. However, data (personally identifiable information, geolocation, etc.) that are collected for DDD purposes need to be governed in ways that minimize the risk of harm to participants. For example, if individuals take personal risks in order to report events of public health importance (i.e., a farmer reporting avian flu at risk of losing his flock), those risks should be mitigated by appropriate policies (e.g., compensation) that acknowledge the societal contribution and the local/personal costs.

For the purposes of ensuring its legitimacy, DDD must develop internal mechanisms such as its own best-practice standards, including monitoring boards with the concrete mandate to ensure that risks and costs to individuals and communities are proportional to benefits. Such boards should also be empowered to negotiate compensation schemes for harms that have been suffered. As in standard public health practice individuals may be adversely affected by a practice that aims to secure the health of the population. However, this laudable goal does not remove the obligation to respect individual rights and dignity in its pursuit. Neither of these standards are to be equated with an automatic insistence on individual consent. Instead, they consist of distinct individual entitlements, of the sort set out in the Universal Declaration of Human Rights, and the inherent value in all human beings, which underlies them.

Conclusions

The emergence of DDD promises tangible global public health benefits, but these are accompanied by significant ethical challenges. While some of the challenges are inherent to public health practice and are only accentuated by the use of digital tools, others are specific to this

approach and largely unprecedented. They span a wide spectrum, ranging from risks to individual rights, such as privacy and concerns about autonomy, to individuals' obligations to contribute to the common good and the demands of transparency and trust. We have grouped these concerns under the headings of context sensitivity, nexus of ethics and methodology, and bootstrapping legitimacy. It is vital that engagement with these challenges comes to be seen as part of the development of DDD itself, not as some extrinsic constraint. We intend this paper to be a contribution to the development of a more comprehensive and concrete ethical framework for DDD, one that will enable DDD to find an ethical pathway to realizing its great potential for public health.

References

1. Brownstein JS, Freifeld CC, Madoff LC (2009) Digital disease detection—harnessing the Web for public health surveillance. N Engl J Med 360: 2153–5. doi: 10.1056/NEJMp0900702 PMID: 19423867
2. Hay SI, George DB, Moyes CL, Brownstein JS (2013) Big data opportunities for global infectious disease surveillance. PLoS Med 10: e1001413. doi: 10.1371/journal.pmed.1001413 PMID: 23565065
3. Salathé M, Bengtsson L, Bodnar TJ, Brewer DD, Brownstein JS, et al. (2012) Digital epidemiology. PLoS Comput Biol 8: e1002616. doi: 10.1371/journal.pcbi.1002616 PMID: 22844241
4. Salathé M, Khandelwal S (2011) Assessing vaccination sentiments with online social media: implications for infectious disease dynamics and control. PLoS Comput Biol 7: e1002199. doi: 10.1371/journal.pcbi.1002199 PMID: 22022249
5. Salathé M, Freifeld CC, Mekaru SR, Tomasulo AF, Brownstein JS (2013) Influenza A (H7N9) and the importance of digital epidemiology. N Engl J Med 369: 401–4. doi: 10.1056/NEJMp1307752 PMID: 23822655
6. Anema A, Kluberg S, Wilson K, Hogg RS, Khan K, et al. (2014) Digital surveillance for enhanced detection and response to outbreaks. Lancet Infect Dis 14: 1035–36. doi: 10.1016/S1473-3099(14)70953-3 PMID: 25444397
7. Chan EH, Brewer TF, Madoff LC, Pollack MP, Sonricker AL, et al. (2010) Global capacity for emerging infectious disease detection. Proc Natl Acad Sci USA 107: 21701–6. doi: 10.1073/pnas.1006219107 PMID: 21115835
8. Madoff LC. ProMED-mail: an early warning system for emerging diseases (2004) Clin Infect Dis 39: 227–32. doi: 10.1086/422003 PMID: 15307032
9. White RW, Tatonetti NP, Shah NH, Altman RB, Horvitz E. (2013) Web-scale pharmacovigilance: listening to signals from the crowd. J Am Med Inform Assoc 20: 404–8. doi: 10.1136/amiajnl-2012-001482 PMID: 23467469
10. Velasco E, Agheneza T, Denecke K, Kirchner G, Eckmanns T (2014) Social media and Internet-based data in global systems for public health surveillance: a systematic review. Milbank Q 92: 7–33. doi: 10.1111/1468-0009.12038 PMID: 24597553
11. The White House (2014) Big data: seizing opportunities, preserving values. http://www.whitehouse.gov/issues/technology/big-data-review. Accessed June 11 2014.
12. Neff G (2013) Why big data won't cure us. Big Data 1: 117–123. doi: 10.1089/big.2013.0029 PMID: 25161827
13. International Telecommunication Unit. (2013) The World in 2013. Facts and figures. http://www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2013-e.pdf. Accessed 1 January 2015.
14. World Economic Forum. Global Agenda Counicls. Social Networks. http://reports.weforum.org/global-agenda-council-2012/councils/social-networks/. Accessed 1 January 2015.
15. Johns Hopkins University Global mHealth Initiative (2013) Mobile health apps—opportunity for patients and doctors to co-create the evidence. http://www.jhumhealth.org/blog/mobile-health-apps-%E2%80%93-opportunity-patients-and-doctors-co-create-evidence. Accessed 16 January 2014.
16. Mackey TK, Liang BA, Attaran A, Kohler JC (2013) Ensuring the future of health information online. Lancet 382: 1404. doi: 10.1016/S0140-6736(13)62215-1 PMID: 24243134
17. The World Economic Forum (2011) Personal Data: The emergence of a new asset class. http://www.weforum.org/reports/personal-data-emergence-new-asset-class Accessed 11 November 2014.
18. Thomas L (2014) Pandemics of the future: Disease surveillance in real time. Surveillance and Society. 12: 287–200.

19. Brockmann D, Helbing D (2014) The hidden geometry of complex, network-driven contagion phenomena. Science 342: 1337–42. doi: 10.1126/science.1245200
20. Fairchild AL, Bayer R (2004) Public health. Ethics and the conduct of public health surveillance. Science 303: 631–2.
21. Vayena E, Mastroianni A, Kahn J (2012) Ethical issues in health research with novel online sources. Am J Public Health 102: 2225–30. doi: 10.2105/AJPH.2012.300813 PMID: 23078484
22. Erlich Y, Narayanan A (2014) Routes for breaching and protecting genetic privacy. Nat Rev Genet. 15: 409–21. doi: 10.1038/nrg3723 PMID: 24805122
23. Vayena E, Mastroianni A, Kahn J. (2013) Caught in the web: informed consent for online health research. Sci Transl Med 5: 173fs6. doi: 10.1126/scitranslmed.3004798 PMID: 23427242
24. United Nations Global Pulse Project. http://www.unglobalpulse.org/blog/data-philanthropy-public-private-sector-data-sharing-global-resilience. Accessed 16 January 2014.
25. Chan EH, Sahai V, Conrad C, Brownstein JS (2011) Using web search query data to monitor dengue epidemics: a new model for neglected tropical disease surveillance. PLoS Negl Trop Dis. 5: e1206. doi: 10.1371/journal.pntd.0001206 PMID: 21647308
26. Brownstein JS, Freifeld CC, Madoff LC (2009) Influenza A (H1N1) virus, 2009—online monitoring. N Engl J Med. 360: 2156. doi: 10.1056/NEJMp0904012 PMID: 19423868
27. Zhang Y, May L, Stoto MA (2011) Evaluating syndromic surveillance systems at institutions of higher education (IHEs): a retrospective analysis of the 2009 H1N1 influenza pandemic at two universities. BMC Public Health 11: 591. doi: 10.1186/1471-2458-11-591 PMID: 21791092
28. Cook S, Conrad C, Fowlkes AL, Mohebbi MH (2011) Assessing Google flu trends performance in the United States during the 2009 influenza virus A (H1N1) pandemic. PLoS ONE 6: e23610. doi: 10.1371/journal.pone.0023610 PMID: 21886802
29. Butler D (2013) When Google got flu wrong. Nature 494: 155–6. doi: 10.1038/494155a PMID: 23407515
30. Lazer D, Kennedy R, King G, Vespignani A (2014) Big data. The parable of Google Flu: traps in big data analysis. Science 343: 1203–5.
31. Nissenbaum H (2010) Privacy in Context: Technology, Policy, and the Integrity of Social Life. Stanford (California): Stanford University Press.
32. Kahn JP, Vayena E, Mastroianni AC (2014) Opinion: Learning as we go: Lessons from the publication of Facebook's social computing research. Proc Natl Acad Sci USA. 111: 13677–9. doi: 10.1073/pnas.1416405111 PMID: 25217568
33. World Health Regulation (2005) International Health Regulation. http://www.who.int/ihr/publications/9789241596664/en/index.html. Accessed 15 January 2014.
34. Rodier G, Greenspan AL, Hughes JM, Heymann DL (2007) Global public health security. Emerg Infect Dis 13: 1447–52. doi: 10.3201/eid1013.070732 PMID: 18257985
35. Vayena E, Tasioulas J (2013) Adapting standards: ethical oversight of participant-led health research. PLoS Med 10: e1001402. doi: 10.1371/journal.pmed.1001402 PMID: 23554580
36. Vayena E, Tasioulas J (2013) The ethics of participant-led research. Nature Biotechnol 31: 786–7. doi: 10.1038/nbt.2692
37. Freifeld CC, Chunara R, Mekaru SR, Chan EH, Kass-Hout T, et al. (2010) Participatory epidemiology: use of mobile phones for community-based health reporting. PLoS Med 7: e1000376. doi: 10.1371/journal.pmed.1000376 PMID: 21151888

Infectious Disease Research Involving Pregnant Women

Ruth Faden

Required Reading

Anne D Lyerly, M.O. Little, Ruth R. Faden, "The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research," International Journal of Feminist Approaches to Bioethics 1(2) (Fall 2008): 5-22.

Anne D Lyerly, M.O. Little, Ruth R. Faden, "Reframing the Framework: Toward Fair Inclusion of Pregnant Women as Participants in Research," The American Journal of Bioethics 11(5) (2011): 50-52. DOI: 10.1080/15265161.2011.560353

PREVENT Working Group, Pregnant Women and Vaccines against Emerging Epidemic Threats for the Prevention," Vaccine (2019) https://doi.org/10.1016/j.vaccine.2019.01.011

Published in final edited form as:
Int J Fem Approaches Bioeth. 2008 ; 1(2): 5–22. doi:10.1353/ijf.0.0047.

The second wave: Toward responsible inclusion of pregnant women in research

Anne Drapkin Lyerly, **Margaret Olivia Little**, and **Ruth Faden**

Abstract

Though much progress has been made on inclusion of non-pregnant women in research, thoughtful discussion about including pregnant women has lagged behind. We outline resulting knowledge gaps and their costs and then highlight four reasons why ethically we are obliged to confront the challenges of including pregnant women in clinical research. These are: the need for effective treatment for women during pregnancy, fetal safety, harm from the reticence to prescribe potentially beneficial medication, and the broader issues of justice and access to benefits of research participation. Going forward requires shifting the burden of justification from inclusion to exclusion and developing an adequate ethical framework that specifies suitable justifications for excluding pregnant women from research.

Introduction

In the 1990s, prominent reports emerged indicating that women were underrepresented in biomedical research. By now, the findings are well-known: many significant studies on aging and heart disease were performed without adequate representation of women, and the health concerns of women were frequently under-investigated (General Accounting Office 1992; Merton 1996). Also well-known by now is the progress made following the establishment in the United States of the Women's Health Initiative at the National Institutes of Health (NIH) and the passage of the NIH Revitalization Act of 1993, with provisions that each NIH-funded study include representative samples of subpopulations unless their exclusion can be justified on a basis other than cost. More than a decade later, though some disparities have persisted (Chronic Disease Prevention and Control Research Center at Baylor College of Medicine and Intercultural Cancer Council 2008), women now make up the majority of participants in clinical research (General Accounting Office 2001).

Although progress was made on the inclusion of non-pregnant women in research, thoughtful discussion of how to reason about the inclusion of pregnant women in clinical research lags

[2]The U.S. Food and Drug Administration classifies medications in one of the following five categories: (a) adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters); (b) animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well controlled studies in pregnant women; (c) animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; (d) there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; (e) studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

[3]We are grateful to Andrea Kalfoglou for bringing this to our attention.

[4]Personal communication of Dr. David Grimes, Clinical Professor of Obstetrics and Gynecology, University of North Carolina Chapel Hill (Chapel Hill, North Carolina, USA) with A. Lyerly on 31 August, 2005 via email.

[5]Personal experience of A. Lyerly.

far behind. Despite a 1994 Institute of Medicine report recommending that pregnant women be "presumed eligible for participation in clinical studies" (Mastroianni, Faden, and Federman 1994), many researchers and institutional review boards (IRBs) continue to regard pregnancy as a near-automatic cause for exclusion, regardless of the costs of exclusion or the magnitude or likelihood of the risks of participation.

This reticence brings with it a profound cost. Of the more than four million women giving birth in the United States every year (Martin et al. 2007), many face medical conditions during their pregnancies that require clinical treatment, but they lack adequate data to inform their care. Indeed, chronic diseases during pregnancy are common: chronic hypertension and diabetes each complicate nearly 4 percent or 40,000 pregnancies each year (Martin et al. 2007); an estimated 500,000 pregnant women experience psychiatric illness (American College of Obstetricians and Gynecologists 2007); cancer, autoimmune disease, and a plethora of other conditions commonly occur with pregnancy and often require treatment. Further, gestation engenders a host of pregnancy-specific conditions that range from difficult (extreme nausea and vomiting) to disabling (sciatic nerve compression) to life-threatening for the woman or her fetus (preeclampsia). Pregnancy is not a prophylaxis against medical illness.

Yet only a dozen medications are approved by the United States Food and Drug Administration (FDA) for use during pregnancy. All of them are medications for gestation- or birth-related issues, such as regional anesthesia, nausea and vomiting, the prevention of congenital malformation, and the induction or delay of labor (Haire 2001). Any medication used to *treat illness* during pregnancy—be it hypertension, diabetes, depression, or cancer—is used without approval from the FDA, often leaving doctors and patients alike worried whenever they face decisions about using medication during pregnancy. Pregnancy, it turns out, is an "off label" condition.

In contemplating treatment of these conditions, an overarching concern, for providers and women alike, is of course the safety of medication for the fetus. Medications can cross the placenta and irreversibly affect fetal growth, structure, and function. Newer research has shown how environmental, nutritional, and other health factors during pregnancy can have an impact on an offspring's gene expression (Jirtle 2008). These potentially profound implications ground the reluctance in the research community to include pregnant women in clinical investigations.

Unfortunately, this conservative stance turns out to enhance neither fetal nor maternal safety. Certainly, guidelines for research in pregnancy must include careful and responsible criteria for protections. Consideration of fetal well-being will, in any framework, constitute a crucial component in shaping criteria for inclusion; further, as in any research involving a party whose capacity for consent is limited or absent, such as children, inclusion will require extra layers of protection and scrutiny of the risks, benefits, and alternatives. But currently, there are few opportunities for such a framework to be applied. With pregnant women effectively deemed untouchable in the research community, obstetricians care for their patients without meaningful data regarding the safety and efficacy of most of the medications used in pregnancy.

In what follows, we review the price of turning a blind eye to pregnancy in research and research ethics. We describe both the knowledge gaps around the use of medication during pregnancy and their costs, highlighting four reasons why ethically we are obliged to confront the challenges of including pregnant women in clinical research studies: the need for effective treatment for women during pregnancy, considerations of fetal safety, the harm from reticence to prescribe potentially beneficial medication, and the broader issues of justice and access to the benefits of research participation.

The costs of exclusion

Effective medical treatment for women during pregnancy

The first reason to confront the challenges of including pregnant women in research is a simple one: women need effective treatment during pregnancy. Without adequate research on how drugs are metabolized during pregnancy, we have very little evidence on how to treat illnesses when they occur in the pregnant body.

Pregnancy extends and alters the impact of sex differences on absorption, distribution, metabolism, and excretion of drugs—often times in ways that are both dramatic and difficult to predict. Pregnancy-related changes in the gastrointestinal tract, the cardiovascular system, the kidneys, and other organs may profoundly alter the ways that drugs are processed by the body (pharmacokinetics) or the ways that drugs act on the body (pharmacodynamics) (Mattison and Zajicek 2006). For instance, a 30–40 percent increase in blood flow through the kidneys means that some medications are cleared at much higher rates during pregnancy (Mattison and Zajicek 2006. Increases in blood volume, decreases in gastric emptying time, changes in the concentrations of sex hormones, alterations in liver enzymes, the presence (to say the least) of a fetal-placental unit, can all alter the activity of a drug. In the end, the pregnant body processes and eliminates drugs in ways that may differ both surprisingly and substantially from the non-pregnant body processing the same substance.

Indeed, evidence suggests that pregnancy often acts as a significant wild card in clinical management. In a 1999 review of the literature reporting pharmacokinetic differences between pregnant and non-pregnant women, the sixty-one studies reporting on pharmacokinetics during pregnancy revealed little or no consistency of results in studies during pregnancy, even for the same class of drugs or the same drug (Little 1999). Sometimes the pharmacokinetic parameters increase, sometimes they decrease, and sometimes they stay the same, suggesting that intuition and even clinical experience may not be trustworthy.

Opportunistic studies of drug metabolism and activity during pregnancy corroborate. In 2003, the Obstetric-Fetal Pharmacology Research Unit (OPRU) Network was founded through the United States National Institutes of Health to identify, characterize, and study drugs of therapeutic value in normal and abnormal pregnancies (Zajicek and Giacoia 2007). Initial studies generated findings that are of concern. For instance, pharmacokinetic measurements on a pregnant woman receiving chemotherapy during pregnancy revealed that the drug was so quickly and thoroughly metabolized and excreted by her pregnant body that the drug never approached a therapeutic range, despite the fact that she and her fetus were exposed to its toxicities.[1]

Of potentially even broader applicability are the implications of knowledge regarding amoxicillin pharmacokinetics during pregnancy. Given heightened concern about bioterrorism, the American College of Obstetricians and Gynecologists (ACOG) recommended using amoxicillin for post-exposure prophylaxis in pregnant women in the setting of penicillin-sensitive bacteria (American College of Obstetricians and Gynecologists 2002). Yet a 2007 OPRU study revealed that concentrations of amoxicillin adequate to prevent anthrax may be unachievable during pregnancy due to altered kidney function and that amoxicillin ultimately may not be an appropriate antibiotic for post-anthrax exposure prophylaxis (Andrew et al. 2007).

With regard to dosing medications, our best predictions can be disastrously wrong. But predictions are largely all that physicians and policymakers have for making decisions. The

[1]Personal communication with M. Little during meeting of the Obstetric-Fetal Pharmacology Research Unit (date?), Washington DC.

same 1999 review that highlighted the variability in pharmacokinetic parameters also highlighted standardized pharmacokinetic studies as a major area of need (Little 1999). Of more than one thousand articles published on pregnancy pharmacokinetics, only sixty-one reported relevant pharmacokinetic data, and only two synthesized data into guidelines for clinical care. When physicians prescribe medications during pregnancy, they do so in the absence of data regarding the dosage required to achieve the desired therapeutic result.

As often is said in research ethics, there is no one-size-fits-all research subject. Children are not just small adults; women are not just men with a bit less on-average muscle. Developmental stage and gender make a difference in how drugs act in the body and how the body acts on drugs (Mattison and Zajicek 2006). So, too, with gestation—a pregnant woman is not just a woman with a bigger belly. The maternal-fetal-placental system brings its own pharmacokinetics and dynamics. If we are to treat pregnant women's illnesses effectively—something crucial to the health of *both* pregnant women and that of the children they may bear—we must study medications in pregnant women.

Fetal safety

The second reason to address the challenges of including pregnant women in research is the very same reason that is given for excluding them—fetal safety. Given their medical needs, pregnant women *do* use medications during pregnancy. The average woman receives 1.3 prescriptions per obstetric visit (Lee et al. 2006), and two-thirds of women use four to five medications during pregnancy and labor (National Institute of Child Health and Human Development 2003). More than 40 percent of pregnant women use drugs classified as C or D by the U.S. FDA risk classification (Food and Drug Adminstration, 2006) (Cragan et al. 2006; Andrade et al. 2004). Further, given that almost half of pregnancies are unintended (Finer and Henshaw 2006), exposure to a fetus can occur when a woman taking medication unexpectedly becomes pregnant. Without information on the fetal safety of these medications, we are left with the variable predictive value of animal studies (Brent 2004), considerable anxiety, and a paucity of data with which to reason about the trade-offs that mark decisions about the use of medication in—or continuation of—pregnancy.

Indeed, a 2002 review of fetal risk associated with all 468 of the medications approved in the United States for use in humans between 1980 and 2000 revealed just how little we know (Lo and Friedman 2002). Only 6.4 percent were recognized as safe in pregnancy (in that their teratogenic risk was considered as “none, minimal or unlikely”); and 2.5 percent were associated with some risk, ranging from small or moderate (fetal growth restriction with cyclophosphamide chemotherapy, goiter with amiodarone) to high (severe limb abnormalities with thalidomide). This leaves us without any substantive guidance regarding the risk to the fetus of more than 91 percent of the drugs on the market. Worse, this percentage has shifted very little over the last two decades. More than 80 percent of drugs are classified as “undetermined” with respect to fetal risk, whether approved 15–20 years ago (96%), 10–14 years ago (83%), 5–9 years ago (88%), or 0–4 years ago (95%) (Lo and Friedman 2002).

Of obvious concern here is that some of the medications currently prescribed to pregnant women may in fact be unsafe for the fetus. Consider ACE inhibitors—a medication widely prescribed for the treatment of hypertension. ACE inhibitors were of known contraindication in the second and third trimesters but had unknown risk status in the first trimester until a 2006 study published in the *New England Journal of Medicine* linked the antihypertensive drug to a small but statistically significant increased risk of fetal cardiovascular and neurological abnormalities (Cooper et al. 2006). The rub, in this case, is that if researchers had studied the drug in pregnancy earlier on, the congenital anomalies that resulted from the three decades of use since the approval of the drug could have been prevented.

For another example, consider the thalidomide disaster. Some of the resistance to the idea of clinical research with pregnant women almost certainly can be traced to the long shadow cast by this devastating episode. But the thalidomide example is in fact instructive. We must remember that the widespread birth defects experienced from its use were *not* the result of women's participation in research trials, but rather the result, at least in part, of inadequate research standards preceding distribution and marketing (Levine 1993). Careful and responsible research might well have attenuated the magnitude of the disaster. Yet the response of policymakers was instead to exclude nearly all women of reproductive potential from future research.

Reticence to use: The cost of uncertainty

Worries about fetal safety obviously loom large not only for researchers, but for pregnant women and their health care providers. These concerns have led some clinicians or patients not to treat, or to undertreat, illnesses that continue or emerge during pregnancy. But the failure to treat illness *also* can lead to significant harm to women and their fetuses—indeed, harm that easily can outweigh the possible risks that might accompany use of medication during pregnancy. These issues point to the third reason that responsible research in pregnancy is required: lack of information can lead to worrisome reticence to treat dangerous medical conditions.

Consider depression, for example. Treatment for depression during pregnancy has been characterized by considerable reticence, despite significant harm that untreated mental illness can entail. The Web site for the National Alliance on Mental Illness (NAMI) admonishes women to “if possible, stop using the drugs before trying to conceive [and] do everything possible to avoid medication in the first trimester of pregnancy”(National Alliance on Mental Health 2008). Yet women who discontinue medication have significantly higher rates of relapse of major depression than those who continued medication (68% compared to 25%) (Cohen et al. 2006). Untreated depression is problematic for pregnant women and the fetuses they carry: it is associated with premature birth, low birth weight, fetal growth restriction, and postnatal complications. It also is associated with decreased social support, poor weight gain, and alcohol and drug use, all of which adversely affect outcomes for women and infants alike (Orr et al. 2007; American College of Obstetricians and Gynecologists 2007).

Women with asthma, too, sometimes are treated suboptimally for fear of fetal exposure to medications (Dewyea and Nelson 2005). Halting medication brings many dangers to maternal health: poorly controlled asthma places a pregnant woman at higher risk of hypertension, preeclampsia, and uterine hemorrhage (Dombrowski 2006; American College of Obstetricians and Gynecologists 2008). Moreover, halting medication for the mother is risky for the fetus. Poorly controlled asthma is associated with fetal growth restriction, premature birth, and low birth weight; in contrast, women with asthma that is well controlled by medication have perinatal outcomes as good as comparable groups without asthma (Tan and Thomson 2000). And sometimes, the results of undertreatment are tragic: women—and the fetuses they carry—have died in emergency situations because physicians are insufficiently aggressive with medications out of concerns for fetal harm.

Here we see the tendency in pregnancy (more accurately, the tendency until we get to labor and delivery) to notice the risks of intervening to the exclusion of noticing the risks to woman and the fetus of *not* intervening (Lyerly et al. 2007). A classic example is the trainee who hesitates, in the midst of resuscitating a pregnant woman who has had a heart attack—a woman whose small chance for life depends on decisive and optimal care—over concerns about whether a cardiac drug is teratogenic. Another example is that of the radiologist who hesitates or refuses to perform standard imaging on a pregnant woman with suspected appendicitis, despite the fact that delayed diagnosis and appendicle rupture carries a ten-fold risk of

miscarriage (Mazze and Kallen 1991). When a medical problem emerges or persists in pregnancy, many—sometimes patients, sometimes providers—feel concern about taking a medication, without appropriately weighing the risks of *not* taking it.

Pregnancy is in this respect no different than other arenas of life. The need to make calculated risks and trade-offs in the context of pregnancy is inevitable. Indeed, even for medications with known teratogenicity, calculated trade-offs may still be a fact of life. For instance, a pregnant woman with a mechanical heart valve who is insufficiently treated with heparin, may be strongly recommended to take warfarin (a blood thinner with a 30% risk of fetal anomaly), given the high risk of maternal (and needless to say, fetal) death entailed by inadequate anticoagulation (James, Abel, and Brancazio 2006).

The third reason to move toward responsible inclusion of pregnant women in clinical trials, then, is to counter unreasoned opposition to treating important medical conditions. If research is important to tell us when medications are unsafe, it is also important to reassure us when drugs *are* safe. The point is worth underscoring. For every drug that is found worrisome, it is likely that many more will bring news of welcome reassurance. Of the 468 drugs approved by the U.S. Food and Drug Administration in the last twenty years, only three drugs approved were judged to pose a "high" teratogenic risk; only eleven are believed to pose any teratogenic risk (Lo and Friedman 2002). Further, for the 6.4 percent of medications categorized as safe, it took an average of more than nine (ranging from two to nineteen) years from the time of FDA approval to ascribe a designation of low or minimal risk (Lo and Friedman 2002). And of course, research also can help us to quantify the risks of medications like warfarin or ACE inhibitors, so that we can proceed with more confidence when faced with the need to make difficult trade-offs in risk.

Access to the prospect of direct benefit

The fourth reason to enhance clinical research of medical treatment during pregnancy has to do with an important subset of trials: those that carry the prospect of direct benefit to participants. Some trials, especially Phase I trials, are designed primarily to gather preliminary information, such as data about the safety, pharmacokinetics, and pharmacodynamics of a drug. These trials, although important for the advance of scientific knowledge, present no prospect of direct medical benefit to participants. But other trials do. Many Phase II and III trials are meant to see whether a given drug is, as hoped, therapeutic for a given medical condition. Those who participate in the active arm of these trials could end up with a significant medical benefit. This means that restriction of trials to non-pregnant individuals excludes a class of potential beneficiaries and places them at an unfair disadvantage when it comes to health and well-being.

Consider an example from current international HIV/AIDS research. Vaginal microbicides were identified as a promising means for women in developing countries to protect themselves from sexual transmission of HIV (Doncel and Mauck 2004). Because pregnancy is a marker of unprotected sexual activity, understanding the effects of a medication aimed at mitigating the risks of such exposure is particularly important for this group. Indeed, any possible teratogenic risk from the gel must be considered in the context of a very clear, real, and life-threatening risk that microbicides aim to prevent—namely, maternal and fetal exposure to HIV infection. Yet pregnant women have been summarily excluded from microbicide trials. In fact, high pregnancy rates in study populations were accompanied by *increased* efforts to exclude pregnant women and to terminate enrollment for participants who do become pregnant (Raymond 2006)—this despite the fact that animal studies have not shown adverse effects of microbicides on fetal development, and the vaginal products do not seem to be systemically absorbed (Lard-Whiteford et al. 2004). And finally, given that pregnant women will certainly

be among the consumers of microbicides if they prove effective, reassurance of the product's efficacy, as well as safety, would be useful.

In this example, the prospect of medical benefit extends to woman and fetus alike. If the microbicide turns out to decrease the transmission of HIV, both women and fetuses in the active arm will benefit. Other trials present more difficult issues, offering the prospect of direct medical benefit only to the fetus or only to the woman. Clearly, there must be strong limits on the risk that research may impose on the fetus, who cannot consent, for the potential medical benefit of the woman. But the current practice—the de facto exclusion of women from participation, even when participation holds a genuine prospect of direct benefit—goes beyond what would be considered reasoned limits and suggests alarm at the prospect of *any* fetal risk whatsoever.

Indeed, some theorists have noted a "cultural anxiety" about the very idea of placing risk on the fetus for the sake of the pregnant woman (Merton 1996). Often, of course, the idea of a conflict is overstated to begin with. Physically, the woman and fetus are interconnected, the health or illness of one influencing the same in the other. More than that, the future well-being of each is, in the usual case, deeply connected. Children are affected by their parents' health and happiness; parents are affected by their children's well-being—and not just contingently, but constitutively. The fact that stopping anti-depressant use during pregnancy increases the woman's chance of severe post-partum depression is not just a "maternal" risk; the fact that lead exposure during pregnancy increases a child's risk of learning disabilities is not just a "fetal" risk.

Nonetheless, just as the bodies are not identical, neither are the goods, projects, and interests. Trade-offs between risks to the woman and the fetus can be real, and decisions about responsible and reasonable trade-offs are critical. Yet the need for thoughtful criteria has been eclipsed by a social tendency to regard the very idea of trading off risks between the woman and her fetus—however well demonstrated and large the former, however theoretical or small the latter—as anathema. Exposing a fetus to a small, even miniscule, risk in the context of research that may entail even a large direct benefit to a woman (and probably to both woman and fetus) has seemed an unreasonable risk to some researchers and policymakers contemplating categories for inclusion.

This form of reasoning carries a worrisome double standard. It holds pregnant women to a standard we do not hold fathers to; more than that, it holds pregnant women to a standard we do not hold mothers to. We accept small risks to our children for our own sakes every day. We believe it reasonable to impose the small risk of fatality introduced every time we put our children in the car (safely restrained in a car seat), even if our errand is mundane. To be sure, balancing such risks can be among the most challenging tasks of parenthood. But as parents and members of families, we recognize that reasoning about risk is inevitable, that thoughtful, responsible trade-offs are a fact of life, and that there are times when benefit to one member of a family comes at the price of a risk to another.

The fourth reason to address the challenges of responsible inclusion of pregnant women in clinical trials, then, is an issue of justice. As scholars have noted in discussions of other underrepresented populations, *access* to research, not just protection from its risks, is a constitutive part of the ethical mandates governing clinical research (Mastroianni, Faden, and Federman 1994). Whereas no one would suggest that justice requires admitting pregnant women to all trials regardless of their risks and benefits, justice does call into question the de facto summary exclusion of pregnant women in research without justification in terms of those risks and benefits.

Risk and responsibility

We suggested that there are profoundly important reasons to enhance clinical research of medical treatment in pregnancy. We also noted that such research raises significant cultural unease: the intersection of risk and the fetus is an uncomfortable one.

Of course, part of the concern has to do with the fetus's inability to consent. But pregnancy is not the only context that raises this ethical issue. Pediatrics has a long history of confronting the need to study a population that cannot consent meaningfully. The fact introduces complexity, and the need for special safeguards, to be sure; what it does not mean is a firewall against research on the population. As a recent report of the Institute of Medicine on research with children pointed out, studies involving that vulnerable population are "essential to the health of future children—and future adults"(Field and Berman 2004). After all, young children also do not consent to being treated with medication that has not been adequately tested on physiologies resembling their own and thus, whose efficacy and risks, for them, are largely unknown. Whereas the details are complex, the bottom line is simple: if a population is going to use a drug, then we need to study that drug *in* that population (Brent 2004; Field and Berman 2004; Zajicek and Giacoia 2007).

But when it comes to reasoning about risk and the pregnant body, the cultural tendency is to retreat from the idea of risk rather than confront the need to make reasoned and responsible decisions about it. The specter of risk can cast an eclipsing shadow over rational decision making. For example, in discussions about pregnancy, evidence that one thing or behavior carries quantifiable risk—say, exposure to oil-based paint or moderate caffeine consumption—can quickly taint another where there is no such evidence—for example, exposure to latex-based paint, or again, modest caffeine consumption. Indeed, the effect can persist even in the face of reassuring findings. For a recent example, we can look to the well-publicized findings of a study designed to explore the possible link of caffeine consumption and early pregnancy loss (Xiaoping, Roxana, and De-Kun 2008). Evidence of a modest increase in miscarriage risk with moderate caffeine consumption in the first trimester was touted as reason to "stop or reduce caffeine intake during pregnancy," even when the self-same study found that caffeine consumption under two cups was found to carry no increase in the miscarriage rate. Rather than reporting reassurance that low caffeine use was demonstrated to be safe, researchers took the finding of risk associated with moderate consumption and extended it against findings of safety.

Cultural reasoning about risk in pregnancy, in short, tends to invoke the precautionary principle in a particularly unfettered way. "Better safe than sorry" is a fine aphorism in general, and a particularly good one to take during pregnancy, where untoward effects on the fetus can be permanent. But when applied without sensitivity to evidence or appreciation of the *cost* of caution—when applied myopically, without due recognition of the long-term price of one's policy—it could turn out that a policy of "better safe than sorry" is the opposite of safe. It can, in fact, lead to significant harm to women and fetuses alike. Applied here, it collides with the animating purpose of the enterprise of clinical research, which is to take responsible, limited, and calculated risks in order to *garner* evidence, lest we visit more risk on more people in the future.

Going forward

Confronting the challenges of research with pregnant women is a critical if complex project. Going forward will require a number of steps. Some are obvious and morally straightforward. These include increasing funding for the OPRU and other groups to perform opportunistic studies involving women already taking medication during pregnancy. Because women in

opportunistic studies already have made a decision to take medication outside of the research context, simple blood draws to measure pharmacokinetic and pharmacodynamic parameters introduces minimal risk and none of the onerous trade-offs that demand a novel ethical framework for inclusion. Also required is funding for research to determine the public health impact of the current lack of knowledge around medications in pregnancy. Such funding could help to answer questions critical to decision making about research priorities: what is the current burden of disease for both pregnant women and their babies that results from the need to make treatment decisions in the absence of any relevant data? What are the emotional and psychological burdens of the anxiety and stress that treatment decisions in pregnancy engender? As newer approaches to treatment in the non-pregnant population are developed, what is the comparative cost of restricting pregnant women to the older medications that obstetrical providers are accustomed to using? For example, is there a health-related cost to the usual practice of replacing new antihypertensive medications with older medications such as methyldopa, which has been prescribed during pregnancy for decades? In both of these efforts, moving forward will involve developing legislative strategies modeled on those that have created incentives for women and children to participate in research.

Other steps will be considerably more complex and controversial. For instance, addressing the liability concerns that animate so much of the behavior around research and drug development during pregnancy will require substantial efforts at both state and federal levels. Just as importantly, considerable efforts will be required to develop guidance for IRBs. Although IRBs are often and understandably focused on safety and protection from the harm of participation, in many ways they are the gatekeepers of access to research. As others have noted, IRB members may lack training or guidance regarding how to recognize or respond to the potential harm of exclusion (Chronic Disease Prevention and Control Research Center at Baylor College of Medicine and Intercultural Cancer Council 2008).

To make progress, we need an adequate ethical framework for determining what are and are not suitable justifications for exclusion of pregnant women from research. Some criteria can be borrowed from approaches to disparities in other underrepresented research populations. For instance, as with women generally, considerations of cost are not adequate justification for exclusion of underrepresented populations. When population-specific evidence is required to treat a particular group, the cost of research is one that must be borne in order to provide responsible, safe, and effective medical care to those who need it. For instance, the fact that sample size must be increased to adequately power a study that includes pregnant participants should not be accepted as valid criteria for their exclusion.

Other issues, though, will require a framework specific to pregnancy. Given the intermingled physiologies distinctly present in pregnancy, and the implications for what are potentially two rather than one person, thoughtful analysis is required to sort through the complex questions of the levels of risk the fetus—or for that matter, the woman—can be subjected for purposes of research that may benefit the other. A number of factors will be relevant, including the applicability of data from animal studies on fetal safety, data about the degree to which "borrowed knowledge" is possible, the balance of direct benefits of participation to the woman and the fetus with any potential harm, and the prevalence and seriousness of the condition in the pregnant population.

Details notwithstanding, we believe the core lesson is a simple one. As with other traditionally excluded populations, progress will not happen until we shift the burden of justification from inclusion to exclusion. There are many trials in which that burden may be met. To give an obvious example, pregnant women are not needed in trials of hormone therapies for prostate cancer. More broadly, and as with pediatric research, we do not include a population that introduces special ethical complexities into trials for medications of marginal medical

importance (pharmacologic treatments for fungal infections of the nail bed). Special attention always must be given to the relevance of the goal in the population under consideration—for instance, new lipid-lowering drugs, of potential benefit to the broad population, are inappropriate for testing during early pregnancy, when the body significantly and importantly increases the production of cholesterol and triglycerides, high levels of which are considered adaptive to maternal and fetal nutritional needs and placental functioning. The claim then, is not that pregnant women belong in all trials. Rather, the claim is that decisions about whether pregnant women belong in a given trial, or type of trial, should be just that—*decisions*—made on the basis of reasoned criteria, reflecting balanced consideration of not only the risks of teratogenicity, but the potential importance of the medication for the health of women and the fetuses they carry. As with other underrepresented populations, it is exclusion, not inclusion, that requires justification.

But such justification is not currently required. Presently, Department of Health and Human Services regulations outline ten criteria that must be met if pregnant women are to be included in research protocols (United States Department of Health and Human Services 2005). Without any legislative or regulatory pressure to include pregnant women, all the incentives line up in favor of excluding pregnant women from clinical research. It is easier for researchers to simply side-step the questions and regulatory burden they represent by not including pregnant women. Until *that* decision *also* requires justification, we will continue to lack data on how to effectively and safely treat pregnant women.

In the absence of information about the safety and efficacy of medications, pregnant women and their providers are left with two unsavory options—take a drug, with unknown safety and efficacy; or fail to treat the conditions, thus leaving the woman and fetus vulnerable to the consequences of the underlying medical problems. They deserve better. Clinical research with pregnant women is morally challenging, but it is a challenge we must confront. For the alternative to responsible research in pregnancy is relegating pregnant women to second-class medical citizens—something, it turns out, that is not good for pregnant women nor the fetuses they carry.

References

American College of Obstetricians and Gynecologists. ACOG Committee Opinion. Number 268, February 2002. Management of asymptomatic pregnant or lactating women exposed to anthrax. Obstetrics and Gynecology 2002;99(2):366–68. [PubMed: 11814522]

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 87: Use of psychiatric medications during pregnancy and lactation. Obstetrics and Gynecology 2007;110(5):1179–98. [PubMed: 17978143]

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 90: Asthma in pregnancy. Obstetrics and Gynecology 2008;111(2):457–64. [PubMed: 18238988]

Andrade, Susan E.; Gurwitz, Jerry H.; Davis, Robert L.; Chan, K Arnold; Finkelstein, Jonathan A.; Fortman, Kris; McPhillips, Heather, et al. Prescription drug use in pregnancy. American Journal of Obstetrics and Gynecology 2004;191(2):398–407. [PubMed: 15343213]

Andrew MA, Easterling TR, Carr DB, Shen D, Buchanan ML, Rutherford T, Bennett R, Vicini P, Hebert MF. Amoxicillin pharmacokinetics in pregnant women: Modeling and simulations of dosage strategies. Clinical Pharmacology and Therapeutics 2007;81(4):547–56. [PubMed: 17329990]

Brent, Robert L. Utilization of animal studies to determine the effects and human risks of environmental toxicants (drugs, chemicals, and physical agents). Pediatrics 2004;113(4):984–95. [PubMed: 15060191]

Chronic Disease Prevention and Control Research Center at Baylor College of Medicine and Intercultural Cancer Council. Major deficiencies in the design and funding of clinical trials: A report to the nation improving on how human studies are conducted: Findings of the eliminating disparities in clinical trials project (EDICT). 2008 [29 April 2008]. http://www.bcm.edu/cdrc/home.html

Cohen, Lee S.; Altshuler, Lori L.; Harlow, Bernard L.; Nonacs, Ruta; Newport, D Jeffrey; Viguera, Adele C.; Suri, Rita, et al. Relapse of major depression during pregnancy in women who maintain or discontinue antidepressant treatment. Journal of the American Medical Association 2006;295(5):499–507. [PubMed: 16449615]

Cooper, William O.; Hernandez-Diaz, Sonia; Arbogast, Patrick G.; Dudley, Judith A.; Dyer, Shannon; Gideon, Patricia S.; Hall, Kathi; Ray, Wayne A. Major congenital malformations after first-trimester exposure to ACE inhibitors. New England Journal of Medicine 2006;354(23):2443–51. [PubMed: 16760444]

Cragan, Janet D.; Friedman, JM.; Holmes, Lewis B.; Uhl, Kathleen; Green, Nancy S.; Riley, Laura. Ensuring the safe and effective use of medications during pregnancy: Planning and prevention through preconception care. Maternal and Child Health Journal 2006;10:129–35.

Dewyea, Victor A.; Nelson, Michael R. Asthma in pregnancy. Allergy and Asthma Proceedings 2005;26 (4):323–26. [PubMed: 16270728]

Dombrowski, Mitchell P. Asthma and pregnancy. Obstetrics and Gynecology 2006;108(3):667–81. [PubMed: 16946229]

Doncel G, Mauck C. Vaginal microbicides: A novel approach to preventing sexual transmission of HIV. Curr HIV/AIDS Rep 2004;1(1):25–32. [PubMed: 16091220]

Field, Marilyn J.; Berman, Richard E., editors. Ethical conduct of research involving children. Washington DC: National Academies Press; 2004.

Finer, Lawrence B.; Henshaw, Stanley K. Disparities in Rates of Unintended Pregnancy In the United States, 1994 and 2001. Perspectives on Sexual and Reproductive Health 2006;38(2):90–96. [PubMed: 16772190]

General Accounting Office. Women's health: FDA needs to ensure more study of gender differences in prescription drug testing. Washington DC: GAO; 1992.

General Accounting Office. Women's health: Women sufficiently represented in new drug testing, but FDA oversight needs improvement. 2001.

Haire, Doris. FDA approved obstetrics drugs: their impact on mother and baby. National Women's Health Alliance. 2001. [cited 17 June 2008] http://nwhalliance.org/FDAAPPROVED.htm

James, Andra H.; Abel, David E.; Brancazio, Leo R. Anticoagulants in pregnancy. Obstetrical and Gynecological Survey 2006;61(1):59–69. [PubMed: 16359570]

Jirtle, Randy. Randy L. Jirtle, PhD: epigenetics a window on gene dysregulation, disease. Interview by Bridget M. Kuehn. Journal of the American Medical Association 2008;299(11):1249–50. [PubMed: 18349082]

Lard-Whiteford SL, Matecka D, O'Rear JJ, Yuen IS, Litterst C, Reichelderfer P. Recommendations for the nonclinical development of topical microbicides for prevention of HIV transmission: An update. Journal of Acquired Immune Deficiency Syndromes 2004;36(1):541–52. [PubMed: 15097296]

Lee, Euni; Maneno, Mary; Smith, Leah; Weiss, Sheila; Zuckerman, Ilene H.; Wutoh, Anthony; Xue, Zhenyi. National patterns of medication use during pregnancy. Pharmacoepidemiology and Drug Safety 2006;15(8):537–45. [PubMed: 16700083]

Levine, Carol. Women as research subjects: New priorities, new questions. In: Blank, RH.; Bonnicksen, A., editors. Emerging issues in biomedical policy: An annual review. Vol. 2. New York: Columbia University Press; 1993.

Little, Bertis B. Pharmacokinetics during pregnancy: Evidence-based maternal dose formulation. Obstetrics and Gynecology 1999;93(5):858–68. [PubMed: 10912434]

Lo WY, Friedman JM. Teratogenicity of recently introduced medications in human pregnancy. Obstetrics and Gynecology 2002;100(3):465–73. [PubMed: 12220765]

Lyerly Anne D, Mitchell Lisa M, Armstrong Elizabeth M, Harris Lisa H, Kukla Rebecca, Kuppermann Miriam, Little Margaret O. Risks, values, and decision making surrounding pregnancy. Obstetrics and Gynecology 2007;109(4):979–84. [PubMed: 17400862]

Martin, Joyce A.; Hamilton, Brady E.; Sutton, Paul D.; Ventura, Stephanie; Menacker, Fay; Kirmeyer, Sharon; Munson, Martha L. Births: Final data for 2005. Atlanta: CDC; 2007. National Vital Statistics Reports.

Mastroianni, Anna C.; Faden, Ruth R.; Federman, Daniel, editors. Women and health research: Ethical and legal issues of including women in clinical studies. DC: National Academy Press; 1994.

Mattison D, Zajicek A. Gaps in knowledge in treating pregnant women. Gender Medicine 2006;3:169–82. [PubMed: 17081950]

Mazze RI, Kallen B. Appendectomy during pregnancy: A Swedish registry study of 778 cases. Obstetrics and Gynecology 1991;77(6):835–40. [PubMed: 2030853]

Food and Drug Administration. Requirements on content and format of labeling for human prescription drug and biological products. Federal Register 2006;71:3921–3997. [PubMed: 16479698]

Merton, Vanessa. Ethical obstacles to the participation of women in biomedical research. In: Wolf, S., editor. Feminism and Bioethics: Beyond reproduction. New York: Oxford University Press; 1996.

National Alliance on Mental Health. Pregnancy pointers for women with psychiatric history 2008. 2008. [cited 15 February 2008]. http://www.nami.org/Content/ContentGroups/Helpline1/Pregnancy_Pointers_for_Women_with_Psychiatric_History.htm

National Institute of Child Health and Human Development. Request for applications for obstetric-fetal pharmacology research units (HD-03-017). 2003. [cited 18 February 2008] http://grants.nih.gov/grants/guide/rfa-files/RFA-HD-03-017.html

National Institutes of Health (NIH) Revitalization Act of 1993, Pub L No. 103–43.

Orr, Suezanne T.; Blazer, Dan G.; James, Sherman A.; Reiter, Jerome P. Depressive symptoms and indicators of maternal health status during pregnancy. Journal of Women's Health 2007;16(4):535–42.

Raymond, E. Issues related to pregnancies in microbicide effectiveness trials. Paper presented at Microbicides Conference; Cape Town, South Africa. 2006.

Tan KS, Thomson NC. Asthma in pregnancy. American Journal of Medicine 2000;109(9):727–33. [PubMed: 11137489]

United States Department of Health and Human Services. Code of Federal Regulations at 45CFR46.204. [cited 17 June 2008] http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#subpartb

Xiaoping, Weng; Roxana, Odouli; De-Kun, Li. Maternal caffeine consumption during pregnancy and the risk of miscarriage: A prospective cohort study. American Journal of Obstetrics and Gynecology 2008;198(3):279.e1–8. [PubMed: 18221932]

Zajicek A, Giacoia GP. Obstetric clinical pharmacology: Coming of age. Clinical Pharmacology and Therapeutics 2007;81(4):481–82. [PubMed: 17375105]

The American Journal of Bioethics

ISSN: 1526-5161 (Print) 1536-0075 (Online) Journal homepage: https://www.tandfonline.com/loi/uajb20

Reframing the Framework: Toward Fair Inclusion of Pregnant Women as Participants in Research

Anne Drapkin Lyerly , Margaret Olivia Little & Ruth R. Faden

To cite this article: Anne Drapkin Lyerly , Margaret Olivia Little & Ruth R. Faden (2011) Reframing the Framework: Toward Fair Inclusion of Pregnant Women as Participants in Research, The American Journal of Bioethics, 11:5, 50-52, DOI: 10.1080/15265161.2011.560353

To link to this article: https://doi.org/10.1080/15265161.2011.560353

The American Journal of Bioethics, 11(5): 50–68, 2011

ISSN: 1526-5161 print / 1536-0075 online
DOI: 10.1080/15265161.2011.560353

Open Peer Commentaries

Reframing the Framework: Toward Fair Inclusion of Pregnant Women as Participants in Research

Anne Drapkin Lyerly, University of North Carolina at Chapel Hill
Margaret Olivia Little, Georgetown University
Ruth R. Faden, Johns Hopkins University

With recent recognition of the need for data about how to treat illness during pregnancy has come appreciation of the myriad challenges to responsibly conducting research involving pregnant women. Among the most pressing of these challenges is the need for an ethical framework to guide when and how research may be responsibly conducted. Noting that urgent need, Chervenak and McCullough (2011) propose a framework based on their concept of "fetus as patient," a concept that they argue helpfully "insulates" the framework from the divisive discourse that often characterizes discussions of reproductive ethics. While we commend their efforts to advance "Second Wave" priorities (Lyerly, Little, and Faden 2008b), and in particular their willingness to take on the difficult contexts of early-phase pharmaceutical research, we are concerned that their approach in fact problematically obscures moral considerations for which an adequate framework must account.

We have three areas of particular concern. First, building a framework for the inclusion of pregnant women around the concept of "patient-hood," whether for women or fetuses, blurs the morally important distinction between *patients* and *research participants*—to whom practitioners and researchers have different obligations, respectively. Second, the framework appears to adopt a default position that current practice is necessarily safer or otherwise in the best interests of pregnant women or their fetuses than participation in research, despite the absence of evidence for the medical management of many medical conditions and risks experienced by pregnant women. Third, by focusing their framework on clinically oriented questions of the potential for fetal harm from medical interventions, their framework fails to account for pressing issues of justice. We address each in turn.

The heart of our first concern stems from the use of the term "patient" to refer to the fetus involved in clinical research protocols. Elsewhere, we have criticized use of "patient" to characterize the fetus in moral frameworks for the therapeutic care of pregnant women (Lyerly, Little, and Faden 2008a): first, for its tendency to encourage thinking of the fetus as separate from the woman, obscuring the physical, physiological, and social relationship between fetus and pregnant women—and at times the woman herself; and second for its tendency to encourage clinicians to regard their obligations to and the value of "each" of their patients—the woman and fetus—as equal. The proclivities of reasoning that the term "patient" entails, we have argued, distorts thinking about the nature of our moral obligations to the fetus and pregnant woman in clinical therapeutic settings.

Characterizing the fetus as "patient" in the context of clinical research, though, is yet more worrisome, as it problematically blurs the distinction between *patients* and *research participants*. To be sure, clinical and research contexts are often joined, as when a clinical trial or other research design is providing some or all of the medical care for the condition under investigation. Commendably, though, Chervenak and Mccullough intend their framework to provide guidance even for cases such as some Phase I and II clinical trials where there is no reasonable prospect of direct clinical benefit. In those cases, the designation of fetus as "patient" obscures the distinction between patient and research subject precisely where the distinction is most apt and morally important. Where no therapeutic benefit is expected, concerns about therapeutic misconception have led a number of commentators to recommend specific procedures and language as means to emphasize the difference between research participation and patienthood (Lidz and Applebaum 2002)—recommendations that have led many to discourage the term "patient" in discussion about and documentation of the research activity. The particularly complex arena of research involving pregnant women is no exception. If "becoming a patient occurs when an individual presents to a physician (or other health care professional) and there exist clinical interventions that are reliably expected to benefit that individual clinically" (Chervenak and McCullough

Address correspondence to Anne Drapkin Lyerly, MD, MA, University of North Carolina at Chapel Hill, Center for Bioethics, 333 South Columbia Street, CB# 7240, 333 MacNider Hall, Chapel Hill, NC 27599-7240, USA. E-mail: alyerly@email.unc.edu

2011, 39), what happens when neither the fetus nor the pregnant woman is a patient at all?

Nor is this an idle concern. Phase I and most Phase II studies on which these authors focus considerable attention are aimed at dose-finding and safety. In some such studies, no indicators of clinical benefit are included as study outcomes; a presumption of benefit (as might be reasonable for a "patient") may be seen as a failure of meaningfully informed consent in early phase trials. If the use of the term "patient" circumvents the divisive dialogue about the moral status of the fetus, it does so at the cost of obscuring a distinction most agree is critical to the ethical conduct of such research—the distinction between patients and research participants.

The second concern is raised by an important default that appears central to the Chervenak and McCullough framework. In setting out the standard against which a proposed protocol is to be assessed for acceptability, the framework appears to adopt a default position that current practice is safer or otherwise in the best interests of pregnant women or their fetuses than participation in research. This is, of course, a standard and apt default for much of research assessment. But there are contexts in which it is not—namely, contexts in which our evidence base for current treatments is so weak that standard practice is itself more like experiment than treatment. Sadly, this is precisely the state of affairs for the treatment of many diseases when they befall pregnant women (Chambers, Polifka, and Friedman 2008; Lyerly, Little, and Faden 2008b). The current evidence base for the care of pregnant women facing illness is widely regarded as deplorable—"a major public health problem" (Zajicek and Giacoia 2007); for a broad range of diseases, from stroke to severe infection, determining how best to treat a woman when pregnant is "anyone's guess" (Rochman 2009).

Our third concern is with a profoundly important lacuna in Chervenak and Mcullough's framework. Their near-exclusive focus on the ethical issues around managing fetal risk—certainly a crucial issue in many studies—fails to address one of the most important ethical issues in research around the needs of pregnant women: justice.

Yet among the moral concerns that responsible inclusion of pregnant women in research entails, issues of justice are perhaps the most pressing. A comprehensive framework must go beyond considerations of protecting research participants from risk—important as those issues are, it must address broad questions of justice. Some concerns center on the question of direct benefit: Pregnant women have been excluded from a breadth of trials from which they might benefit as individuals, ranging from microbicide trials for prevention of HIV to cancer therapies not available outside the clinical setting. Although no one would suggest that justice requires admitting pregnant women to all trials regardless of their risks and benefits, justice does call into question the de facto summary exclusion of pregnant women in research without justification in terms of those risks and benefits. As scholars have noted in discussions of other underrepresented populations, access to research and the benefits that sometimes accrue is a constitutive part of the ethical mandates governing clinical research (Mastroianni, Faden, and Federman 1994), and pregnant women have not benefited fairly.

Other concerns pertain to benefit of pregnant women as a class: Due to the underrepresentation of pregnant women in research, clinicians and women face treatment decisions in the context of a dearth of evidence about how drugs work in pregnant bodies, what doses are safe and effective for women, and which drugs pose teratogenic risk for fetuses—a dearth that often leads to reticence to prescribe or take indicated drugs, to the detriment of maternal and fetal health (Lyerly, Little, and Faden 2008b, 2009b). Justice also requires ensuring that not only pregnant women but also their health interests are justly represented in medical research.

For example, among the most important and overlooked opportunities for gathering valuable data are studies that impose no additional risk to pregnant women or the fetuses they carry. These include opportunistic pharmacokinetic studies, population-pharmacokinetic studies, cohort registries, and case-control surveillance studies that ensure the collection of data pertaning to maternal as well as neonatal outcomes. Yet the funding for such efforts is extraordinarily low, and a number of "low-hanging fruit" opportunities to collect these critical data have passed. The ongoing National Children's Study is a classic example: Plans to enroll 100,000 women before and during pregnancy to study the effects of the environment on their children remarkably do not include collection of outcomes specific to women's health (Lyerly, Little, and Faden 2009a). This raises questions not of managing fetal risk and benefit, but about justice and inclusion, questions that a "comprehensive framework" (Chervenak and McCullough 2011) to guide the ethical conduct of research with pregnant women must address.

A framework that grounds its approach on the concept of fetus as patient can in fact exacerbate tendencies to overlook these questions of justice. The term "patient," in general, encourages a tendency to focus on clinically oriented questions of the potential for harm from medical interventions; it also focuses us on how best to benefit the individual who "presents to the physician." The very core of clinical research, though, is about gathering evidence to benefit *populations*, and a comprehensive moral framework for that enterprise must perforce include moral commentary on which populations are—and which are not—being attended to for that benefit. ■

REFERENCES

Chambers, C. D., J. E. Polifka, and J. M. Friedman. 2008. Drug safety in pregnant women and their babies: Ignorance not bliss. *Clinical Pharmacology and Therapeutics* 83(1): 181–183.

Chervenak, F. A., and L. B. McCullough. 2011. An ethically justified framework for clinical investigation to benefit pregnant and fetal patients. *American Journal of Bioethics* 11(5): 39–49.

Lidz, C. M., and P. S. Applebaum. 2002. The therapeutic misconception: Problems and solutions. *Medical Care* 40(9): V55–V63.

Lyerly, A. D., M. O. Little, and R. Faden. 2008a. A critique of the fetus as patient. *American Journal of Bioethics* 8(7): 42–44.

Lyerly A. D., M. Little, and R. Faden. 2008b. The second wave: Toward responsible inclusion of pregnant women in research. *International Journal of Feminist Approaches to Bioethics* 1(2): 5–22.

Lyerly, A. D., M. O. Little, and R. Faden. 2009a. The National Children's Study: A golden opportunity to study the health of pregnant women. *American Journal of Public Health* 99(10): 1742–1745.

Lyerly, A.D., M. O. Little, and R. R. Faden. 2009b. Pregnancy is no time to refuse a flu shot. *New York Times*, September 29. Available at: http://www.nytimes.com/2009/09/29/health/views/29essa.html

Mastroianni, A., R. R. Faden, and D. Federman, eds. 1994. *Women and health research: Ethical and legal issues of including women in clinical studies*. Washington, DC: National Academy Press.

Rochman, B. 2009. The risks (and rewards) of pills and pregnancy. *Time Magazine*, June 8. Available at: http://www.time.com/time/magazine/article/0,9171,1901482,00.html

Zajicek, A., and G. P. Giacoia. 2007. Obstetric clinical pharmacology: Coming of age. *Clinical Pharmacology and Therapeutics* 81(4): 481–482.

Moral Status and the Fetus: Continuation of a Dialogue

Carson Strong, University of Tennessee College of Medicine

There is a problem with the claim by Chervenak and McCullough (2011) that the relationship between physician and fetal patient creates a "dependent moral status" for the fetus. An important feature of the concept of moral status is that it implies general obligations toward those who have moral status. Here I draw upon the distinction between general and special obligations. General obligations are ones that all moral agents have toward individuals that have a particular moral status. For example, if an individual has the moral status of personhood, then all moral agents have a prima facie obligation not to cause harm to that individual. By contrast, special obligations are created by special relationships. For example, role-related obligations that physicians have toward their patients are special obligations. Special obligations are owed by an individual in the special relationship, not by all moral agents. That all moral agents have some type of moral obligation toward one is a feature of the concept of moral status, regardless of whether the moral status in question is personhood or a lesser degree, intrinsic or conferred. It is a feature that is presupposed by virtually every major author on moral status. Moreover, each moral agent has the relevant obligations toward *all* individuals who have the moral status in question. These aspects of the concept of moral status are articulated well by Mary Anne Warren:

> Ascriptions of moral status serve to represent very general claims about the ways in which moral agents ought to conduct themselves toward entities of particular sorts. Thus, one important feature of the concept of moral status is its generality. Moral status is usually ascribed to members of a group, rather than merely to specific individuals. Moreover, it is usually ascribed on the basis of some property or properties that are thought to be possessed by all or most group members. (Warren 1997, 10)

It follows from this generally accepted meaning of the concept of moral status that special relationships do not give rise to moral status. Special relationships can give rise to *obligations* owed by a moral agent in the relationship, but special relationships do not give rise to obligations owed by *all* moral agents. If they do not give rise to general obligations, then they do not give rise to moral status.

In stating that fetal patients have "dependent moral status," Chervenak and McCullough misapply the concept of moral status. The misapplication is not avoided by qualifying the term with the word *dependent*; what they refer to by the expression "dependent moral status" is not a *type* of what we commonly understand as moral status because it is not a moral status at all. Chervenak and McCullough would be more clear if they were to use a different term or defend giving a new meaning to the term. Their not taking one of these approaches makes it difficult to understand, much less agree with, what they say about the moral features of the fetus–physician relationship.

Their misapplication of the concept of moral status has additional ramifications. They assert that a central feature of their theory is that it avoids the divisive controversy over abortion. They claim to sidestep this controversy by not using any view about the independent moral status of the fetus. Unfortunately, they do not succeed in skirting the issue, given that they claim that the only justifiable basis for

Address correspondence to Carson Strong, Ph.D., Professor, Department of Medicine, University of Tennessee Health Science Center, 956 Court Avenue, Suite G212, Memphis TN 38163, USA. E-mail: cstrong@uthsc.edu

A Dilemma Confronting Payments to Research Subjects

Tom Beauchamp

Required Reading

Neal Dickert and Christine Grady, "What's the Price of a Research Subject? Approaches to Payment for Research Participation," New England Journal of Medicine 341 (1999): 198–203.

Suggested Further Reading

Tom L. Beauchamp, "The Exploitation of the Economically Disadvantaged in Pharmaceutical Research," in Denis Arnold, ed., Ethics and the Business of Biomedicine (Cambridge: Cambridge Univ. Press, 2009): 83-102.

Christine Grady, "Payment of Clinical Research Subjects," Journal of Clinical Investigation 115 (2005 July 1): 1681–1687.

David Resnick, "Research Participation and Financial Inducements," American Journal of Bioethics 1 (2001): 54–56.

Margaret L. Russell, Donna G. Moralejo, and Ellen D. Burgess, "Paying Research Subjects: Participants' Perspectives," Journal of Medical Ethics 26 (2000): 126–30.

VanderWalde, S. Kurzban, "Paying Human Subjects in Research: Where Are We, How Did We Get Here, and Now What?" Journal of Law, Medicine, and Ethics 39 (2011): 543-58.

Erin P. Williams, Jennifer K. Walter, "When Does the Amount We Pay Research Participants Become 'Undue Influence'?" AMA Journal of Ethics 17(12) (2015): 1116-1121.

Outline

A DILEMMA CONFRONTING PAYMENT TO RESEARCH SUBJECTS
Tom L. Beauchamp

1. The Problem

A. What level of payment should research subjects receive?
B. The problem begins with the potential vulnerability of human research subjects.

2. The Populations I am Considering

A. I will focus on "economically disadvantaged" populations, but we can generalize my conclusions about payments far beyond this population.
B. These disadvantaged subjects are healthy volunteers with significant financial needs, and I consider only these subjects here.

3. Unjust Ways to Protect Subjects

A. An unacceptable strategy of protection is to exclude economically disadvantaged persons *categorically* from participation in research.
B. This strategy is an unjust and paternalistic form of discrimination that might serve to further marginalize, deprive, or stigmatize these subjects.
C. The two major problems are how to avoid *undue inducement* and how to avoid *undue profit* when using these research subjects.

4. The Problem of Undue Inducement

A. Undue inducement starts with the problem of subjects feeling heavily pressured to enroll in clinical trials.
B. These subjects also may be in desperate need of money.
C. Constraining Situations
   1. These subjects can feel controlled by the constraints of a situation, such as severe illness, lack of money, and lack of food or shelter.
   2. These subjects often feel "threatened" by their situation.
D. Monetary payments and related offers such as medical treatments can be undue inducements when: (1) they carry significant risks, (2) highly attractive inducements are offered, and (3) the subjects' economic disadvantage is elevated.
E. The problem of the exploitation of these subjects centers on whether solicited persons are situationally disadvantaged and lack viable alternatives, feel forced or compelled to accept offers that they otherwise would not accept, and take on increased risk in their lives.
F. The presence of an *irresistibly* attractive offer is a necessary condition of "undue inducement," but this condition is not by itself sufficient to make an inducement *undue*. A situation of undue inducement must also involve a person's assumption of a risk of harm that he or she would not ordinarily assume.

5. The Problem of Undue Profit

A. Undue inducements should be distinguished from undue profits, which occur from a distributive injustice of too small a payment to subjects, by contrast to an irresistibly attractive, large payment.
B. In the undue-profit situation, subjects in research receive an unfairly low payment, while the sponsor of research garners more than is justified.
C. Pharmaceutical research has often been criticized on grounds that companies reap unseemly profits without paying subjects fairly.
D. The basic moral problem is how to determine a nonexploitative, fair payment for service as a research subject.

6. How Can We Handle These Two Moral Problems of Exploitation?

A. These two problems of unduly large and irresistible payments and unduly small and unfair payments resist a tidy solution.
B. These problems present *a dilemma* about payments for research: To avoid undue inducement, payment schedules must be kept at reasonably low levels. But if payments are steeply lowered to avoid the problem of undue inducement, research subjects will receive so little money that the scheme is exploitative by virtue of undue profits that are gained by taking advantage of a person's misfortune.
C. If payment scales were then increased to avoid this undue profit, they would at some point become high enough to attract persons from the middle class. At or around this point, the offers could become excessively large and attractive, *undue* inducements for economically impoverished persons interested in the payments.
D. Addressing this dilemma can generate a deep social injustice if the pool of research subjects is composed more or less *exclusively* of the economically disadvantaged.

Editorials

Management of Acute Colonic Pseudo-Obstruction

Acute colonic pseudo-obstruction, also called Ogilvie's syndrome, refers to marked dilation of the colon in the absence of mechanical obstruction. It generally develops in hospitalized patients over a period of days, and up to 95 percent of affected patients have an associated medical or surgical condition,[1,2] such as trauma, recent surgery, or serious infection.

The chief criterion for the diagnosis is the diameter of the colon on abdominal radiographs. However, there is no consensus regarding the minimal diameter required for the diagnosis. Perhaps the most commonly used value is 9 cm, based on a frequently cited study from 1956, in which 19 surgically treated patients who had cecal perforation or "impending" cecal perforation due to colonic obstruction all had cecal diameters of at least 9 cm and only 3 of 100 control patients had such cecal diameters after cecal distention during a barium enema.[3] The applicability of these data to acute colonic pseudo-obstruction is questionable.

The most clinically meaningful diagnostic criterion for acute colonic pseudo-obstruction should be the threshold diameter above which there is a risk of colonic perforation. In a review of 400 cases, perforation or ischemia was not seen when the diameter of the cecum was less than 12 cm.[1] Other studies have also suggested that perforation is uncommon unless the diameter of the cecum is at least 12 cm.[4] However, there is a broad overlap in cecal diameters between patients in whom acute colonic pseudo-obstruction resolves and those in whom perforation occurs. Thus, once the threshold diameter is reached in an individual patient, the actual extent of dilation does not appear to matter. Some have suggested that the duration of dilation may be a more important risk factor.[5,6]

Acute colonic pseudo-obstruction can lead to colonic perforation and death. In a 1997 review of published studies, Rex reported that the risk of perforation was approximately 3 percent.[2] However, since this figure is largely based on retrospective case series, its generalizability is unclear and it may represent an overestimate. At best, we can conclude that perforation does occur in patients with acute colonic pseudo-obstruction, but that it is uncommon. Furthermore, although perforation appears to increase the risk of death, patients with acute colonic pseudo-obstruction may die of their underlying conditions, even when the pseudo-obstruction resolves without complications.

The initial management of acute colonic pseudo-obstruction is conservative: the underlying cause is treated if possible, metabolic disturbances are corrected, and medications that may decrease colonic motility (e.g., narcotics, anticholinergic agents, and calcium-channel antagonists) are stopped. Nasogastric suction, rectal tubes, and frequent changes in the patient's position are often used. If symptoms persist or worsen and if the colonic diameter increases or remains above a certain level (e.g., 12 cm), colonoscopy is generally performed. Colonoscopic decompression reduces the diameter of the cecum on abdominal radiographs in about 70 percent of patients.[2] However, the condition will recur in 40 percent of these patients, requiring repeated colonoscopy.[2] The risk of recurrence may be decreased by the placement of a drainage tube into the right side of the colon at the time of initial colonoscopy.[7,8] Bedside colonoscopy of an unprepared bowel is technically difficult and not without risk: a number of cases of perforation have been reported in this setting.[2]

Surgery is generally recommended for patients with persistent or worsening acute colonic pseudo-obstruction despite colonoscopic decompression. However, surgery also carries a risk in patients with serious concurrent illnesses, even in the absence of perforation: the mortality rate was 26 percent in a review of 125 surgically treated patients who were found to have viable bowel at operation.[1] Thus, in the absence of randomized trials, it is uncertain whether the benefit of colonoscopic or surgical therapy outweighs the risks in these patients. Some have questioned the need for early endoscopic or surgical treatment.[9]

In this issue of the *Journal,* Ponec et al.[10] present the results of a randomized, double-blind, controlled trial of neostigmine for patients with acute colonic pseudo-obstruction. Ten of 11 patients who were treated with intravenous neostigmine had prompt passage of flatus or stool, with reduced abdominal distention (median time to response, four minutes), as compared with none of the 10 patients who received placebo injections. Significant decreases were also seen in abdominal circumference and colonic diameters on radiographs. All the patients had had no response to at least 24 hours of conservative treatment. Two of the 10 patients with an initial response had a recurrence and underwent colonoscopy, surgery, or both. All seven patients in the placebo group who were given open-label neostigmine also had an immediate clinical response, and none had a recurrence. Symptomatic bradycardia requiring atropine developed in two patients; other side effects included abdominal pain, excessive salivation, and vomiting. Two of the 18 patients who received neostigmine died of causes unrelated to acute colonic pseudo-obstruction or its treatment, reinforcing the fact that such patients often die of their underlying illness.

The response to neostigmine, which increases cholinergic activity, may shed light on the cause of acute colonic pseudo-obstruction. In 1948, Ogilvie suggested that sympathetic activity of the colon was interrupted, allowing unopposed sacral parasympathetic innervation.[11] More recently, it has been proposed that the condition is due to sympathetic overactivity, parasympathetic suppression, or both. Hutchinson and Griffiths[12] studied sequential treatment with guanethidine (an adrenergic inhibitor) and neostigmine and found that improvement occurred only after neostigmine was given. Two subsequent uncontrolled studies reported that intravenous neostigmine was effective in over 80 percent of patients.[13,14] These studies support the theory that acute colonic pseudo-obstruction is due to decreased parasympathetic activity.

How should we integrate the findings of Ponec et al. and others into clinical practice? Acute colonic pseudo-obstruction should be diagnosed only when symptoms and signs of abdominal distention are present and when marked dilation of the cecum or right colon is seen radiographically without evidence of distal obstruction. Although a diameter of 9 cm may be used as a threshold for diagnosis, 12 cm may be a more appropriate measure in terms of concern about perforation. Conservative treatment should still be used initially. If the condition persists or worsens after 24 hours of conservative measures and if there are no contraindications, such as bradycardia, neostigmine should be given. The most common potentially serious side effect is bradycardia. Therefore, patients should be monitored and remain supine before and for some period after the infusion.

Because colonic perforation is uncommon and the risk of death is greatly influenced by the underlying illness, it seems unlikely that any trial could be large enough to address adequately the effects of neostigmine on these important clinical outcomes. Nonetheless, the findings of Ponec et al. suggest an important role for neostigmine, which may speed the resolution of acute colonic pseudo-obstruction and reduce the need for colonoscopy and surgery.

LOREN LAINE, M.D.
University of Southern California School of Medicine
Los Angeles, CA 90033

REFERENCES

1. Vanek VW, Al-Salti M. Acute pseudo-obstruction of the colon (Ogilvie's syndrome): an analysis of 400 cases. Dis Colon Rectum 1986;29:203-10.
2. Rex DK. Colonoscopy and acute colonic pseudo-obstruction. Gastrointest Endosc Clin North Am 1997;7:499-508.
3. Lowman RM, Davis L. An evaluation of cecal size in impending perforation of the cecum. Surg Gynecol Obstet 1956;103:711-8.
4. Gierson ED, Storm FK, Shaw W, Coyne SK. Caecal rupture due to colonic ileus. Br J Surg 1975;62:383-6.
5. Johnson CD, Rice RP, Kelvin FM, Foster WL, Williford ME. The radiologic evaluation of gross cecal distension: emphasis on cecal ileus. AJR Am J Roentgenol 1985;145:1211-7.
6. Baker DA, Morin ME, Tan A, Sue HK. Colonic ileus: indication for prompt decompression. JAMA 1979;241:2633-4.
7. Harig JM, Fumo DE, Loo FD, et al. Treatment of acute nontoxic megacolon during colonoscopy: tube placement versus simple decompression. Gastrointest Endosc 1988;34:23-7.
8. Geller A, Petersen BT, Gostout CJ. Endoscopic decompression for acute colonic pseudo-obstruction. Gastrointest Endosc 1996;44:144-50.
9. Sloyer AF, Panella VS, Demas BE, et al. Ogilvie's syndrome: successful management without colonoscopy. Dig Dis Sci 1988;33:1391-6.
10. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. N Engl J Med 1999;341:137-41.
11. Ogilvie WH. Large-intestine colic due to sympathetic deprivation: a new clinical syndrome. BMJ 1948;2:671-3.
12. Hutchinson R, Griffiths C. Acute colonic pseudo-obstruction: a pharmacological approach. Ann R Coll Surg Engl 1992;74:364-7.
13. Stephenson BM, Morgan AR, Salaman JR, Wheeler MH. Ogilvie's syndrome: a new approach to an old problem. Dis Colon Rectum 1995; 38:424-7.
14. Turegano-Fuentes F, Munoz-Jimenez F, Del Valle-Hernandez E, et al. Early resolution of Ogilvie's syndrome with intravenous neostigmine: a simple, effective treatment. Dis Colon Rectum 1997;40:1353-7.

AORTIC SCLEROSIS — A WINDOW TO THE CORONARY ARTERIES?

IN a provocative study in this issue of the *Journal,* Otto and colleagues report that aortic sclerosis, a condition without obvious hemodynamic consequences, was associated with an increased risk of death from any cause and from cardiovascular causes.[1] Although aortic sclerosis tended to be present in conjunction with other factors known to be associated with coronary disease and death from cardiovascular causes, the risk remained elevated after adjustment for these factors. What makes these data remarkable is the fact that this condition has been well known for decades and yet has generally been considered benign. The guidelines on valvular heart disease that were recently issued by a combined task force of the American Heart Association and the American College of Cardiology did not specifically address aortic sclerosis.[2] Textbooks that mention the condition usually do so in passing, noting that it is generally of no clinical consequence.

Why have the more grave implications of this condition gone unrecognized? First, in the past the condition was diagnosed primarily by physical examination, an approach with a somewhat limited ability to identify sclerosis. Furthermore, any adverse clinical events that did occur were ascribed to coincidence, since it was generally believed that the condition was benign. In fact, the Cardiovascular Health Study, the source of the data for the study by Otto et al., represents one of the few opportunities to examine the natural history of this disease.[3] The investigators performed diagnostic echocardiography on more than 5000 randomly selected men and women at base line and obtained follow-up data from which to establish the risk of aortic sclerosis.

Although the data of Otto et al. are interesting, they obviously raise the question of the mechanism by which aortic sclerosis contributes to or is associated with increased cardiovascular risk. Four potential explanations can be proposed: the findings may be the result of coincidence, infective endocarditis, or unrecognized outflow tract obstruction, or they may be associated with other cardiovascular conditions.

Otto et al. found that subjects with aortic sclerosis had an increased risk of death from heart disease as compared with subjects with normal aortic valves and those with stenotic aortic valves. Although the differences in risk were significant, coincidence is still a possible explanation for the association. There have been many instances in which one variable or another was related statistically to outcome in one study but the finding was not supported by subsequent studies. I would discount this explanation. Errors of this nature usually result from the use of small numbers of subjects or from the fact that the number of adverse events, although small, was significant. In such circumstances there may be a large difference in the rates of events between two groups but only a small difference in the number of events, as few as 10 events in some cases. However, in the study by Otto et al., over 5000 subjects were followed, almost 1000 died, and the difference in the risk between the groups was relatively large. Furthermore, another study that used different methods reached a similar conclusion.[4] Thus, I believe the findings are real.

The second potential explanation for the findings of Otto et al. — that the subjects with diseased valves were at increased risk for infective endocarditis, which could have accounted for the higher mortality rate in this group — also seems unlikely. The cardiovascular events included death, myocardial infarction, angina pectoris, congestive heart failure, and stroke. Although endocarditis could cause death, congestive heart failure, and stroke, one could assume that if endocarditis were an important cause of the increased risk of death, it would have been easily diagnosed. From the data presented, we cannot say for certain whether endocarditis developed in any of the subjects during the period of observation.

Otto et al. defined aortic sclerosis as focal areas of increased echogenicity and thickening of the leaflets without restriction of leaflet motion on echocardiography. Such an abnormality should cause only a small transvalvular pressure gradient (or none at all) when the patient is at rest. However, because the transvalvular gradient increases by the square of the cardiac output (if output doubles, the gradient quadruples), there may have been a substantial gradient during periods of exercise.[5] Since it appears that short periods of hemodynamic overload can induce hypertrophy that may then take much longer to regress,[6] unrecognized hemodynamic overload during exercise may have led to cardiac hypertrophy, a known risk factor for death from heart disease.[7] In fact, the left ventricular mass was slightly greater in the group with aortic sclerosis than in the group with normal aortic valves. However, it is unlikely that this small difference (6 percent) could account for the findings of the study.

I believe that the results of this study can best be explained by assuming that aortic sclerosis is an objective marker of other forms of cardiovascular disease, especially coronary disease. Although the presence of documented coronary disease at entry was controlled for in the study, unidentified coronary disease, of course, could not be. Since most coronary disease is silent and not identified by the standard screening techniques of history taking, electrocardiography in subjects at rest, and physical examination, many subjects could have had occult coronary disease at entry. It is likely that once echocardiography is added to the standard evaluation, as it was in this study, this potential new marker of coronary disease (aortic sclerosis) will not escape notice. As Otto et al. note, aortic-valve disease and coronary disease share many risk factors.[8-10] The pathologic processes that may be occurring in the coronary arteries may be identified more easily in the aortic valve, which serves as a window to the coronary artery, and this finding can then serve as a harbinger of future events.

What do the findings of Otto et al. mean in terms of daily practice? Although aortic sclerosis was defined echocardiographically in this study, the potential for detecting it on the basis of the finding of a systolic ejection murmur by simple auscultation during the physical examination may provide physicians with a potential marker for future coronary disease. Should the patient who has a soft systolic ejection murmur and normal carotid pulses (previously considered benign findings) undergo more intensive screening, be assessed for other risk factors for coronary disease, and undergo routine echocardiography to assess the morphology of the aortic valve? Although much additional study is required before these questions can be answered, it is intriguing to think that a new screening procedure for assessing coronary risk in an asymptomatic population may simply consist of the careful use of a stethoscope.

BLASE A. CARABELLO, M.D.
Houston Veterans Affairs Medical Center
Houston, TX 77030

REFERENCES

1. Otto CM, Lind BK, Kitzman DW, Gersh BJ, Siscovick DS. Association of aortic-valve sclerosis with cardiovascular mortality and morbidity in the elderly. N Engl J Med 1999;341:142-7.
2. Bonow RO, Carabello B, De Leon AC, et al. ACC/AHA guidelines for the management of patients with valvular heart disease: a report of the

American College of Cardiology / American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients with Valvular Heart Disease). J Am Coll Cardiol 1998;32:1486-588.
3. Gardin JM, Wong ND, Bommer W, et al. Echocardiographic design of a multicenter investigation of free-living elderly subjects: the Cardiovascular Health Study. J Am Soc Echocardiogr 1992;5:63-72. [Erratum, J Am Soc Echocardiogr 1992;5:550.]
4. Teerlink JR, Newman TB, Schiller NB, Foster E. Aortic sclerosis, as well as aortic stenosis, is a significant predictor of mortality. Circulation 1997; 96:Suppl I:I-82. abstract.
5. Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. Am Heart J 1951;41:1-29.
6. Muntz KH, Gonyea WJ, Mitchell JH. Cardiac hypertrophy in response to an isometric training program in the cat. Circ Res 1981;49:1092-101.
7. Ghali JK, Liao Y, Simmons B, Castaner A, Cao G, Cooper RS. The prognostic role of left ventricular hypertrophy in patients with or without coronary artery disease. Ann Intern Med 1992;117:831-6.
8. Mohler ER, Sheridan MJ, Nichols R, Harvey WP, Waller BF. Development and progression of aortic valve stenosis: atherosclerosis risk factors — a causal relationship? A clinical morphologic study. Clin Cardiol 1991;14: 995-9.
9. Gotoh T, Kuroda T, Yamasawa M, et al. Correlation between lipoprotein(a) and aortic valve sclerosis assessed by echocardiography (the JMS Cardiac Echo and Cohort Study). Am J Cardiol 1995;76:928-32.
10. Aronow WS, Schwartz KS, Koenigsberg M. Correlation of serum lipids, calcium, and phosphorus, diabetes mellitus and history of systemic hypertension with presence or absence of calcified or thickened aortic cusps or root in elderly patients. Am J Cardiol 1987;59:998-9.

EHRLICHIOSIS — TICKS, DOGS, AND DOXYCYCLINE

THE ehrlichia are obligate intracellular bacteria that infect a variety of animals, usually with ticks as vectors. *Ehrlichia sennetsu,* the first species recognized to infect humans, causes a mononucleosis-like illness that so far has been seen only in Asia.[1] In 1987, the first case of human ehrlichiosis in the United States was reported. Because of serologic cross-reaction, the infection was thought to be caused by an agent of ehrlichiosis in dogs, *E. canis*.[2] The organism was subsequently isolated in cell culture, was shown to be distinct from *E. canis,* and was named *E. chaffeensis*.[3] Because the organism often forms characteristic ehrlichial colonies (morulae) within monocytes, the disease has been called human monocytic ehrlichiosis. Human monocytic ehrlichiosis, which is recognized primarily in the south central and southeastern United States, is an acute febrile illness characterized by headache and myalgia and usually accompanied by leukopenia, thrombocytopenia, and elevated levels of hepatic aminotransferases.[4] Central nervous system manifestations or nonspecific rashes develop in 15 to 30 percent of patients. Humans acquire *E. chaffeensis* from the bite of the Lone Star tick, *Amblyomma americanum,*[5] and deer may be an important reservoir host.[6] *E. chaffeensis* may also infect dogs.[7]

In 1994, infection with an organism seen within granulocytes was described among patients from Minnesota and Wisconsin.[8] Polymerase-chain-reaction (PCR) amplification of the agent's 16S ribosomal gene[9,10] has demonstrated that the organism is closely related to species of ehrlichia that infect horses (*E. equi*) and ruminants (*E. phagocytophila*). The etiologic organism was subsequently isolated[10] and, until now, has generally been referred to as "the agent of human granulocytic ehrlichiosis." Human granulocytic ehrlichiosis is clinically similar to the monocytic form of the disease, although rash occurs in fewer than 10 percent of patients with granulocytic ehrlichiosis. Humans acquire granulocytic ehrlichiosis from deer ticks (*Ixodes scapularis*) in eastern and central North America and from related ticks in other geographic areas.[11] The agent of human granulocytic ehrlichiosis and closely related agents infect a variety of wild and domestic animals, including dogs.

In this issue of the *Journal,* Buller and colleagues present an exciting twist in the evolving story of ehrlichiosis.[12] They describe four patients with fever who were from Missouri, an area where *E. chaffeensis,* but not the agent of human granulocytic ehrlichiosis, is endemic. Although inclusions were seen in granulocytes from two of the patients, it appears that the patients tested seronegative for the agent of human granulocytic ehrlichiosis but seropositive for *E. canis* and *E. chaffeensis* antigens. The infection was identified as ehrlichiosis by means of "broad-spectrum" PCR primers, but results were negative with the use of primers specific for agents of human monocytic or human granulocytic ehrlichiosis. Sequencing of the amplified 16S RNA gene from the patients' blood yielded a surprising result: it was identical to that of *E. ewingii,* a pathogen previously known only as a cause of canine granulocytic ehrlichiosis.[13,14] One of the patient's dogs also had positive results for E. *ewingii* on PCR analysis. Once again, a new suspect has been implicated in human disease by its PCR footprints, which constitute circumstantial but reasonably convincing forensic evidence of a microbial crime.

This report raises interesting questions and has important implications. Three of the four patients were immunocompromised. Does *E. ewingii* usually not infect immunocompetent humans, or does it produce in them an infection that is mild or asymptomatic? What are the clinical spectrum and natural history of the disease? In dogs, *E. ewingii* can cause arthritis and chronic infection. What are this organism's zoonotic hosts other than dogs? What is its geographic range? Given that *A. americanum* may also be the vector for *E. ewingii,* can coinfection with *E. chaffeensis* occur? Isolation of this agent will be critical for understanding the disease and developing specific serologic tests. Currently, the finding of morulae in granulocytes in combination with negative results on serologic testing for the agent of human granulocytic ehrlichiosis and positive results

for *E. chaffeensis* should suggest *E. ewingii* infection. Finally, there is now another "agent of human granulocytic ehrlichiosis," and it occurs in a geographic area where previously only human monocytic ehrlichiosis was known to exist.

Our understanding of the organisms that can cause ehrlichiosis and their geographic ranges is expanding. It is likely that additional ehrlichial diseases affecting humans will be discovered, which may be shared by animals. To discover new associations among diseases and agents, it is important not only to keep an open mind but also to cast wide molecular nets. Although in the study by Buller et al. it is unclear how clinicians selected patients for PCR testing at the Missouri laboratory, it is noteworthy that *E. chaffeensis* or *E. ewingii* was identified in only 60 of 413 samples, even with the use of broad-range ehrlichial primers. Other new or previously unsuspected agents, tick-borne or not and ehrlichial or not, were probably involved in causing the illnesses of some of the patients with PCR-negative results.

So, what does a clinician need to do? Most important is to remember that ehrlichial infections can be severe or even fatal if untreated. A diagnosis of ehrlichiosis must be considered in anyone who presents with an acute febrile illness after potential or documented exposure to ticks. Leukopenia, thrombocytopenia, elevations in aminotransferase levels, or a combination of these findings is usually present or soon develops in patients with ehrlichiosis. The differential diagnosis is extensive. Diseases such as endocarditis, other forms of septicemia, vasculitis, and thrombotic thrombocytopenic purpura must be considered. The presence of inclusions in leukocytes on Wright- or Giemsa-stained blood smears should be sought, although their absence does not exclude the possibility of ehrlichiosis. The other tests currently available are primarily used to confirm a diagnosis and usually are not helpful when the patient presents for care.

Serum samples can be obtained during the acute phase of the illness and during convalescence to test for the agent of human granulocytic ehrlichiosis or *E. chaffeensis*. However, it is critical to realize that most patients with ehrlichiosis are seronegative for these agents at presentation. PCR analyses for the organisms associated with human granulocytic and human monocytic ehrlichiosis (and perhaps *E. ewingii*), if available, would be expected to be positive in untreated patients. However, PCR is technically demanding, and its current reliability outside the research setting in the diagnosis of ehrlichiosis is unknown. Culture of the agents of human granulocytic and human monocytic ehrlichiosis is diagnostic, but the process takes several days and the results are reliable only in a few specialized research laboratories.

If a patient has an unexplained febrile illness that is clinically consistent with ehrlichiosis — particularly if it is severe, accompanied by typical laboratory abnormalities, or seemingly unresponsive to antibiotic therapy — physicians must consider prompt treatment for ehrlichiosis. Because these diseases are frequently forgotten, are difficult to diagnose, and respond readily to therapy, it may be helpful to think of the ehrlichioses (and other rickettsial infections) as "doxycycline-deficiency diseases." Of course, given the growing problem of antibiotic resistance among other pathogens, patients with mild or short-lived febrile or typical respiratory illnesses should not undergo extensive testing or receive doxycycline simply because they live in areas of endemic ehrlichiosis or have been exposed to ticks.

Patients with ehrlichiosis usually have a response to treatment within 24 to 48 hours, and the lack of a response should suggest another diagnosis. It remains unclear how best to treat pregnant women and children younger than nine years old, since in these populations tetracyclines are usually considered to be contraindicated. Chloramphenicol, the rifamycins, and some of the newer quinolones may be active against some or all ehrlichial infections,[15,16] but clinical experience with these agents is limited. Expert consultation should be obtained before therapy with a drug other than a tetracycline is considered.

Buller et al. have expanded our awareness of ehrlichial pathogens as causes of human disease. Although there is currently no evidence that "man's best friend" transmits human granulocytic ehrlichiosis, human monocytic ehrlichiosis, or *E. ewingii* infection to its master, both people and dogs can play host to the same invaders — with sometimes dire, but often preventable, consequences.

JESSE L. GOODMAN, M.D., M.P.H.
University of Minnesota
Minneapolis, MN 55455

REFERENCES

1. Fukuda T, Kitao T, Keida Y. Studies on the causative agent of "Hyaganetsu" disease. I. Isolation of the agent and its inoculation trial in human beings. Med Biol 1954;32:200-9.
2. Maeda K, Markowitz N, Hawley RC, Ristic M, Cox D, McDade JE. Human infection with *Ehrlichia canis,* a leukocytic rickettsia. N Engl J Med 1987;316:853-6.
3. Anderson BE, Dawson JE, Jones DC, Wilson KH. *Ehrlichia chaffeensis,* a new species associated with human ehrlichiosis. J Clin Microbiol 1991; 29:2838-42.
4. Fishbein DB, Dawson JE, Robinson LE. Human ehrlichiosis in the United States, 1985 to 1990. Ann Intern Med 1994;120:736-43.
5. Anderson BE, Sims KG, Olson JG, et al. *Amblyomma americanum:* a potential vector of human ehrlichiosis. Am J Trop Med Hyg 1993;49:239-44.
6. Lockhart JM, Davidson WR, Stallknecht DE, Dawson JE, Howerth EW. Isolation of *Ehrlichia chaffeensis* from wild white-tailed deer (*Odocoileus virginianus*) confirms their role as natural reservoir hosts. J Clin Microbiol 1997;35:1681-6.
7. Dawson JE, Biggie KL, Warner CK, et al. Polymerase chain reaction evidence of *Ehrlichia chaffeensis,* an etiologic agent of human ehrlichiosis, in dogs from southeast Virginia. Am J Vet Res 1996;57:1175-9.
8. Bakken JS, Dumler JS, Chen SM, Eckman MR, VanEtta LL, Walker DH. Human granulocytic ehrlichiosis in the upper midwest United States: a new species emerging? JAMA 1994;272:212-8.

9. Chen SM, Dumler JS, Bakken JS, Walker DH. Identification of a granulocytotropic Ehrlichia species as the etiologic agent of human disease. J Clin Microbiol 1994;32:589-95.
10. Goodman JL, Nelson C, Vitale B, et al. Direct cultivation of the causative agent of human granulocytic ehrlichiosis. N Engl J Med 1996;334: 209-15. [Erratum, N Engl J Med 1996;335:361.]
11. Pancholi PC, Kolbert CP, Mitchell PD, et al. *Ixodes dammini* as a potential vector of human granulocytic ehrlichiosis. J Infect Dis 1995;172: 1007-12.
12. Buller RS, Arens M, Hmiel SP, et al. *Ehrlichia ewingii,* a newly recognized agent of human ehrlichiosis. N Engl J Med 1999;341:148-55.
13. Ewing SA, Roberson WR, Buckner RG, Hayat CS. A new strain of *Ehrlichia canis.* J Am Vet Med Assoc 1971;159:1771-4.
14. Anderson BE, Greene CE, Jones DC, Dawson JE. *Ehrlichia ewingii* sp. nov., the etiologic agent of canine granulocytic ehrlichiosis. Int J Syst Bacteriol 1992;42:299-302.
15. Brouqui P, Raoult D. Susceptibilities of Ehrlichiae to antibiotics. In: Raoult D, ed. Antimicrobial agents and intracellular pathogens. Boca Raton, Fla.: CRC Press, 1993:181-98.
16. Klein MB, Nelson CM, Goodman JL. Antibiotic susceptibility of the newly cultivated agent of human granulocytic ehrlichiosis: promising activity of quinolones and rifamycins. Antimicrob Agents Chemother 1997;41: 76-9.

Sounding Board

WHAT'S THE PRICE OF A RESEARCH SUBJECT? APPROACHES TO PAYMENT FOR RESEARCH PARTICIPATION

SUCCESSFUL clinical research depends on the ability to recruit research subjects. Tension between the need to recruit subjects and the obligation to offer them certain types of protection has made recruitment a persistent ethical challenge. One important and difficult issue involves whom investigators should enroll in research studies. A different but equally crucial issue concerns the types of inducement investigators should use to recruit subjects.

For decades, many investigators have paid subjects for participating in research studies, and this practice remains one of the most controversial methods of recruitment.[1] Despite discussions over many years, ethical issues about payment remain unresolved. The predominant concern expressed is that payment of subjects might represent "undue inducement," by leading to a decrease in either the voluntariness or the understanding with which subjects agree to participate.[2-6] A second concern is that the payment of subjects may result in economically disadvantaged populations' bearing an unduly large share of the risks and burdens of research participation.[2,4,5] Many people also worry that the use of money as a recruitment tool will lead to putting subjects at risk who do not care about or support the goals of the study.[2-4,6,7] Finally, some believe that the payment of subjects violates the ethical norms of the investigator–subject relationship by turning it into a commercial relationship.[6,8,9] This worry is particularly apparent when subjects are very ill.

Although some argue that the payment of subjects is never ethical, this practice has long been an integral part of the recruitment of research participants. In fact, the payment of subjects is likely to become even more pervasive as the need to recruit grows along with the capacity for technological discovery and the level of commercial funding for clinical research. The frequency of payment may also increase in response to requirements for greater inclusion of women, minorities, and children in research studies.[10,11] As this practice becomes more frequent, it is essential to recognize that payment can be made in various ways, some of which are more ethically acceptable than others.

No consensus has emerged on when and in what manner it is ethical to pay subjects. Although federal regulations and guidelines call attention to some of the moral issues that payment raises, they offer little substantive guidance for clinical investigators, institutional review boards, or contract research organizations on how to pay subjects ethically. The federal "common rule"[12] never mentions the payment of subjects, and the guidelines of the Office of Protection from Research Risks[13] and the Food and Drug Administration (FDA)[14] merely reflect the controversy over how to approach payment. For instance, FDA information sheets offer seemingly contradictory advice, suggesting that payment should be viewed as a "recruitment incentive" while simultaneously requiring institutional review boards to ensure that payment is not "unduly influential."[14]

PAYING PATIENTS OR HEALTHY SUBJECTS

Most of the literature on the payment of subjects reflects the common perception that only healthy subjects — those who do not have the condition under study — are paid for their participation in clinical research. It is true that patients are rarely or never paid in some types of research, such as clinical trials of cancer chemotherapy. However, listings and advertisements of ongoing clinical trials are evidence that patients with such diseases as asthma and human immunodeficiency virus infection are frequently paid for participating in clinical research.[15]

The ethical argument against the payment of patients rests on one or both of the following premises: patients are particularly vulnerable, and patients are deriving medical benefit in a way that healthy subjects are not. The special vulnerability of patients is most often attributed to two factors: the inability of patients to distinguish clinical care from research, often called the "therapeutic misconception,"[16] and a perceived difference in power between patients and investigators, especially when an investigator is both the clinician and the researcher. In the absence of empirical data, however, it is not clear how payment exploits either source of vulnerability. Because patients typically pay for their clinical care, it seems plausible that paying patients for participating in research may, in fact, reduce the therapeutic misconception by distinguishing the procedures that are undertaken purely for research purposes from those that are performed as part of clinical care. Paying patients may also help to minimize the power differential by making participation seem less like a "favor" the patient is being asked to do for the physician-investigator.

The second premise — that patients are deriving benefit — also fails to justify an absolute prohibition against paying patients. After all, many studies enrolling patients offer little or no prospect of direct benefit. In fact, some of these studies also involve healthy subjects who are paid to participate. For example, a researcher may use positron-emission tomography to study the differences in brain function between patients with obsessive–compulsive disor-

TABLE 1. THE THREE MODELS OF REIMBURSEMENT AND THEIR APPLICATIONS TO A HYPOTHETICAL CASE.

VARIABLE	MARKET MODEL	WAGE-PAYMENT MODEL	REIMBURSEMENT MODEL
Justification for payment	Recruitment of subjects is vital to research; monetary incentives help to recruit the needed subject pool.	Participation in research requires little skill but takes time and effort and requires endurance of uncomfortable procedures.	Participation in research should not require financial sacrifice by subjects.
Function of payment	Incentive.	Working wage.	Reimbursement for expenses.
Strategy	Payment is based on supply and demand; completion bonuses and other incentives for completing the study are used.	Payment is based on standard wage for unskilled labor; payment is augmented for particularly uncomfortable procedures.	Payment is determined by subject's expenses and can include payment for lost wages or other expenses incurred.
Components of payment	$25/hr, $200 for taking medicine, and $200 completion bonus.	$10/hour, $50 for following the drug schedule, and $50 for serial blood collection.*	Different for every subject.
Total payment	$1,125.	$390.	$195 (with no wage); $398 (with student's wage); $1,645 (with professor's wage).

*Data are from the Department of Labor, 1998.[18]

der and healthy controls. In cases in which neither patients nor healthy subjects would receive any immediate or direct benefit from the procedure, not paying patients while paying healthy subjects appears to violate the principle of justice, which demands that like cases be treated alike.[17] In studies that offer potential benefits, such as many phase 3 studies, there may be no reason to pay patients, but it is not clear why it would be unethical to do so simply because they may benefit from participating.

There is no inherent reason to treat patients and healthy subjects differently with respect to payment. Therefore, our analysis of payment generally applies to both types of participants.

THREE MODELS OF PAYMENT

In this article, we evaluate three models of payment: the market model, the wage-payment model, and the reimbursement model (Table 1). Careful consideration of these models will help in choosing the most ethical approach. Other types of "payment," such as free medical services, do raise many of the same considerations, but this discussion refers only to payments in cash. Because cash payments are so pervasive and influential, and because they are more fungible than other forms of inducement, a careful analysis of their use is important.

The Market Model

The market model is grounded in traditional libertarian theory.[19] The principle of supply and demand determines whether and how much subjects should be paid for participating in a given study at a specific site. When research is arduous or risky and offers little or no prospect of direct benefit to subjects, there is little apparent reason for a person to participate. This model allows money to be the reason. For example, money may be an incentive for a healthy person to participate in a study of natural patterns of sleep, or in a phase 1 pharmacokinetic study of a treatment for a disease the person does not have. Similarly, it may be an incentive for a patient to participate in a nontherapeutic "challenge study" to examine the pathophysiologic features of a particular condition.

Use of the market model would probably result in high payment for participation in studies that offer subjects no prospect of direct benefit but involve risky or uncomfortable procedures. Payment may also be high when investigators want to recruit subjects very quickly, or when few people are eligible to participate. In addition, the market model sanctions the use of large completion bonuses and other incentives to encourage compliance with the protocol. After all, the value of a subject's participation is often dependent on the subject's completion of the study. The market model would, however, suggest that there be little or no payment when people are eager to enroll in a study, as may be the case for studies involving such agents as trastuzumab (Herceptin) and antiangiogenesis factors for the treatment of cancer.

The Wage-Payment Model

The wage-payment model operates on the notion that participation in research requires little skill but does require time, effort, and the endurance of undesirable or uncomfortable procedures. This model adopts the egalitarian position that subjects performing similar functions should be paid similarly. Participating in research is similar to many other forms of unskilled labor in that it requires little skill

or training, may involve some risk, and often involves relatively little "labor."[2,4,20] The wage-payment model thus involves the payment of subjects on a scale commensurate with that of other unskilled but essential jobs. Application of the wage-payment model would lead to the payment of a fairly low, standardized hourly wage, augmented by increases for particularly uncomfortable or burdensome procedures.[2,3] The payment of completion bonuses is also consistent with this model; however, they should not constitute a large proportion of the payment, because this model bases payment primarily on the time subjects spend "working" (i.e., participating in the research).

The wage-payment model is not entirely distinct from the market model, but there are two fundamental differences between them. First, in the wage-payment model, payment is set according to the unskilled-labor market rather than the supply of persons eligible for participation. Second, the wage-payment model requires standardization, both among different protocols and between research and other forms of unskilled labor.

The Reimbursement Model

According to the reimbursement model, payment is provided simply to cover subjects' expenses. This model reflects a different form of egalitarianism, and it is based on the view that research participation should not require financial sacrifice but should be "revenue neutral" for participants. One application of this model would involve reimbursing subjects only for expenditures such as travel, meals, and parking. Alternatively, use of this model could involve reimbursing subjects for their time away from work at whatever rate the subjects are typically paid in addition to reimbursement for expenses. With either version, each subject would be paid according to his or her own expenses.

The reimbursement model differs from both of the other models in three important ways. First, it precludes subjects' making a profit. Second, it does not use money to compensate for nonfinancial "expenses," such as effort or discomfort. Third, payment does not depend on any market, either for research participation or for unskilled labor.

APPLYING THE MODELS TO A CASE

Delineating the practical implications of each model is crucial; people who appear to agree in theory often use different models in determining payment for a particular study, resulting in widely divergent payment practices. Consider a study testing the effect of a protease inhibitor on the bioavailability of a narcotic pain medication. The subjects are healthy persons, and the study requires them to take the protease inhibitor daily for 12 days and to come to the clinic eight times. For two of the visits, the subjects must remain at the clinic all day. Overall, the study takes 29 hours and involves a screening examination, administration of the pain medication with serial blood collections, and follow-up. This protocol offers no direct benefit, involves the discomfort of serial blood collection, and requires taking medications that may cause diarrhea, nausea, or other side effects.

The three models would lead to very different payments for participation in this study (Table 1). True application of the market model would depend on the current market. On the basis of amounts commonly offered today, it is reasonable to estimate that subjects might be paid $25 an hour, $200 for taking the medications, and a $200 completion bonus, leading to a total payment of $1,125. The wage-payment model would lead to payment of about $10 per hour, just below the 1998 total national average for nonfarm production workers,[18] as well as $50 for the inconvenience of taking the drug for two weeks and $50 for the more invasive serial blood collection. Total payment would be $390. One formulation of the reimbursement model would involve payment only for travel, meals, and parking expenses. If parking cost $3 per hour, lunch cost $6 for each of the two days the subject was required to remain at the clinic all day, and the subject traveled 40 miles round trip and was reimbursed at $0.30 per mile, total payment would be $195. Alternatively, in addition to reimbursement for their expenses, subjects could also be paid their regular wages for 29 hours. A professor might then be paid $50 per hour for a total of $1,645. Yet, a student who worked outside of class for $7 per hour would receive $398. Applying the three models to this case illustrates that different models can lead to large variations in the amount paid to subjects for participating in the same study.

ADVANTAGES AND DISADVANTAGES OF EACH MODEL

The market model has four potential advantages. First, it is likely to ensure a sufficient number of subjects in the time frame in which they are needed. Similarly, large completion bonuses are likely to ensure that the subjects complete the study. A third advantage is that the market model may allow subjects to make money while making a socially beneficial contribution.[2,21] Finally, this model is likely to reduce or eliminate the financial sacrifice of participation. The latter two advantages depend, of course, on the study's popularity, because this model will lead to little or no payment for participation in studies in which many subjects are eager to enroll without being paid.

Conversely, there are several possible disadvantages. One potential problem is that payment may be so high that all other factors become irrelevant to subjects' decisions to participate or to remain in re-

search studies. Whether escalating payment can really compromise voluntariness is controversial.[4,5,21-23] But, it may be ethically problematic to commercialize research participation by "hiring" subjects who are motivated only by profit[8,9,24,25] or to offer very high payments to economically vulnerable groups. In addition, large total payments and completion bonuses may provide an incentive for the subject not to explore carefully the risks and benefits of the research or to conceal important health information in order to become or remain eligible for the study and thus receive payment.[1,5] Finally, the market model is likely to lead to situations in which researchers are competing with each other for subjects on the basis of the amount they pay their subjects.

There are five potential advantages of the wage-payment model. First, the possibility of undue inducement or exploitation is lessened if subjects have other options for earning similar amounts of money.[5] Second, this model would lead to the standardization of payment among studies, lessening interstudy competition based on payment and potentially creating an incentive for investigators to minimize risks to subjects. The wage-payment model reduces the financial sacrifice of participation for subjects. In addition, the wages offered by similarly risky unskilled jobs serve as a lower limit on the amount offered for paid studies. Finally, the wage-payment model allows people to be paid for work that is valuable to society.[2,21]

This model may be less likely than the market model to yield a sufficient number of subjects in the desired time frame. The wage-payment model could also make paid studies attractive primarily to people with low incomes, particularly because it might involve financial sacrifice for wealthier participants.[2,4,5] Finally, treating the subject's role as an unskilled job may be seen as inappropriately commercializing participation in research.[8,9,24,25]

The reimbursement model has four potential advantages. By prohibiting monetary inducement, it not only alleviates any concern about undue inducement, but it also presents no incentive to conceal information or remain uninformed about risks and benefits. Furthermore, the reimbursement model does not preferentially induce vulnerable populations to participate. Finally, this model lessens the financial sacrifice of research participation to some degree.

The most obvious disadvantage of the reimbursement model is that it may yield an insufficient number of subjects within the desired time frame.[26] After all, in the current climate of commercialization, it provides no incentive to participate, and it will actually require financial sacrifice for almost all subjects if time away from work is not reimbursed. The only people who would not incur additional expenses if their time were not reimbursed would be those who are already hospitalized or who are unemployed. On the other hand, if time as well as other expenses are accounted for, different people will be paid unequally for the same contribution to research, a disparity that seems unfair.[5] The latter formulation is also likely to lead to either exorbitant costs or the targeting of low-income people in order to avoid paying higher participation costs.

THE MODEL OF CHOICE: WAGE PAYMENT

We recommend the adoption of the wage-payment model for three principal reasons. First, the wage-payment model greatly reduces the common worry about undue inducement. Because most potential subjects are likely to have other options for earning similar amounts of money, they will presumably choose participation in research when they prefer it to other options for earning an unskilled-labor wage. Given the prevalent view that subjects should to some extent support the goals of research,[7] money should not be the only factor influencing participation. Although money may be a motivating factor in subjects' decisions, it will not have such a predominant role as to negate the influence of other considerations. Because this concern is especially important when a study is very risky, not allowing payment to escalate according to risk constitutes a crucial safeguard.

Second, standardization among studies is extremely valuable for several reasons. The minimization of competition for subjects on the basis of payment will help to contain the cost of research. Standardization also averts the creation of barriers to the success of less well funded studies and the encouragement of research on potentially lucrative drugs over equally important research on disease mechanisms and rarer diseases. Because the level of funding of a research study often correlates most closely with the commercial potential of the drug or device under study and not necessarily with its quality or social value, it is important to adopt practices that do not favor only well-funded studies. Standardized payment schedules will also be extraordinarily helpful to institutional review boards and investigators as a means of determining payments. Furthermore, not altering payments on the basis of risk creates an incentive for investigators to minimize risks in order to recruit subjects effectively.

Third, because payment is based on the contribution subjects make, the wage-payment model adheres to a basic assumption of the principle of justice: that similar people should be treated similarly.[27] This feature represents a great advantage over the reimbursement model, according to which already well-paid subjects would be paid more than those with lower incomes enrolled in the same study. It is also an advantage over the market model, which would allow site-specific markets to lead to very dif-

ferent levels of payment at different sites in multicenter studies.

The disadvantages of the market model are too serious for it to be the best approach. The chances that money would overshadow such factors as risk would be greatest in the studies with the greatest risks. Even for people who believe that subjects need no protection from monetary influence,[18,21] there are important reasons to reject the market model. Its likely effect on which studies are conducted and on the cost of research is profound. In addition, the potential effect of large completion bonuses on subjects' willingness to report side effects or withdraw from studies is problematic. Such an effect could compromise the validity of study data, thereby placing future patients and subjects at risk.

The reimbursement model is too restrictive, unfair, and unworkable. The mere payment of expenses incurred without reimbursement for time spent would no doubt hamper recruitment. Although reimbursement for these expenses may be incorporated into some versions of the wage-payment model, such reimbursement on its own would still entail considerable financial sacrifice for most participants. Alternatively, paying subjects the equivalent of their salaries for the time they spend participating appears unjust and will either drive up the cost of research or lead to the selection of only low-income people.

CONCLUSIONS

We believe that the wage-payment model represents the most ethical approach to paying research subjects, and we think it is an approach that can be successfully implemented through several key steps. To ensure local standardization of payment, research institutions and institutional review boards should develop specific policies or guidelines outlining how investigators should determine in which cases and in what manner to pay subjects who enroll in their studies. We also encourage the FDA and the Office of Protection from Research Risks to publish guidelines suggesting this model of payment, so that there will be more national standardization of payment practices. Finally, we encourage pharmaceutical and biotechnology companies to develop industry standards conforming to the wage-payment model.

Although we recommend the broad implementation of this model, it is important to emphasize that further investigation of the payment of research subjects is critical, given the current lack of data. Four types of research will be particularly helpful in refining this model. First, it is crucial to evaluate the extent to which the cognitive, social, and physical status of potential subjects should alter decisions about payment for research participation. Second, there is a need for empirical research to determine the ways in which offers of money affect the quality of subjects' informed consent. Third, it is important to study whether payment leads to the recruitment of a disproportionate number of poor subjects. Finally, there is a need for data on the importance of payment with respect to successful recruitment; little is known about the effect of different amounts or methods of payment on recruitment efforts.[26]

For the present, the wage-payment model, coupled with a commitment to rigorous research, will most effectively balance the increasing need for human research subjects with adequate protection of the subjects who make such research possible.

NEAL DICKERT, B.A.
CHRISTINE GRADY, PH.D.
National Institutes of Health
Bethesda, MD 20892

The opinions expressed herein are those of the authors and do not necessarily reflect those of the National Institutes of Health.

We are indebted to Ingrid Burger, Stephan Burton, Franklin Miller, Steve Piscitelli, and especially Ezekiel Emanuel for their contributions to the development of this article.

REFERENCES

1. Cohen L. Stuck for money: to screen new drugs for safety, Lilly pays homeless alcoholics. Wall Street Journal. November 14, 1996:1.
2. Ackerman TF. An ethical framework for the practice of paying research subjects. IRB 1989;11(4):1-4.
3. McGee G. Subject to payment? JAMA 1997;278:199-200.
4. Levine RJ. Ethics and regulation of clinical research. 2nd ed. New Haven, Conn.: Yale University Press, 1986.
5. Macklin R. "Due" and "undue" inducements: on paying money to research subjects. IRB 1981;3:1-6.
6. Wartofsky M. On doing it for money. In: Research involving prisoners: report and recommendations. Washington, D.C.: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1976:3-1–3-24.
7. Jonas H. Philosophical reflections on experimenting with human subjects. In: Freund PA, ed. Experimentation with human subjects. New York: George Braziller, 1970:1-31.
8. Titmuss RM. The gift relationship: from human blood to social policy. New York: New Press, 1997.
9. Murray TH. Gifts of the body and the needs of strangers. Hastings Cent Rep 1987;17(2):30-8.
10. NIH policy and guidelines on the inclusion of children as participants in research involving human subjects. NIH Guide Grants Contracts. March 6, 1998. (Or see: http://www.nih.gov/grants/guide/notice-files/not98-024.html.)
11. Guidelines for the inclusion of women and minorities as subjects in clinical research. NIH Guide Grants Contracts. March 18, 1994.
12. Title 45, CFR (Code of Federal Regulations), Part 46.
13. The official IRB guidebook. Washington, D.C.: Office of Protection from Research Risks, 1993.
14. Information sheets: guidelines for institutional review boards and clinical investigators. Rockville, Md.: Food and Drug Administration, 1998.
15. CenterWatch clinical trials listing service. Boston: CenterWatch, 1999. (Or see: http://www.centerwatch.com.)
16. Appelbaum PS, Roth LH, Lidz CW, Benson P, Winslade W. False hopes and best data: consent to research and the therapeutic misconception. Hastings Cent Rep 1987;17(2):20-4.
17. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont report: ethical principles and guidelines for the protection of human subjects of research. Washington, D.C.: Government Printing Office, 1979.
18. Average hourly earnings of production workers. Washington, D.C.: Department of Labor, 1998.
19. Epstein RA. Mortal peril: our inalienable right to health care? Reading, Mass.: Addison–Wesley, 1997:503.
20. Arendt H. The human condition. 2nd ed. Chicago: University of Chicago Press, 1998:352.

21. Wilkinson M, Moore A. Inducement in research. Bioethics 1997;11: 373-89.
22. Faden RR, Beauchamp TL. A history and theory of informed consent. New York: Oxford University Press, 1986:392.
23. Newton L. Inducement, due and otherwise. IRB 1982;4:4-6.
24. Anderson E. Value in ethics and economics. Cambridge, Mass.: Harvard University Press, 1993:245.
25. Radin MJ. Contested commodities. Cambridge, Mass.: Harvard University Press, 1996:279.
26. Bigorra J, Baños JE. Weight of financial reward in the decision by medical students and experienced healthy volunteers to participate in clinical trials. Eur J Clin Pharmacol 1990;38:443-6.
27. Beauchamp TL, Childress JF. Principles of biomedical ethics. New York: Oxford University Press, 1994:546.