Regulatory discrepancies between the Council of Europe and the EU regarding biomedical researches

Andorno, R

Regulatory Discrepancies Between the Council of Europe and the EU Regarding Biomedical Research

Roberto Andorno

Introduction

This chapter aims to outline the *human rights* approach to biomedical research adopted by the Council of Europe's Convention on Human Rights and Biomedicine (henceforth, the Biomedicine Convention),[1] and to contrast it with the more *market-oriented* provisions of the Clinical Trials Directive of the European Union.[2] At the same time, it intends to stress that, while this difference in approach is understandable in light of the dissimilar objectives of both European bodies, it has resulted in some unfortunate regulatory inconsistencies that may lead to less protection of research participants, particularly the most vulnerable ones. To illustrate these normative discrepancies, this chapter will briefly compare some of the requirements for biomedical research, as they result from the provisions of both instruments.

Two different approaches to the regulation of biomedical research in Europe

The regulation of medical research on human subjects always takes place in a context of tension between two fundamental aspirations of every society. On the one hand, there is the legitimate desire to contribute to people's health and quality of life through the development of new preventive, therapeutic, and diagnostic tools. This aspiration justifies the widely held view that biomedical research activities should enjoy the greatest possible freedom to advance and develop new procedures and techniques. On the other hand, there is also the

---

1 Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Biomedicine Convention) (opened for signature on 4 April 1997, entered into force on 1 December 1999) ETS No 164.

2 Council Directive (EC) 2001/20 of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [2001] OJ L121/34.

conviction that medical research, like any other activity within society, does not have absolute autonomy to operate at the margin of respect for human dignity and human rights. This stems from science not being an end in itself, but rather a means to promote the well-being of society and every individual. In other words, medicine exists to serve people, not people to serve medicine. Consistent with this, modern societies have made serious efforts to ensure, first, that participants in biomedical research understand the nature, risks, benefits and alternatives of prospective research and freely consent to it; second, that participants are not exposed to disproportionate risks; and third, that a qualified independent body reviews compliance with the two precedent requirements, as well as the fulfilment of other conditions (for instance, scientific validity of the planned research, respect for the privacy of participants, etc.).

The first international set of principles for research involving human subjects was the Nuremberg Code, which was drafted in 1947 by the Allied Military Tribunal, which judged and convicted the Nazi physicians who had used the prisoners of concentration camps as subjects of brutal experiments. The Nuremberg Code embodied the idea that there are some principles for the protection of research subjects that are non-negotiable. In this regard, Jay Katz says that:

> "The Nuremberg Code is a remarkable document. Never before in the history of human experimentation, and never since, has any code or any regulation of research declared in such relentless and uncompromising a fashion that the psychological integrity of research subjects must be protected absolutely."[3]

Since the Nuremberg Code, scientists have been strictly required to comply with basic conditions for conducting research on human beings. Regarding the requirement of informed consent, the Nuremberg Code emphasizes from the very beginning that "voluntary consent of the human subject is absolutely essential", and that that "the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice (...); and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision" (Principle 1).

The Nuremberg Code also requires that research "should be so conducted as to avoid all unnecessary physical and mental suffering and injury" (Principle 4); that it should not be conducted "where there is an a priori reason to believe that death or disabling injury will occur" (Principle 5); and that "the degree of

3 J Katz, 'The Consent Principle of the Nuremberg Code: Its Significance Then and Now' in GJ Annas and MA Grodin (eds), *The Nazi Doctors and the Nuremberg Code* (OUP, New York 1992) 227-239, at 227.

risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment" (Principle 6).

In contemporary societies, research on human beings is inconceivable if at least these basic requirements are not fulfilled. This is of course also the case in Europe, where specific policies regarding this issue have been adopted, not only at the domestic level, but also at the level of the common institutions, namely the European Union and the Council of Europe. It should not be forgotten, after all, that Europe was at the very centre of the tragic event from which both modern medical ethics and international human rights law emerged: the Second World War. As George J. Annas points out emphatically, "World War II was the crucible in which both human rights and bioethics were forged, and they have been related by blood ever since".[4]

The promulgation of the Nuremberg Code indeed marked the birth, not only of modern medical ethics, but also of modern human rights law. Only one year after the Nuremberg Code was developed, the most significant event in human rights in the modern era occurred: the adoption of the Universal Declaration of Human Rights by the United Nations.[5] This document, recognized today as the cornerstone of the entire international human rights system, not only paved the way for the adoption of more than seventy treaties that are applied today on a permanent basis at global and regional levels, but also served as a model for many constitutions and laws throughout the world, and helped to ground uncountable decisions of national and international courts.

The historical relationship between bioethics and human rights is much closer than generally believed. Robert Baker asserts that the 1948 Declaration was in part informed by the revelations that led to the adoption of the Nuremberg Code. Indeed, he claims that "... the details revealed daily at Nuremberg gave content to the rights recognized by Articles 4 through 20 of the Declaration".[6]

Regarding the specific topic with which this paper is concerned, it is interesting to note that the first issue with which both new disciplines – modern medical ethics and human rights law – were confronted was precisely medical research on human beings. It is therefore not surprising that many, if not most, international instruments relating to biomedical research appeal to a human rights framework to establish minimal common standards in this field. But beyond this coincidence of history, there are various substantive reasons explaining this phenomenon: first, biomedical practice is *per se* directly related to the most basic human rights, such as the right to life, to physical and mental integrity, to privacy, etc. Thus, it is perfectly sound to have recourse to the um-

---

4 GJ Annas, *American Bioethics. Crossing Human Rights and Health Law Boundaries* (OUP, New York 2005) 160.

5 Universal Declaration of Human Rights (adopted 10 December 1948 UNGA Res 217 A(III) (UDHR).

6 R Baker, 'Bioethics and Human Rights: A Historical Perspective' (2001) 10:3 CQHE 241-252.

brella of international human rights law to ensure the protection of such basic human claims in this field; second, the human rights framework facilitates the formulation of transnational standards, because international human rights law is based on the assumption that basic rights transcend cultural diversity; third, there are few mechanisms available other than human rights to respond to emerging bioethical challenges at a transnational level. As a well-known public health expert has observed, "the human rights framework provides a more useful approach for analysing and responding to modern public health challenges than any framework thus far available within the biomedical tradition."[7]

At present, biomedical research is simultaneously regulated in Europe by two different bodies, the Council of Europe (henceforth CoE) and the European Union (henceforth, EU), each of them adopting a different approach to the matter.

The norms of the Biomedicine Convention dealing with research on human subjects place clear emphasis on promoting the dignity and rights of research participants. All the provisions of this instrument are a natural extension of this basic objective. It is not by chance that the title itself of the Convention explicitly refers to human rights. In addition to this, Article 1 is very clear in this regard, when it provides that the Convention aims to:

> "protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine."

The importance of the Biomedicine Convention lies precisely in the fact that it is the only binding intergovernmental instrument that comprehensively addresses the link between human rights and biomedicine.[8] Moreover, it is probably not exaggerated to say that the Biomedicine Convention and its Additional Protocol on Biomedical Research of 2005[9] represent the most elaborate and systematic effort ever undertaken at a transnational level to address, by means of legally binding instruments, the challenges to human rights posed by biomedical research.

The Convention's purpose, as indicated by its Preamble, is to give a specific application in the field of biomedicine to the general rights contained in the

7 J Mann, 'Health and human rights. Protecting human rights is essential for promoting health' (1996) 312 BMJ 924-925.

8 R Andorno, 'The Oviedo Convention: A European Legal Framework at the Intersection of Human Rights and Health Law' (2005) 2 JIBL 133-143.

9 Additional Protocol to the Convention on Human Rights and Biomedicine Concerning Biomedical Research. (Additional Protocol on Biomedical Research) (opened for signature 25 January 2005) ETS No 195.

European Convention on Human Rights.[10] The Convention can indeed be regarded as an extension of human rights law into the biomedical field.

Article 15 of the Biomedicine Convention is coherent with the priority assigned to human rights when it states that "scientific research in the field of biology and medicine shall be carried out freely, subject to the provisions of this Convention and the other legal provisions ensuring the protection of the human being." Similarly, the Explanatory Report to the Convention stresses that "the whole Convention, the aim of which is to protect human rights and dignity, is inspired by the principle of primacy of the human being, and all its articles must be interpreted in this light" (para. 22).[11] On this basis, the specific rules contained in the Biomedicine Convention to protect the rights of patients and research subjects are explicitly recognized as being able to guide the interpretation of the European Convention on Human Rights in cases where the European Court of Human Rights considers there to have been a violation of one of the rights recognized by the latter instrument.[12]

In contrast to the human rights approach of the Council of Europe's Biomedicine Convention, the European Union is, in this specific field, mainly concerned with the harmonization of the administrative provisions governing clinical trials for medicinal products. This is the key objective of the Directives adopted in this area, namely the Directive 2001/20 on Clinical Trials, and its "offspring", the Directive 2005/28 on Good Clinical Practice. Certainly, as we will see below, the Clinical Trials Directive also includes substantive provisions relating to informed consent of participants, to the proportionality of risks, to the confidentiality of personal data, to the need of the favourable opinion of an ethics committee, etc. But these elements do not seem to embody the main objective of this document. Rather, they clearly play a secondary role in regulation that is "market oriented," as it is primarily linked to the control of the medicinal products market in Europe.[13] This particular approach has been explained on the grounds that "the initial impetus for the Clinical Trial Directive came from the pharmaceutical industry, which desires a harmonized process and set of standards for the granting of REC [Review Ethics Committees] approval for clinical trials."[14]

Although the official documents that were issued during the long gestational process of the Directive – approximately ten years – routinely stressed that the

---

10 A Plomer, *The Law and Ethics of Medical Research: International Bioethics and Human Rights* (Cavendish, London 2007) 21.

11 Explanatory Report to the Convention on Human Rights and Biomedicine. Strasbourg, Council of Europe, 1997.

12 Ibid, para. 165.

13 D Sprumont and A Gytis, 'The Importance of National Laws in the Implementation of European Legislation of Biomedical Research' (2005) 11 EJHL 250.

14 D Beyleveld and S Sethe, 'The European Community Directives on Data Protection and Clinical Trials' in E Emanuel and others (eds), *The Oxford Textbook of Clinical Research Ethics* (OUP, Oxford 2008) 184.

intention was to protect participants, while facilitating high-quality research and a competitive industry, "it is difficult to shake the feeling that the voices of industry received more than due attention".[15] In this regard, it is revealing that the principal instrument on which the Directive was inspired was not the Declaration of Helsinki, but the European Good Clinical Practice guidelines, which are based on the ICH-Guidelines for Clinical Trials.[16] The ICH process (which stands for "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use") is partly led by pharmaceutical industry associations. It aims to negotiate guidelines on the authorisation of medicines acceptable to industry and the regulatory authorities of the United States, Europe, and Japan, in order to reduce the barriers to global trade. Furthermore, it is also interesting to note that the Clinical Trials Directive was drafted not by units in the European Commission responsible for health or human rights (such as, for instance, the Directorate-General for Health and Consumers), but by the DG for Enterprise and Industry.[17]

It is therefore not surprising that the Directive was generally received with satisfaction by the pharmaceutical industry. However, researchers from public and academic institutions complain about the stringent application processes and bureaucratic procedures put in place by the new regulation, which have increased the trial costs almost to the point that only big companies can afford them. In this regard there is evidence that the number of non-commercial clinical trials has dramatically fallen since 2004.[18] [19]

The contrast between the philosophies that inspire the European Union and the Council of Europe regarding biomedical research could not be more striking. At the risk of oversimplifying the comparison, it could be said that, while the EU emphasizes freedom of research in a rather utilitarian manner, the Council of Europe is essentially concerned with the protection of research subjects, relying for that purpose, at least to some extent, on a deontological (i.e. Kantian) approach.

This difference of perspectives becomes more understandable if one remembers the history of each organization. On the one hand, the European Union has its origins in the "European Coal and Steel Community," formed among six countries in 1951, and in the "European Economic Community" (EEC) created in 1957. The purpose of these structures was of economic nature, namely the creation of a single market within Europe. On the other hand, the

15 K Liddell and others, 'Medical Research Involving Incapacitated Adults: Implications of the EU Clinical Trials Directive 2001/20/EC' (2006) 14 MLR 367-417.

16 Ibid

17 Ibid

18 R Hoey, 'The EU Clinical Trials Directive: 3 years on' (2007) 369 Lancet 1777-78.

19 M Hartmann and F Hartmann-Vareilles (2006), 'The Clinical Trials Directive: How Is It Affecting Europe's Noncommercial Research?' 1(2) PLos Clin Trials e13. DOI:10.1371/journal.pctr.0010013.

Council of Europe was established to promote respect for human rights in the Old Continent. To achieve this purpose, this body adopted the European Convention on Human Rights of 1950 and various mechanisms aimed at ensuring respect for human rights in Europe, such as the European Court of Human Rights, which was established in 1959. Certainly, the European Union has also a jurisdictional instance, the European Court of Justice, which is based in Luxembourg. However, its role is totally different from that of the European Court of Human Rights. The Luxembourg court was not created to guarantee respect for human rights, but rather to make sure that EU legislation is interpreted and applied in the same way in all EU countries.

Given that the European Union and the Council of Europe have different objectives, it is perfectly understandable that they adopt different approaches to biomedical research. This is not in itself problematic; it is the logical consequence of the complementary nature of both institutions. Furthermore, the efforts to make the European pharmaceutical research more competitive by establishing uniform procedures for the ethical review of clinical trials are perfectly legitimate. This chapter does not intend to criticize such goal, nor to disapprove the difference *per se* of the approaches adopted by the EU and the CoE to regulate this matter, but rather to point out that such difference is problematic when it results – as it unfortunately does – in significant regulatory discrepancies between the regulations adopted by both European bodies, especially when they may lead to lower protection of vulnerable research participants.

Points in common between the CoE's and the EU's regulations

At first sight, there are no major discrepancies between the regulations of the Council of Europe and the European Union regarding the requirements for biomedical research. Moreover, the conditions that are set out in the aforementioned CoE and EU instruments are basically the same conditions that can be found in virtually all ethical and legal guidelines relating to this matter. As mentioned above, there are at least three basic requirements that make biomedical research ethical, two internal and one external. The two internal conditions are: a) research subjects must give their free, explicit and informed consent (subjective condition); b) the risks for the research subject should not be disproportionate to the potential benefits of the research (objective condition). The external requirement is that the research project should be approved by an independent body, which must assess its scientific merit and its ethical acceptability.

The need for informed consent means that medical interventions can only be carried out after the individual has been informed of the purpose, nature, risks and consequences of the intervention, and has freely consented to it. As pointed out above, this requirement has its origins in the "Nuremberg Code"

of 1947, having thereafter been endorsed by the Declaration of Helsinki of the World Medical Association, the first version of which dates back to 1964. However, both documents do not have per se the status of legal instruments. The first international legally binding instrument that requires the consent of participants in medical research is the International Covenant on Civil and Political Rights of 1966, which provides in Article 7 that "[n]o one shall be subjected without his free consent to medical or scientific experimentation."[20] But it is interesting to note that it only refers to *free* consent, and there is no mention of the need that the consent should also be *informed,* as the Biomedicine Convention does. Indeed, according to Article 5 of this latter document, the participants must be informed about "the purpose and nature of the intervention" as well as its "consequences and risks". The consent must be given in written (Article 16.5). In the case of individuals who are not able to give consent for themselves, such as minors and persons suffering from mental disorder, the consent of their legally authorized representatives is needed (Article 6.2). All these provisions are developed in detail by the Additional Protocol on Biomedical Research of 2005 (for instance, Article 13 contains a long enumeration of the information that must be provided to research participants).

Also the Clinical Trials Directive requires the informed consent of research subjects. Article 3, entitled "Protection of clinical trials subjects", provides that the trial subject, or his legal representative in case the person is unable to consent, must be informed of "the nature, significance, implications and risks" of the trial (para. d), as well as of its "objectives, risks and inconveniences", (...) "the conditions under which it will be conducted" (..), and of his "right to withdraw from the trial at any time" (para. b). The consent must, in principle, be given in written (para. d).

The "objective condition" for research on human beings is that it should not pose disproportionate risks to participants, to their life and physical and mental integrity. Otherwise such research would constitute an unacceptable instrumentalization of human beings and therefore would be contrary to human dignity. In this regard, Article 16(ii) of the Biomedicine Convention provides that risks should not be "disproportionate to the potential benefits of the research". Similarly, the Clinical Trials Directive stipulates that a clinical trial may be undertaken only if "the foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and other present and future patients" (Article 3.2(a)).

In addition to the internal (subjective and objective) conditions for conducting research on human beings, there is an external requirement: the proposal must be approved by an independent body (i.e. a review committee, or review board), which must examine its scientific merit and its ethical acceptability.

20 International Covenant on Civil and Political Rights (adopted 16 December 1966, entered into force 23 March 1976) 999 UNTS 171 (ICCPR).

This is a fundamental condition because research on human beings is ethically justifiable only if it really offers a prospect of contributing to people's health, and is carried out in conformity with scientific criteria and in ways that respect and protect the rights of participants. All these elements cannot be assessed by the same team that is conducting the research, but should be evaluated by a third, impartial party. This requirement can be found in Article 16(iii) of the Biomedicine Convention, in Articles 9 to 12 of the Convention's Additional Protocol on Biomedical Research, as well as in Article 6 of the Clinical Trials Directive.

Discrepancies between the CoE's and the EU's regulations

Despite apparent similarities between the aforementioned instruments adopted by the CoE and the EU, a careful analysis of these reveals serious differences between them, particularly regarding the protection of the most vulnerable research subjects, like children.[21] These normative discrepancies can be summarized in the following points:

a. *Benefit for the individual versus benefit for the group*

Biomedical research may present the prospect of a direct benefit to the participants themselves, or just to the age or health status category to which they belong (e.g. "children", "pregnant women", etc.), or simply to society at large. The question of who the potential beneficiaries of the research outcomes will be is to such an extent important that the consent cannot be considered really "informed" if the point has not been clearly understood by participants.[22]

According to the Biomedicine Convention, in the case of individuals who are not able to give a valid consent, such as minors and adults suffering from mental disorder, biomedical interventions must be aimed at benefiting them directly (Article 6.1). This condition excludes in such cases non-therapeutic research, which, by definition, is carried out in the interest of third parties. The requirement of direct benefit can be exceptionally waived when the research entails minimal risk and minimal burden for the participant (Article 17.2(ii)).

The different level of accepted risk depends on whether or not the prospect of a direct benefit that the research offers to the subject makes sense. Regarding competent participants, it is reasonable that research without the prospect of direct benefit can only be undertaken within certain limits, in particular, if it entails "no more than acceptable risk and acceptable burden for the indivi-

21 See A Altavilla, 'Clinical Research with Children: The European Legal Framework and its Implementation in French and Italian Law' (2008) 15 EJHL 109-125.

22 Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, Geneva 2002), Guideline 5.

dual."[23] On the other hand, when the research may be of direct benefit to the health of participants, "then a higher degree of risk and burden may be acceptable, provided that it is in proportion to the possible benefit."[24]

Regarding participants unable to consent, such as children or individuals with mental disorders, as they lack self-determination, even stricter regulation is necessary. Such individuals need to be especially protected from the instrumentalization that would result from exposing them to research presenting more than a minimal risk and that only aims to benefit other individuals or the progress of science in general. In this regard, as it has been stated in relation to research on children, it seems to be that "parental consent is not sufficient if proposed non-therapeutic research involves more than minimal risk to the child."[25]

The Clinical Trials Directive is in this regard particularly unsatisfying. As a legal expert has pointed out, "the provisions [of the Directive] are couched in a language so convoluted as to make it unintelligible."[26] According to Article 4 on clinical trials on minors, "some direct benefit for the group of patients [must be] obtained from the [pediatric] clinical trial." (para. e). In addition, the clinical trial "must relate directly to a clinical condition from which the minor concerned suffers or be of such nature that it can only be carried out in minors" (*idem*). The key question is: does the "group of patients" referred to in Article 4(e) necessarily include the subject himself? One may infer that the answer is in the negative when comparing this provision with Article 5 on clinical trials on incompetent adults, which explicitly requires that there should be "grounds for expecting that administering the medicinal product to be tested will produce a benefit to the patient outweighing the risks or produce no risk at all" (para. i). It is indeed unclear why a similar provision is lacking in the norms relating to research on children. Should one conclude that the principle, emphatically enunciated by Article 4(i) of the Directive, that "the interests of the patient always prevail over the interest of science or society", is a mere rhetorical statement when applied to minors?

b. Minimal risks versus minimization of risks

Closely related to the precedent issue is the requirement that non-therapeutic research on participants unable to consent can only be conducted when it does not involve more than a minimal risk and a minimal burden for the individual. This principle, which can be found in Article 17.2 of the Biomedicine Convention, is based on the assumption that some very minor procedures (for exam-

23 Additional Protocol on Biomedical Research, article 6.
24 Ibid
25 JK Mason, A McCall Smith, and G Laurie, *Law and Medical Ethics* (OUP, Oxford 2006), 687.
26 V Junod, *Clinical drug trials. Studying the safety and efficacy of new pharmaceuticals* (Bruylant, Bruxelles 2005) 398.

ple, taking a single blood sample from a newborn) do not constitute an unfair instrumentalization of incompetent persons, and may contribute in a decisive way to diagnostic and therapeutic progress for the benefit of other individuals in the same condition.[27]

This provision was often criticized on the grounds that it fails to offer a definition of "minimal risks and minimal burden". The Additional Protocol on Biomedical Research attempts to clarify this point. According to Article 17 of this latter document, "minimal risk" means that the research "will result, at the most, in a very slight and temporary negative impact on the health of the person concerned" (para. 1). The expression "minimal burden" is used to indicate that it is expected "that the discomfort will be, at the most, temporary and very slight for the person concerned" (para. 2).

The Explanatory Report to the Additional Protocol on Biomedical Research takes care of providing very concrete examples of research with minimal risk and minimal burden such as: obtaining bodily fluids without invasive intervention, e.g. taking saliva or urine samples or cheek swab; taking small additional tissue samples at the time that other tissue samples are being taken, for example during a surgical operation; taking a blood sample from a peripheral vein or taking a sample of capillary blood; minor extensions to non-invasive diagnostic measures using technical equipment, such as sonographic examinations; taking an electrocardiogram following rest; one X-ray exposure; carrying out one computer tomographic exposure, or one exposure using magnetic resonance imaging without a contrast medium.[28]

It is noteworthy that the last version of the Declaration of Helsinki (2008) includes the same requirement as it provides that "a potential research subject who is incompetent (...) must not be included in a research study that has not the likelihood of benefit for them unless (...) the research entails only minimal risk and minimal burden" (para. 27). Similarly, the CIOMS Guidelines stipulate that, in cases of research with individuals unable to consent, "the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons".[29]

In contrast to this, the Clinical Trials Directive omits any reference to minimal risk and minimal burden. Articles 4(g) and 5(f) only include the requirement that clinical trials must be designed "to minimise pain, discomfort,

---

27 Explanatory Report Biomedicine Convention, paras. 111 and 112.

28 Explanatory Report to the Additional Protocol to the Convention on Human Rights and Biomedicine concerning Biomedical Research. ETS No 195. Strasbourg, Council of Europe, 2005, para. 100.

29 Council for International Organizations of Medical Sciences (CIOMS), *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, Geneva 2002), Guideline 9. It should be noted, however, that the same Guideline 9 allows slight or minor increases above such minimal risk, "when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them."

fear and any other foreseeable risk in relation to the disease and developmental stage." Strangely, this provision only appears in the aforementioned articles, which cover research on persons unable to consent. This may inadvertently give readers of the Directive the impression that a lower level of risk is required in such cases, and that special protection is granted to vulnerable individuals. However, this would be a misleading interpretation of those provisions, because "minimizing risk" is not synonymous with "minimal risk". The minimization of risks is a general requirement for all research on human subjects, not only on persons unable to consent but also on competent adults. The Additional Protocol on Biomedical Research explicitly refers to it when it provides that "all reasonable measures shall be taken to ensure safety and to minimise risk and burden for the research participants" (Article 21). Similarly, the Declaration of Helsinki (2008) states that "every precaution must be taken (...) to minimize the impact of the study" on the physical, mental and social integrity of research subjects (para. 23).

The general requirement of a minimization of risks in biomedical research is often formulated by saying that the research should present "a favourable risk-benefit ratio"[30] or, in other words, that the risks should be proportionate to the expected benefits. This means that, while the "minimization of risk" is a relative notion, as much dependent on the particular circumstances of each research study and on the expected benefits, the requirement of "minimal risk" embodies an objective standard. It is precisely because it is objective that it is possible to provide concrete examples of risks that are regarded as "minimal", as does the Explanatory Report to the Additional Protocol on Biomedical Research (para. 100).

c. Respect for the minor objection

Although children cannot give a valid consent for participating in medical research, and the permission of their parents or legal representatives is always required, this does not mean that they should be totally excluded from the informed consent process. On the contrary, the willing cooperation of the children should be sought, after they have been informed to the extent that their maturity and intelligence permit. Some children can understand the basic implications of participating in research and can go through the necessary procedures. They may also be able to express a refusal of a proposed procedure. Such refusal should always be respected, even if the parents have given permission, unless the child needs treatment that is not available outside the context of the research, the research offers a direct therapeutic benefit, and there is no acceptable alternative therapy.[31] In this regard, the Declaration of Helsinki

30 E Emanuel, D Wendler, C. Grady, 'What Makes Clinical Research Ethical?' (2000) 283 JAMA 2702-2711.

31 CIOMS (n 29), Guideline 14 and commentary.

states that "the potential subject's dissent should be respected" (para. 28). Other recent guidelines emphasize the importance of respecting a child's refusal to participate or continue in a research study.[32]

Consistent with this requirement, the Biomedicine Convention sets out the general principle, which is valid for both clinical and research interventions, that "the opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity" (Article 6.2). Regarding research on persons unable to consent, Article 17.1(v) provides that it can only be undertaken "if the person concerned does not object". This means that the wish of the individual "prevails and is always decisive."[33] The Additional Protocol on Biomedical Research specifies that the "objection to participation shall not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care" (Article 15.3).

In contrast, the Clinical Trials Directive avoids any clear reference to the imperative of respecting the child's objection to participate in a clinical trial and to its possible consequences in terms of discrimination regarding his or her right to health care. Article 4(c) only provides that the wish of the minor to refuse participation or to be withdrawn from the clinical trial at any time will be "considered" by the investigator. This norm offers little guidance as to the value of the minor's refusal and opens the door to potential abuse. This is especially a cause for concern when one considers that the Directive does not exclude minors from participating in research without direct benefit to them and entailing more than minimal risk. It should be noted that Article 5(c), which deals with the refusal to participate in a clinical trial made by an incapacitated adult, also states that such refusal will be simply "considered" by the investigator.

d. Inducements to participating in research

The promise of financial incentives to participate in research is prohibited by most ethical and legal regulations on the grounds that they compromise the voluntariness of subjects' consent decisions, may lead to exploitation of people in need, and can persuade potential participants to take risks against their better judgment. Nevertheless, a distinction is commonly made between "due" and "undue" inducements. In this regard, the CIOMS Guidelines stipulate that

> "Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct bene-

32 Mason and others (n 25) 688.
33 Explanatory Report Biomedicine Convention (n 27), para. 108.

> fit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ("undue inducement")."[34]

Similarly, the Convention's Additional Protocol on Biomedicine Research provides that the ethics committee, at the time of reviewing a research project, must come to the conclusion that "no undue influence, including that of a financial nature, will be exerted on persons to participate in research. In this respect, particular attention must be given to vulnerable or dependent persons" (Article 13). The Explanatory Report specifies that compensation to the participants, and eventually to their representatives, is not regarded as "undue influence" if it is "appropriate to the burden and inconvenience [to which they are exposed]" (para. 64). However, such financial influence becomes "undue", and therefore must not be exerted, when "it is provided at a level that might encourage participants to take risks that they would not otherwise find acceptable" (ibid). It will be up to the ethics committee to decide, case by case, whether the promised payment or any other kind of influence on potential participants becomes "undue" (ibid).

The Clinical Trials Directive is not satisfactory in this regard. Certainly, it provides that "no incentives or financial inducements" can be offered to minors or to incapacitated adults (Articles 4(d) and 5(d)). However, it should be noted that this requirement does not appear among the general conditions for the protection of research subjects. It is difficult to believe that this was an accidental omission, since the point was carefully included in the two articles dealing with persons unable to consent. Therefore, one may infer that the promise of financial incentives are regarded by the Directive as legitimate without limits, insofar as participants are competent adults, and regardless of whether they are vulnerable for some other reason (educational, socio-cultural, economic, etc.). This, of course, enters in open contradiction with most guidelines on biomedical research, which set up a general rule to protect all potential research participants from exploitation or coercion, not only those who are unable to consent.

e. Clinical equipoise

The principle of "clinical equipoise" stipulates that a patient should not be involved in a randomised-clinical trial (i.e. a trial that randomly assigns patients to two or more treatments) unless there is a state of genuine uncertainty within the expert medical community about the comparative therapeutic merits of

34 CIOMS (n 29) Guideline 6.

each arm of the trial. In other words, as a trial begins, treatments (including any placebo arm) must be regarded as having equal merit in treating a particular condition. The expression "clinical equipoise" was first used by Benjamin Freedman in 1987.[35] The rationale for observing this principle is that it ensures that patients involved in studies are not prescribed treatments that are known to be less effective that some other treatments for their condition.[36] It provides a moral foundation to the requirement that the health care of subjects should not be disadvantaged by research participation. At the same time, it aims to make compatible physicians' roles as scientists dedicated to conducting the best studies to gain knowledge, and as healers dedicated to adapting treatments to each patient's needs, goals and values.[37]

The requirement of clinical equipoise is endorsed by the Declaration of Helsinki (2008), which states, as a general principle, that "the benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention" (para. 32). Similarly, the CIOMS Guidelines stipulates that "as a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention" (Guideline 11).

Similarly, the Biomedicine Convention's Additional Protocol on Biomedical Research endorses the principle of clinical equipoise in Article 23, entitled "Non-interference with necessary clinical interventions", which states that "in research associated with prevention, diagnosis or treatment, participants assigned to control groups shall be assured of proven methods of prevention, diagnosis or treatment" (para. 2).

In contrast with the precedent guidelines, which clearly support the principle of clinical equipoise, the relevant provision of the Clinical Trials Directive is drafted in obscure terms. Article 3.2(a) states that "(...) a clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored."

Some authors have pointed out the serious interpretative difficulties posed by this norm, among other reasons, because it allows "the benefit to the public to outweigh any degree of risk to the individual" and "no mention is made of clinical equipoise, nor it is stated that the risks should be necessary, proportionate or minimised".[38] Trying to understand why the principle of clinical equipoise was overlooked in this way, authors suggest the explanation that

35 B Freedman, 'Equipoise and the ethics of clinical research' (1987) 317 NEJM 141-145.

36 K Liddell and others, 'Medical Research Involving Incapacitated Adults: Implications of the EU Clinical Trials Directive 2001/20/EC' (2006) 14 MLR 367-417.

37 L Kopelman, 'Research methodology. II Clinical trials' in S Post (ed), *Encyclopedia of Bioethics*, vol. 4, (3rd edn Macmillan Reference USA, New York 2004) 2334-2342.

38 Liddell and others (n 36).

"those drafting the Directive were strongly influenced by the pharmaceutical industry which, preferring the ease of placebo-controlled trials, downplayed the importance of clinical equipoise."[39]

f. *Independence of ethics committees*

The credibility of the review of medical research projects largely depends on the independence of the committee responsible for conducting such a review. This means, concretely, that any conflict of interest should be avoided. For instance, the members of the review board must be independent from the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review.[40]

The Additional Protocol on Biomedical Research develops the principle, included in Article 16(iii) of the Biomedicine Convention, according to which each research project should be submitted to a competent body for independent examination of its scientific merit and ethical acceptability. According to Article 10 of the Additional Protocol, "[p]arties to this Protocol shall take measures to assure the independence of the ethics committee. That body shall not be subject to undue external influences" (para. 1). Furthermore, the members of the ethics committee "shall declare all circumstances that might lead to a conflict of interest. Should such conflict arise, those involved shall not participate in that review" (para. 2).

This is another issue in which the diversity of approaches followed by the EU and the CoE becomes visible. The Clinical Trials Directive just mentions in passing, in the definition of terms, that the ethics committee is an "independent body" (Article 2(k)), but avoids explaining or developing this fundamental element. This omission is especially notable given that a large (if not the largest) part of the Directive is precisely devoted to the functioning and tasks of ethics committees. This is not to insinuate that the drafters of the Directive acted consciously against the requirement that review boards must perform their task in complete independence from any external influence. But one may suspect that the Directive is not particularly interested in this essential feature of ethics committees, but rather in the rapidity of the decision making process. According to Article 6.5, ethics committees have a maximum of 60 days to give an opinion and, in the case of multi-centre clinical trials, there must only be one opinion of an ethics committee in each Member State (Article 7). Some have expressed the view that the interests of the pharmaceutical industry are clearly behind these two requirements, and that "the limits are arguably too tight and restrictive to be suitable in all cases if the safety and rights of research subjects are paramount".[41]

39 Ibid
40 CIOMS (n 29) Guideline 2.
41 Beyleveld and Sethe (n 14) 185.

Conclusion

The compar
biomedical r
EU's Clinica
tween them.
focuses on d
them has its
difference in
may lead to
the most vul

This cont
necessarily c
above: the pr
particular, pl
interested in
common goo
should have t

The princ
direct corolla
ple, which su
(Article 2) bu
dealing with
5(h)), aims to
itself but only
ple should no
tainly, the fac
in some way
preferences.
of society or s
boundaries o
people, not pe

Conclusion

The comparative analysis of the two main European regulations relating to biomedical research, the Council of Europe's Biomedicine Convention and the EU's Clinical Trials Directive, puts in evidence significant discrepancies between them. Although it is perfectly understandable that each European body focuses on different regulatory aspects of biomedical research, since each of them has its own objectives and competences, it is a matter of concern that the difference in approach has resulted in serious normative discrepancies, which may lead to watered-down protection for research participants, in particular, the most vulnerable ones.

This contrast shows well that any legal regulation of biomedical research is necessarily confronted with the tension between the two paradigms mentioned above: the protection of participants' rights, and the promotion of medical (in particular, pharmaceutical) research. Nevertheless, although every society is interested in supporting both objectives, both of which aim to contribute to the common good, it is clear that, in case of conflict between them, the first one should have the priority.

The principle of primacy of the human being over science and society is a direct corollary of the requirement of respect for human dignity. This principle, which surprisingly can be found not only in the Biomedicine Convention (Article 2) but also in the Clinical Trials Directive (ironically, in the provisions dealing with research on minors and incapacitated adults: Articles 4(i) and 5(h)), aims to emphasize one fundamental idea: that science is not an end in itself but only a means for improving the well-being of individuals. Thus, people should not be reduced to mere instruments for the benefit of science. Certainly, the fact of living in society renders it indispensable that citizens should in some way contribute to the common good, according to their capacities and preferences. However, in democratic societies, people do not live for the sake of society or science, but have their own purpose, which greatly transcends the boundaries of social or scientific interests. In sum, science is made to serve people, not people to serve science.