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The Importance of National Laws in the Implementation of European Legislation of Biomedical Research*

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Abstract

The industrialization and internationalization of biomedical research is not without consequences on the regulation of research or, at least, on the interpretation of that regulation. As more research is done at the international level, the pharmaceutical industry and the research community are calling for a harmonized regulation to limit the administrative burden of controlling clinical trials and to fasten the R&D process. The purpose of this paper is to analyse briefly the role of the national laws in that process. Part I will outline the structure and the nature of the international regulation of research in a European perspective. Using the examples of research ethics committees (RECs), informed consent and the question of liability and liability insurance, Part II will analyze the importance of the national laws in the implementation of this international regulation.

Introduction

During the last decade, there has been a trend towards industrialization and internationalisation of biomedical research. In the 90s, the share of research financed by the pharmaceutical industry increased from 40 to 80 %.[1] Of course, this is not without raising serious concerns about the independence and integrity of science. There are growing concerns about the conflicts of interest that may occur, for instance, when research is conducted with private funding in universities. The industrialization of research is also linked to an increase of its international dimension. The costs of drug development are such that products need to be marketed worldwide to meet profitability. According to the Tufts Centre for the Study of Drug Development, average drug R&D costs have reached $ 802 million

in 2001. In order to speed up the development process and increase the chances of obtaining the necessary authorization for marketing, the research industry has become increasingly internationalized. For instance, in July/August 2003, the Impact Report of the Tufts Centre acknowledged the fact that "During 2000-02, one third of all U.S.-based contract research organizations (CROs) opened a foreign office and increased their global recruitment of clinical trial subjects and that eastern Europe is the most attractive arena for recruiting clinical trial participants outside of the United States, western Europe, and Japan."[2] It is interesting to note the attractiveness of Eastern Europe. The dramatic increase of the research activities in this region may in part be explained by the interest of the pharmaceutical industry to have access to this new and promising market. Its interest may have more to do also with the availability of facilities to conduct research in those countries.

The industrialization and internationalization of biomedical research is not without consequences on the regulation of research or, at least, on the interpretation of that regulation. As more research is done at the international level, the pharmaceutical industry and the research community are calling for a harmonized regulation to limit the administrative burden of controlling clinical trials and to fasten the R&D process. The purpose of this paper is to analyse briefly the role of the national laws in that process. In part I, we will outline the structure and the nature of the international regulation of research in a European perspective. In part II, using the examples of research ethics committees (RECs), informed consent and the question of liability and liability insurance, we will analyze the importance of the national laws in the implementation of this international regulation.

I. The international regulation of biomedical research

1.1 In general

At first sight, the international regulation of biomedical research is characterized by a large number of rules, whether deontological, ethical or legal.[3] The Code of Nuremberg (1947) enunciated for the first time some fundamental principles aimed at the protection of the human subjects, in particular the rule of informed consent. No research can be carried out if the human research subjects have not given their free and informed consent prior to their participation. In principle, the rule of free and informed consent as stated in the Nuremberg Code prohibits research with children or incapacitated adults. Indeed, the Code of Nuremberg has been praised as well as criticized for the very fact that it seems to authorize solely research with persons capable of giving their consent.[4] We should keep in mind that it was adopted in reaction against the crime against humanity com-

mitted in the name of the Nazi science. The understanding of biomedical research has dramatically improved during the last few decades. The public interest to pursue research with children or incapacitated adults is now widely recognized.[5] Those researches are not by themselves immoral contrary to the famous quote of Jean Bernard: "Research is necessary immoral but morally necessary".

Nevertheless, two major international law conventions confirmed that prohibition, namely the UN Covenant on civil and political rights (1966) insisting on the fact that "no one shall be subjected without his free consent to medical or scientific experimentation", assimilating research "to torture or to cruel, inhuman or degrading treatment or punishment", as well as the Geneva Conventions (1949) prohibiting any type of human experimentation in time of war.[6] To the best of our knowledge, there has been so far no case in front of the International Court of Justice or report to the Human Rights Committee of the United Nation addressing the prohibition of biomedical research with children and incapacitated adults. Anyhow the main rules of international law applying in the field of biomedical research remain rather conservative.[7]

In the early 90s, with a strong support of the pharmaceutical industry, the first ICH meeting took place in Brussels.[8] ICH stands for The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The objective of ICH was the development of harmonized guidance on technical issues concerning the marketing of drugs. The idea was to eliminate the unnecessary duplication of tests and procedures in the authorization for marketing process, thus, creating a minimum of delay in making new treatments available to the patients. Among other more technical matters, the ICH also developed guidelines on clinical trials. Those are the Good Clinical Practice: Consolidated Guideline (hereafter: ICH-GCP) adopted in 1996 and later introduced in the regulation of the European Medicine Evaluation Agency (EMEA), the US Food and Drug Administration (FDA) and the Ministry of Health, Labour and Welfare in Japan.

The ICH-GCP cannot be considered as a treaty in public international law. The participating authorities are not involved as representatives of their government. Theses guidelines are not submitted to the usual process of signature and ratification of international treaties. They are adopted by each regulatory authority as one of their own guidelines. Their legal force is therefore limited.[9] As mentioned in its introduction:

> "Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible."

As we can see, the ICH GCP refers to another essential international code of conduct for researchers: the World Medical Association Declaration of Helsinki on the Ethical Principles for Medical Research Involving Human Subjects, first adopted in 1964 and since revised five times in 1975, 1983, 1989, 1996 and 2000 (seven times if we include the notes of clarification added in 2002 and 2004).[10] As indicated in the Declaration of Helsinki:

> "The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects."

The Declaration of Helsinki is mainly targeted at the medical profession. As such, the Declaration of Helsinki is not a binding document but is intended to guide the researchers in their practice. It remains an ethical code. In fact, the Declaration stresses that "research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements." The Declaration is subsidiary to existing regulatory framework. It has yet acquired a new legal status with the entry into force of the new Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.[11] According to article 3 of this new directive:

> "Clinical trials shall be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996)."

It is interesting to notice that the directive refers to the 1996 version of the Declaration, which corresponds to the version annexed to the ICH-GCP. This provision in the European legislation gives a new dimension to the Declaration of Helsinki that certainly deserves more attention for the future.

In the early 80s, another international set of rules was developed by the Council of International Organization of Medical Sciences (CIOMS). The CIOMS was created under the auspices of WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO) in 1949 with among its mandates that of maintaining collaborative relations with the United Nations and its specialized agencies, particularly with UNESCO and WHO. In 1982, the CIOMS adopted the first version of its International Ethical Guidelines for Biomedical Research Involving Human Subjects, later revised in 1993 and 2002. As mentioned in their background, those guidelines are:

> "Designed to be of use, particularly to low-resource countries, in defining national policies on the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving human subjects."

The CIOMS guidelines are responding to the specific needs of least developed countries, offering guidance in the conduct of North-South research projects. As the ICH-GCP and the Declaration of Helsinki, the CIOMS guidelines are a non binding document.

This brief overview of the regulation of biomedical research at the international level shows a tension between rather conservative (even prohibitive) rules and those more favourable to research. The present trend seems to go toward a regulation more responding to the needs of the researchers and the sponsors, even if the protection of the human subjects remains a crucial objective. Recent controversies, especially concerning the latest revision of the placebo rule of the CIOMS guidelines,[12] showed the difficulties to reach an agreement on those conflicting interests.

1.2. In Europe

Biomedical research at the European level is regulated by both the European Union and the Council of Europe.[13] In the field of drug trials, there is the Directive 2001/20/EC of the European Parliament and of the Council 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[14] (hereafter the Directive on Clinical Trials). The scope of this directive covers all clinical trials with medicinal products for human use carried out in one or several Member States of the European Union. It is meant to harmonize the implementation of the Good Clinical Practices in the conduct of drug trial within the European Union. The Directive 2001/20/EC has recently been completed by the new Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.[15]

According to the annex 1 of the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use,[16] "All clinical trials, conducted within the European Community, must comply with the requirements of Directive 2001/20/EC". Even more "to be taken into account during the assessment of an application,

clinical trials, conducted outside the European Community, which relate to medicinal products intended to be used in the European Community, shall be designed, implemented and reported on what good clinical practice and ethical principles are concerned, on the basis of principles, which are equivalent to the provisions of Directive 2001/20/EC. They shall be carried out in accordance with the ethical principles that are reflected, for example, in the Declaration of Helsinki." Thus, if the Directive on Clinical Trial is aimed at protecting human subjects, it has also for an objective to facilitate the recognition of clinical data on the efficacy and safety of drugs during and after the procedure of authorization for marketing. It could be said that this regulation is "market oriented" as it is primarily linked to the control of the medicinal products' market in Europe. This creates some problems of implementation. For instance, the drug agencies – as the competent authorities in assuring the safety of the medical products market – may not always have the necessary resources to control clinical trials, such control having more often to do with medical practice than with medical products.

Another important regulatory instrument of biomedical research in Europe is the Convention for the protection of Human Rights and dignity of the human beings with regards to the application of biology and medicine: Convention on Human Rights and Biomedicine, Oviedo, April 4, 1997[17] (hereafter: the Convention on Biomedicine). According to article 1, the purpose of the Convention is 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." Specific provisions regulate biomedical research, namely article 15 to 18. In contrast with the Directive on Clinical Trials, the Convention on Biomedicine is mainly oriented toward the protection of human rights in the field of biomedicine. On June 30, 2004, the Committee of Ministers of the Council of Europe completed the Convention by adopting the Additional Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research (hereafter: the additional protocol).[18] The scope of the additional protocol is all research on a person, except epidemiological studies and research with biological material.

With the Directive on Clinical Trials, and the Convention on Biomedicine and its additional protocol, it seems that the harmonization process of the legal framework of biomedical research in Europe is at an advance stage. Those sets of rules demonstrate a strong political will to guarantee for all patients in Europe a high standard of protection in the field of clinical trial. One would expect that the same conditions apply now from the south of Italy to the North Pole and that every human subject in Europe is entitled to the same level of protection. Yet, there are still many steps before speaking about uniformly harmonized regulation. In fact, the very nature of the European legislation illustrates the difficulties to achieve some degree of harmonization.

The doctrine of direct effect is a legal principle that underpins EU law. Such supremacy of EU law created a means for individuals to pull the EU law into national policy debates and an obligation for national courts to set aside laws and policies that violate European law.[19] One of such obligatory documents are the directives as stated for the first time in 1963 Van Gend en Loos case.[20] However, a directive in the EU legislation is only meant to impose an obligation to the Member States to take the necessary measures for its implementation. "A directive is binding with regard to the result to be achieved but allows Member States to choose the means to achieve that result".[21] Obligatory directives will remain declarative provisions at the national level if a Member State does not undertake necessary actions to implement it. However, in such case the Commission, as the "treaty guardian", or other Member States can invite the non complying State to provide explanation or put it on trial for non compliance to the given directive.

On the other hand, though means and remedies for a directive implementation are prerogatives of choice of the Member States, a State is not absolutely free in this process. The national remedies have to properly reflect the content of the directive and a EU Member State must chose the most proper forms and methods for incorporating the provisions of a directive.[22] Thus, a directive is not in principle directly applicable in the Member States, but it obliges the national subjects – legislators, government and all those who are directly or indirectly responsible for implementation of the provisions of a directive – to act purposefully and competently.[23]

According to its articles 23ff, it is the duty of the parties to the Convention on Biomedicine to provide appropriate judicial protection, compensation and sanction in case of unlawful infringement of the rights and principles set forth in the Convention. There is no provision granting an appeal to the European Court of Human Rights if a State fails to fulfil its responsibilities in this matter. At best, a plaintiff may invoke the Convention on Biomedicine in the interpretation of the European Convention on Human Rights in a case in front of the European Court of Human Rights. This is also true for the additional protocols to the Convention.[24]

In both cases, the Directive and the Convention, the EU Member States and the parties to the Convention bare important responsibilities in their implementation. This is confirmed in the wording of those laws. For instance, article 22 of the Directive states that:

> "1. Member States shall adopt and publish before 1 May 2003 the laws, regulations and administrative provisions necessary to comply with this Directive. They shall forthwith inform the Commission thereof.
> 2. Member States shall communicate to the Commission the text of the provisions of national law which they adopt in the field governed by this Directive."

End of 2004, six Member States had not yet made the necessary changes in their legislation or, at least, had not yet informed the Commission to what extent their legislation already met the requirements of the Directive.[25] As we will see in part II of this paper, this may not mean that those States are reluctant to implement the Directive, but more simply that they are satisfied with their present system of protection of the human subjects in clinical trials. According to article 30 of the Convention on Biomedicine:

> "On receipt of a request from the Secretary General of the Council of Europe any Party shall furnish an explanation of the manner in which its internal law ensures the effective implementation of any of the provisions of the Convention."

Yet, as mentioned above, there is no direct sanction against a State which has ratified the Convention if it does not meet its obligation to implement it.

II. National laws in the implementation of the international regulation

To assess the degree of protection granted by the Directive on Clinical Trial and the Convention on Biomedicine, it is necessary in any case to refer to the national legislation. We should now analyse more in detail in a comparative law perspective, the rules on research ethics committees (REC), on research with minors and incapacitated adults (especially in relation with their informed consent and their legal representative), and on liability and liability insurance in clinical trials. In this process, we will refer in particular to the legislation in the Baltic countries, namely Estonia, Lithuania and Latvia.[26]

2.1. Research Ethics Committees (RECs)

In the 1975 Tokyo revision of the Declaration of Helsinki was introduced the obligation to submit the protocol of all clinical trials for review by an "independent committee" prior to their initiation. It is now a common rule in all regulation of biomedical research, whether ethical or legal, that such review takes place to assess the scientific merits of the research project, its ethical acceptability and the adequate level of protection of the human subjects. Such bodies can be designated as "research ethics committee" (REC), "ethical review committee",[27] "independent ethics committee"(IEC),[28] or "institutional review board" (IRB) in the US regulation.

According to paragraph 1.27 of the ICH-GCP:

> "The legal status, composition, function, operations and regulatory requirements pertaining Independent Ethics Committees *may differ among countries,* but should allow the IEC to act in agreement with GCP as described in this guideline."

Neither the Directive on Clinical Trials, nor the Convention on Biomedicine is more explicit concerning the research ethics committees. Article 6 paragraph 1 of the Directive only prescribes that "for the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment and operation of Ethics Committees." In fact, the status and organization of the REC are different in each country due to various factors, such as the organization of the healthcare system and the universities, or the existence of a centralized or decentralized administration. Some legislations are rather detailed, while others leave the competence to local or regional authorities to define the operating procedures of the REC. Several models of legislation can be identified.[29]

For instance, in France or in Denmark, the laws on biomedical research define precisely the composition of the RECs, their jurisdiction, under which authority they accomplish their task, their funding, etc. There are even provisions on the appeal procedure in case of a REC's negative opinion. It may be interesting to point out that in France, RECs are called "Commission for the protection of persons participating in biomedical research" or "Commission for the protection of persons". This stresses their primary duty which is indeed the protection of the human subjects, and not to provide a service to the investigators or the sponsors. Other countries, such as Germany, have opted for a more flexible regulation. The law imposes some minimal standards but it is up to the local authorities to implement them. According to the Drug Act of Germany, it is the competence of the Länder to regulate the REC, which can be done either in their health legislation or through the legislation of the universities. In many countries, the trend is to define the jurisdiction of the REC on a geographical basis, meaning that they are competent to review clinical trials in a given region or local area. Sometimes, there can be several competent RECs in the same region (e.g. in France), but in general only one REC is recognized in a given territory, thus avoiding the risk of forum shopping, and of possible conflicts between the RECs. In some countries, RECs are linked to an institution (hospital, university, research centre), as in the US model of the IRB. This may prove problematic for the review of clinical trials performed outside those institutions. The review system may be lacking in such case. Some countries, such as the United Kingdom, have also a different network of REC for multi-centre clinical trials. It should be underlined that for such multi-centre research, the Directive on Clinical Trial imposes a single

opinion in each country.[30] This may create some difficulties in countries where local RECs have a veto right on research carried out in their jurisdiction.

In Estonia, article 13 paragraph 4 of the Medical Products Act of 1996 prescribes that "A clinical trial of a medicinal product shall not commence without the approval of the medical ethics committee for clinical trials." This Act is completed by more detailed regulation from the Minister of Social Affairs, mainly:

- Procedure for Conduct of Clinical Trials of Medicinal Products, Regulation No. 79 of the Minister of Social Affairs of 9 July 2001;
- Requirements for Membership of Medical Ethics Committee for Clinical Trials, Rules of Procedure of Committee, Rate of Fee for Evaluation of Clinical Trials and List of Information to Be Submitted in Order to Obtain Approval, Regulation No. 77 of the Minister of Social Affairs of 9 July 2001.

There are presently two RECs in Estonia, one in Tallinn, linked to the National Institute for Health Development and the other in Tartu, linked to the University. The jurisdiction of the REC is not specified in the legislation, but article 9 paragraph 1 of the Requirements for Membership of Medical Ethics Committee for Clinical Trials, Rules of Procedure of Committee, Rate of Fee for Evaluation of Clinical Trials and List of Information to Be Submitted in Order to Obtain Approval states that "the applicant for approval is not permitted to address another ethics committee". Forum shopping for a more lenient Ethics committee seems therefore prohibited in Estonia.

In Latvia, biomedical researches are regulated first by the Pharmacy Law of 1998. There is one Central Medical Ethics Committee and three regional RECs designated by the Minister of Health. Section 5 paragraph 6 of the Pharmacy Act gives the Cabinet of Ministers the authority "to determine the procedures for conducting clinical trials". According to the section 6 paragraph 7, it is the responsibility of the Minister of Health to "approve the model by-law for the medicinal products clinical trials ethics committees and the membership of such committees". It is also in his or her jurisdiction to determine the requirements for Good Clinical Practice based on paragraph 8 of the same provision.

The Pharmacy Law was completed in 2000 with the Procedure for clinical trials on medicines and pharmaceutical products and for observational studies (Cabinet regulation No. 312). Paragraph 31 of this procedure specifies the requirement for submitting a protocol to an Ethics Committee. The procedure for assessing the compliance with the standard of Good Clinical Practice (Cabinet Regulation no. 374) defines the authority of the State Agency of Medicines in controlling clinical trials. Interestingly, article 11 specifies that the Agency is entitled to involve the Ethics committee that has given its favourable opinion about a specific protocol in the evaluation of that protocol. It seems that the regional RECs are

linked to given research institution, but it is unclear whether their jurisdiction is limited by those institutions.

In Lithuania, requirements and principles applying to biomedical research, the procedure for giving approval to conduct biomedical research, the procedure for controlling biomedical research and the liability for infringement of these requirements are set forth by 2000 May 11 Law on Ethics of Biomedical Research No. VIII-1679 (2004-07-04 edit[31]) and its regulations of implementation.

The scope of this law is not limited to clinical trials with medical products, but includes all research, the subjects of which being individuals or groups, foetuses, tissues, organs, cells and genetic material, cadavers and medical documents. Such researches can be carried out only if previously approved by the Lithuanian Bioethics Committee or the Regional Biomedical Research Ethics Committee. Permission for clinical trials of medicinal products shall be issued by the State Medicines Control Agency with the approval of Lithuanian Bioethics Committee or the Regional Biomedical Research Ethics Committee. Conduct of biomedical research without prior approval is unlawful (Article 12).

The basic rules of the Lithuanian Bioethics Committee are defined by law. According to article 13, the Lithuanian Bioethics Committee shall be established and its composition and regulations shall be approved by the Ministry of Health. It is granted an important role in the field of biomedical researches according to article 14 of the law. The Lithuanian Bioethics Committee is responsible for defining the quotas of representation in the Regional Biomedical Research Ethics Committees, the number of members and composition of those committees, as well as the territory of their jurisdiction. The same article sets forth that Regional Biomedical Research Ethics Committees shall be created in the counties having universities (4 out of the 10 existing counties in Lithuania). So far only one was established on December 12th, 2001 in the Kaunas county by command No. 09-44 of the Lithuanian Bioethics Committee's chairperson. The scope of activities of those Regional Biomedical Research Committees is defined by the Lithuanian Bioethics Committee which can give them some specific functions and which is also in charge of their control.

As we can see, there is a mix between centralized and regional jurisdiction of the REC in the Baltic countries.

2.2. Research with children and incapacitated adults

According of article 3 paragraph 1 of the Directive on Clinical Trial, "Member States shall, insofar as they have not already done so, adopt detailed rules to protect from abuse individuals who are incapable of giving their informed consent". Article 4 of the Directive defines the requirements for doing research with children,

while article 5 concerns research with incompetent adults. In both cases, the rule of informed consent as stated in article 3 paragraph 2 littera d applies. It reads as follows: "A clinical trial may be undertaken only if, in particular: […] the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial."

Concerning research with children and incapacitated adults, the Convention on Biomedicine also imposes a higher degree of protection to human research subjects. Article 6 paragraph 2 states that "Where, according to law, a minor does not have the capacity to consent to an intervention, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law." The same rule exists for incompetent adults (article 6 paragraph 3). Beside the rule of informed consent by the legal representative, article 17 specifies then under which conditions research can be carried out with persons not able to consent.

In both the Directive and the Convention, the definitions of a minor, in other words the legal age limit between childhood and adulthood, of the capacity to consent and of the legal representatives are not found.[32] The answer to these questions lays in the national legislation. Thus it is necessary to refer to these national laws to implement the Directive and the Convention and assess whether they are respected. One key problem is that none of these issues are regulated within the legislation of biomedical research. Those questions are dealt primarily in the Civil Code or in private law. It is therefore necessary to examine the civil law concerning the rights of personality to analyse more precisely the actual level of protection granted to minors and incapacitated adults in the field of biomedical research. This alone demonstrates the difficulty to harmonize the regulation of biomedical research when such sensitive concepts are outside the scope of that regulation.

In the three Baltic countries, a minor is defined as a person under the age of 18 years old. Such age limit tends to become the rule in most European countries, but this has not always been the case. The three legislations also authorize a minor's emancipation:

For example, in Lithuania, a minor can be declared legally competent by the age of 16 (Civil Code, article 2.9). This is also true in Latvia, but excluded in Estonia. In case of marriage, the minor is also emancipated from that day (Lithuanian Civil Code, article 2.5). The permitted age to contract a marriage is set forth in the Civil Code, article 3.14. The person intending to marry before the age of 18 should request permission from a court which may, in a summary procedure, reduce for him or her the legal age for consenting to be married, but by no more than three years. In case of a pregnancy, the court may give its authorization even for a minor under 15 years old.[33] As such, the Civil Code of the Republic of

Lithuania does not prescribe a minimal age, contrary to the law in Latvia and Estonia which set the limit at 16. Anyway, in case of divorce or vitiation of the marriage, the minor does not lose his or her declared legal competence. In this situation, it is unclear whether he or she should be granted the same level of protection as a minor in a clinical trial.

This brief review of the legal age to become an adult shows some difference in the Baltic region. An important element is also the fact that there are instances when persons under 18 are entitled to the same rights as adults, thus raising the question whether the stricter rules of protection apply to them or not. Even if such cases are rare, they should be taken into consideration as they raise difficult legal problems that can not be solved with certainty by applying the regulation of biomedical research alone.

Comparing the regulation of biomedical research in each country shows even more differences and possible problems of interpretation. In Estonia and in Latvia, the child's own desire shall always be taken into consideration when he or she is above seven years old.[34] Such requirement is conformed to the rule of informed consent in the Directive and in the Convention. For instance, according to article 6 paragraph 3 of the Convention, "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." The fact that the Estonian and Latvian regulations make it an obligation since the age of seven is reinforcing the effectiveness of that rule. Surprisingly, the Lithuanian Law on Ethics of Biomedical Research does not mention such an age from which it is necessary to obtain the minor's consent.[35] Could this be interpreted as a denial of the children right to consent? Fortunately, a closer look at article 3.164 of the Lithuanian Civil Code and article 12 of the Convention on the Rights of the Child shows that this right also exists according to the Lithuanian legal order. In fact, the Lithuanian law proves to be even more protective as it also requires a specific approval of the Children's rights protection agency of the city or the district before conducting a research involving minors.

Concerning research with incapacitated adults, it is authorized in Estonia and Latvia under similar conditions than the ones set forth in the Directive and the Convention. In particular, the subject's legal representative must have given his or her approval and the subject's own consent must be taken into consideration, subject to the extent of his or her capacity. The situation is different in Lithuania where, in principle, research with incapacitated adults is prohibited. Such limitation is based on article 21, part 4, of the Constitution of the Republic of Lithuania,[36] which reads as follows "No person may be subject to scientific research or medical tests without his free and informed consent".

Article 5 of the Law on Ethics of Biomedical Research identifies competent adults suffering from mental disorders as a vulnerable group. Article 7 states that biomedical research with such persons is lawful only if their consent is attested

by two witnesses and by the head of the health care establishment where the research is conducted. Both the approval of the Medical Ethics Commission and the competent Research Ethics Committee must also be obtained. The same requirements can be found at article 18, part 3, of the Lithuanian Law on Mental Health Care (1995-06-06 No.I-924).

Any scientific or medical trial without the human subject's free and informed consent seems thus prohibited in Lithuania. This prohibition prevents the development of adequate treatment for all patients who lack legal competency. This is important because with the aging of the population, the number of legally incompetent persons, who need such trials, is growing. The present ban in the Lithuanian law is limiting their right of obtaining the care corresponding to their health status. Of course, there are new drugs available today which respond to their needs, drugs that have been tested with the participation of incapacitated patients in other countries. If Lithuania prohibits doing research with such patients, it would then be coherent that the use of those new drugs would also be prohibited as they were tested under unacceptable conditions according to Lithuanian laws. The situation is not new. For instance, it was the one existing in France before the adoption of the new law on biomedical research in 1988. It should also be remembered that the Lithuanian law is congruent on that issue with the international law instruments that we discussed above, namely the Nuremberg Code and the UN Covenant on Civil and Political Rights, even if circumstances of their enactment, as we have already analysed, were different. This is a challenge to the Lithuanian legislature to face that problem, and solve the incoherence of the present law. This is certainly a complex problem that requires further analysis and discussion to identify the fundamental principles at stake and find the appropriate solution according to the needs of one of the most vulnerable group of the population.

So far, the Constitutional Court of the Republic of Lithuania has not provided an interpretation of the above mentioned provisions of the Constitution and the specific laws on biomedical research and mental health care. If some defend that the prohibition is absolute and unconditional, it should be underlined that the Court would still need to balance all the rights and interest at stake before reaching its conclusion. In this process, it would have first to take into consideration the fact that the legislature has already introduced an exception to that rule by allowing research with minors, even when they do not have the capacity to consent. Second, if the risks for the subjects remain minimal, and the tested medical intervention is potentially beneficial for the subjects and it concerns a severe condition, the prohibition to conduct the study may prove to be more prejudicial for the subjects than the research itself. At last, as we have already mentioned, a too strict interpretation of this rule would lead to an overall prohibition of all treatments which were not developped in accordance with that requirement. This would mean a severe limitation of the patient's right to health care.

2.3. Biomedical research liability and liability insurance

Concerning the coverage of research induced damages, article 3 paragraph 2 of the Directive requires that: "A clinical trial may be undertaken only if, in particular: […] (f) provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor". Article 31 of the additional protocol on biomedical research of the Convention on Biomedicine also prescribes that: "The person who has suffered damage as a result of participation in research shall be entitled to fair compensation according to the conditions and procedures prescribed by law".

Research is by definition a risky business and the human subjects ought to be informed about the associated risks. Yet, the mere fact they have agreed to participate does not imply that the human subjects should bare all those risks in case of damages. On the contrary, it is a moral and a legal obligation to take all the necessary measures to prevent the occurrence of those risks, to provide the human subjects with a medical follow-up, and, when needed, an adequate treatment and a fair compensation. The latest note of clarification of the Declaration of Helsinki insists on the need that "every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study" (paragraph 30). This obligation is even stricter when a human subject suffered from his or her participation in a protocol. Thus, in principle, the need to protect the human subject for trial-related injuries is widely admitted. But again, this principle remains undetermined in the international rules and its implementation may vary from one country to another. In a recent study mandated by the Dutch Ministry of Health on liability for and insurability of biomedical research with human subjects in several European States, the authors reached the conclusion that "it might be clear that in the field of biomedical research involving human subjects, national regulations concerning insurance and liability remain of great importance for the protection of test subjects in case of trial-related injuries".[37]

The Lithuanian law provides detailed rules on this issue. Articles 6 and 11 of the Law on Ethics of Biomedical Research set forth that biomedical researches can only be carried out when the principal investigator and the sponsor are covered for civil liability by an authorized insurance company. On December 20th, 2000, the Minister of health confirmed by prescription No. 745 the rules of compulsory civil liability insurance for the principal investigator and the sponsor (hereafter: the Insurance Rules), and set forth that these provisions must be incorporated into each insurance contract. Item 20 of the Insurance Rules prescribed that the insured sum is established by agreement of the insurer and the policyholder, but can be no less than 100.000 Lt (29000 €) for damages which were inflicted during or occurred because of the subject's participation in the research.[38] Such provision raises a problem when the foreseeable risks are above the minimal sum as the

competent Research Ethics Committee is not formally granted the authority to require that the insured sum be adapted in accordance. Based on the fundamental responsibility of the Research Ethics Committee to protect the dignity, rights and welfare of the human subjects, the Committee should have in any case the competency to refuse approval if the insured sum appears insufficient to cover the expected risks. Furthermore, article 6.251 and 6.254 part 2 of the Civil Code require that the person responsible for causing damages is due to compensate completely his or her victim, even above the maximal amount covered by insurance. Of course, the effectiveness of this rule depends on the financial capacity of the liable person. Another limitation in the protection of the human subjects in case of damages is given by item 19 of the Insurance Rules. According to that provision the insurance is not obliged to compensate damages when, for instance:

- the research has been conducted outside the Republic of Lithuania;
- if during the biomedical research, the research subject was infected by one or several of the following viruses: human T lymphotrophic virus I, human T lymphotrophic virus II, human immunodefficiency virus, hepatitis virus;
- if the research was unlawful (for instance, the study was not conducted in accordance with the Law on Ethics of Biomedical Research or when the insured or the researchers deliberately infringed the rules of Good Clinical Practice).

In this case, the sponsor and the researchers will be directly liable for covering the damages at their own expenses. For the subjects, this means that they are less likely to be compensated and only after a long procedure. Such provision is favourable to insurance companies, but for the research subjects, regardless of their own responsibilities, it means that they could suffer twice – not only the damage is inflicted upon them, but they may never be compensated. In this case, one should question the liability of the Research Ethics Committee and the competent authorities for having authorized the research to be carried out in such conditions if there were evidence from the beginning that the investigator could not face his or her liability.

In Latvia, the paragraph 20 of the Procedure for clinical trials on medicines and pharmaceutical products and for observational studies also imposes an obligation for the sponsor to have an insurance covering possible injury and damages during the trial. Yet, surprisingly, paragraph 21 excludes the liability of the sponsor for "the injury caused to the trial subject by the investigator or other persons, involved in the clinical investigation, intentionally or due to negligence." Apparently, in such case, the damage should be covered directly by investigator or his or her aides. Thus, the liability of the sponsor is limited to case where the investigator acted with due care and in accordance with the protocol. This creates a potential for abuses as the human subjects who should deserve the greatest protection are

in fact less protected than those being followed by the best trained and experienced investigators. The law does not mention what type of liability should apply in such case. Most likely, the applicable rules would be those of medical liability, which can be expected to be less favourable to the subjects.

In Estonia, according to § 13 paragraph 9 of the Medicinal Products Act: "(1) A doctor, dentist or veterinarian conducting a clinical trial of a medicinal product shall be liable for a violation of his or her obligations only if circumstances depending on the doctor, dentist or veterinarian occur. (2) If a doctor, dentist or veterinarian who conducts a clinical trial of a medicinal product is acting upon conducting the clinical trial of the medicinal product on the basis of an employment contract or another contract entered into with a third person, the third person shall be liable together with the doctor, dentist or veterinarian." According to § 13 paragraph 5, the investigator should submit – among other things– to the Ethics committee a copy of the insurance certificate. Yet, there is no specific provision on the minimal requirements concerning the insurance coverage. More detailed insurance rules are certainly needed to guarantee a better protection to the research subjects.

Table 1[39]

	Germany	France	Austria
Compulsory insurance	Yes, but only for drugs and medical devices	Yes, for all biomedical research	Yes, but only for drugs and medical devices
Per Subject Per Study	Euro 500'000 < 1000 subjects Euro 10 mio. < 3000 subjects Euro 20 mio. 3000 subjects < Euro 30 mio.	Euro 760'000 Euro 4'570'000	Euro 370'000 Euro 2'500'000
Duration	2 years after the year the study ended	10 years after the end of the study	3 years after the end of the study

As we have seen, the issue of liability and insurability of biomedical research is dealt with differently in each Baltic country. Even if those rules conformed to the EU Directive and the Convention which only require that those questions need to be addressed in law, the overall protection of the human subjects is not completely satisfactory. This is a concern, especially in case of multi centre clinical trials. The covered sums in the Baltic countries are much lower than those, for instance, in France, Germany or Austria (see Table 1). As the cost of the premiums are rising in Western Europe, there is a potential risks that research could be carried

out in the Baltic countries by sponsors trying to escape their responsibilities and benefit from the weakest protection granted to human subjects in those countries.

Conclusion

The regulation of biomedical research in the European Union and the Council of Europe is in a harmonization process. As we have seen this is only a beginning. Each Member State and the international community have to put more efforts so that the process of harmonization would not seem only a utopian idea. So far, the international regulation is mainly based on general principles that remain too broad and vague to provide a sufficient protection of the rights and well-being of the research subjects. This should encourage the States to set forth the necessary more detailed national rules instead of solely referring to international principles which themselves are not satisfactorily defining the rights and duties of investigators, sponsors and ethics committees members. However, this could end in a regulatory competition by which a State could try attracting research by imposing more flexible standards for the protection of human subjects. Depending on their direct interests, the pharmaceutical and research industries would favour those less protective States to conduct their studies, regardless the risks for the human subjects.

This issue of international regulatory competition is better recognized in trade law. It concerns the tension between harmonization and competition among national rules in an international market. The industry reacts to variations in the regulation, seeking the most favourable conditions to suit its interests. It may not necessarily lead to a "race to the bottom" as the market players main interest remains security for their investment.[40] For instance, the bad reputation induced for doing business in States with the most lenient regulation is limiting the industry's interests to do so. Even more, there is a potential liability risk that has to be taken into account when products or services are exported to countries with more restrictive rules. Thus, the most permissible regulation is not necessarily the most appealing to investors. In any case, the legislation has become a key factor in the orientation of the players on the market.

When the duplication of procedures at the national level without mutual recognition becomes too high of a burden to compensate the benefits of competition, there is a trend toward harmonization. There is a similar trend when the substantial requirements differ too radically from one country to another, thus creating discrepancies in the protection of the public interests at stake. Such situations are identified as market failure. The pharmaceutical sector in the European Union is a good example. In a slow, but constant process, the European Commission moved toward a two level approach of drug registration: one central-

ized through the European Medicines Agency (EMEA), the other de-centralized through mutual recognition of registration done by the national drug agencies. A key element in this process is the build-up of mutual trust.[41] The ICH process is another illustration of such trend toward harmonization. Yet, depending on the level of trust and the direct interests of the players involved, some level of competition remains. The key question here is whether such competition can apply in the field of human rights' protection. We defend that this is not the case. The natural consequence is the adoption of more stringent regulation at the international level.

What does it mean? The fundamental rules aimed at protecting the dignity, rights and well-being of the research subjects should be embedded in binding provisions of international law. For instance, liability and insurance liability rules should be defined internationally, at least at the European level. The rule of informed consent should also be applied under the same conditions, especially regarding vulnerable population, minor, person lacking legal competency or research in emergency setting. Last, but not least, the Research Ethics Committees should be provided with a clear authority and jurisdiction – as this is the case, for instance, in the Baltic countries -, but also with the proper resources to fulfil their responsibilities. It would be useful to apply the same standards everywhere in Europe. As we have highlighted, this is not an easy task as it interferes with important parts of the national legislation such as civil law, tort law and administrative law, without mentioning the issue of constitutional law.

Another important measure to promote a better protection of the human subjects and, yet improve the attractiveness of the European research activities, is certainly a better training programme of the investigators and of the ethics committees' members. Training implies the definition of a minimal programme that could become the basis for new standard operating procedures (SOPs) for the ethics committees. It would certainly be a useful way to improve the awareness of the investigators and the ethics committees' members and of the general public on the conflicting interests at stake in biomedical research. It would mean in particular the need to develop all the necessary material to provide the courses. This would help improving the quality of research in general and reinforce the protection of human subjects. One element of great interest is the fact that all legislations of the Baltic countries include specific forms to submit an application to the REC and the Drug agency. Those documents present some similarities, and it may prove an interesting move to harmonize those forms in a near future. The forms being harmonised it would make it easier to exchange experience and work together with the same procedures. This is a relatively easy task that could facilitate not only the conduct of multi-centre trials in the Baltic region, but also the set up of common training programme. If the rules vary from one country to another, it would be a constructive step to develop some common agreements on the inter-

pretation and implementation of those norms. This could be organized by the RECs themselves or by the controlling authorities. Such meeting as the one that took place in Vilnius in 2004 under the auspice of the Council of Europe is certainly a first step in that direction. It should be mentioned that the European Commission is also making serious effort in this field as it organized the first European Conference of the REC in Brussels in January 2005.[42] Such initiatives are certainly welcome.

Notes:

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1. See Rettig R.A., The industrialization of clinical research, in Health Affairs 19 (2000), pp. 129-146.
2. http://csdd.tufts.edu/InfoServices/ImpactReportPDFs/ImpactReportSummaryJulAug2003.pdf (last consulted December 27th, 2004).
3. See Lucas Berkamp, Medical Research Involving Human Beings: Some Reflections on the Main Principles of the International Regulatory Instruments, in European Journal of Health Law 11 (2004), pp. 61-69. Bartha Knoppers and Dominique Sprumont, Human Subjects Research, Ethics, and International Codes on Genetic Research, in Encyclopedia of Ethical, Legal and Policy Issues in biotechnology, John Wiley & Sons, 2000, pp. 566-576.
4. See Dominique Sprumont and Pascal Arnold, The 'Nuremberg Code': Rules of Public International Law, in Ulrich Tröhler and Stella Reiter-Theil (eds.), Ethics Codes in Medicine: Foundations and Achievements of Codification since 1947, Ashgate, Aldershot 1998, pp. 84-96.
5. See for instance in the European Union, the Council Resolution of 14 December 2000 on paediatric medicinal products, O. J. C 017, 19/01/2001 P. 0001-0001. See also in the USA, the Pediatric Research Equity Act of 2003 (Public Law No: 108-155) and the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule (21 CFR Parts 201, 312, 314 and 601).
6. See for instance article 13 of the Geneva Convention relative to the Treatment of Prisoners of War, article 12 of the Geneva Convention for the Amelioration of the Condition of the Wounded and Sick in Armed Forces in the Field or article 32 of the Geneva Convention relative to the Protection of Civilian Persons in Time of War.
7. This being said, it is surprising that none of those international law instruments were raised in two cases before the European Court of Human Rights having to do with nuclear tests conducted by the UK in the Pacific Ocean in 1957-1958 (McGinley and Egan v. the United Kingdom, Strasbourg, 28 January 2000 (Applications nos. 21825/93 and 23414/94) and L.C.B. v. the United Kingdom (9 June 1998, Reports of Judgments and Decision 1998-III, p. 1404). In their dissenting opinion in the case McGinley and Egan v. the United Kingdom,

the Judges de Meyer, Valticos and Morenilla acknowledged the fact that the UK should have taken more adequate measures to protect its servicemen during the nuclear tests, i.e. by establishing the state of health of the participants before and after the tests and by monitoring its development. Yet, there is no mention in their opinion of the basic rules applying to biomedical research, not even questioning whether such rules were relevant in the case.

8. Proceedings of the First International Conference on Harmonization : Brussels 1991, P.F. D'Arcy and D.W.G. Harron (eds), Belfast 1992.
9. See Dominique Sprumont, Legal Protection of Human Research Subjects in Europe, in European Journal of Health Law 6 (1999), pp. 25-43.
10. http://www.wma.net/e/policy/b3.htm (last consulted December 27th, 2004).
11. OJ L 91, 9.4.2005, p. 13
12. See Trudo Lemmens et al., CIOMS' Placebo Rule and the Promotion of Negligent Medical Practice, in European Journal of Health Law 11 (2004), pp. 153-174.
13. See Peteris Zilgalvis, European Law and biomedical research, in Council of Europe (ed.), Ethical Eye, Biomedical research, Strasbourg, 2004, pp. 163-176.
14. OJ L 121/34.
15. OJ L 91, 9.4.2005, p. 13
16. OJ L 311, 28.11.2001, p. 67.
17. http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm (last consulted on December 27th, 2004). See Zilgalvis Peteris, European Law and biomedical research, in Council of Europe (ed.), Ethical eye, Biomedical research, Strasbourg 2004, pp. 166 ff. See also Henriette D.C. Roscam Abbing, The Convention on Human Rights and Biomedicine, An Appraisal of the Council of Europe, in European Journal of Health Law 5 (1998), pp. 377-387.
18. http://www.coe.int/T/E/Legal%5FAffairs/Legal%5Fco%2Doperation/Bioethics/Activities/Biomedical_research/Protocol_Biomedical_research.pdf (last consulted on December 27th, 2004).
19. Desmon Dian (ed.), Encyclopedia of the European Union, London, Macmilan, 1998, p. 140.
20. Judgment of the Court of 5 February 1963. – NV Algemene Transport- en Expeditie Onderneming van Gend & Loos v Netherlands Inland Revenue Administration. – Reference for a preliminary ruling: Tariefcommissie – Pays-Bas. – Case 26-62, European Court Reports 1963, p. 1.
21. Desmon Dian (ed.), Encyclopedia of the European Union, London, Macmilan, 1998, p. 141. See also Jo Shaw, Law of the European Union, Houndmills 2000, p. 244; P.J.G. Kapteyn and VerLoren van Themaat, Introduction to the Law of the European Communities, London 1998, p. 326.
22. See P.J.G. Kapteyn and VerLoren van Themaat, Introduction to the Law of the European Communities, London 1998, p. 330.
23. See Jean-Marc Favret, Droit et pratique de l'Union européenne, Paris 2003, p. 333.
24. See Henriette D.C. Roscam Abbing, The Convention on Human Rights and Biomedicine, An Appraisal of the Council of Europe Convention, in European Journal of Health Law 5 (1998), pp. 377-387. See also Glass v. the United Kingdom, Strasbourg, 9 March 2004 (Application no. 61827/00), paragraph 58 and 75.
25. France, Ireland, Luxembourg, Netherlands, Portugal and Sweden.

26. For an overview of those legislations, see also Eugenijus Gefenas, Central and eastern Europe: research-related problems for transition countries, in Council of Europe (ed.), Ethical eye, Biomedical research, Strasbourg 2004, pp. 121-132.
27. Paragraph 13 of the 5th revision of the Declaration of Helsinki, Edinburgh, Scotland, October 2000.
28. ICH-GCP
29. See Marie Hirtle, Trudo Lemmens and Dominique Sprumont, A Comparative Analysis of Research Ethics Review Mechanisms and the ICH Good Clinical Practice Guideline, in European Journal of Health Law 7 (2000), pp. 265-292.
30. See EU Directive article 7.
31. In an affix of this law it is stated, that the law is in compliance with 2001 April 4 European Parliament and Council directive. 2001/20/EC 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.
32. The Convention on the Rights of the Child does not either impose an age limit to define childhood and the States keep some autonomy in defining the scope of protection of the convention. See article 1 of the United Nations Convention on the Rights of the Child: "For the purposes of the present Convention a child means every human being below the age of 18 years unless, under the law applicable to the child, majority is attained earlier. For more details on this issue, see Sharon Detrick (ed.), The United Nations Convention on the Rights of the Child, A Guide to the "Travaux Préparatoires", Dordrecht Boston London 1992, pp. 115-119. See also Philip E. Veerman, The Rights of the Child and the Changing Image of Childhood, Dordrecht, Boston, London 1992, pp. 17-19, 185-187.
33. According to provisions of the Lithuanian Civil code, while deciding on the reduction of a person's legal age to consent to marriage, the court must hear the opinion of the minor's parents, guardians or curators and take into account his or her mental or psychological condition, financial situation and other important reasons why the person's legal age to consent to marriage should be reduced. Pregnancy shall provide an important ground for the reduction of the person's legal age of consent to marriage.
34. § 3 paragraph 3 of the Estonian Procedure for Conduct of Clinical Trials of Medicinal Products and paragraph 11 of the Latvian Procedure for clinical trials on medicines and pharmaceutical products and for observational studies.
35. Article 5 of the Law on Ethics of Biomedical Research states that minors are ascribed to vulnerable subjects group, but the age limit, when it is compulsory to get consent of such persons for conducting biomedical researches, is not stated. Provision of article 7, stating that conducting biomedical research with a minor, a consent of both parents must be obtained (one, if they live separately) or a consent of legally acceptable representatives of the minor, and the children's rights protection agency of a district or a city, is logically misleading, because the provision itself does not impose the minor's participation in this process. Such provisions of the law should be detailed, altering their formulation or the limit of age, when opinion of a minor should be considered important, stated in law.
36. The Constitution of the Republic of Lithuania, which is a single and directly applicable act, was approved by the citizens of the Republic of Lithuania in the Referendum on 25 October 1992.

37. Liability for and Insurability of Biomedical Research with Human Subjects in a Comparative Perspective, in J. Dute, M.G. Faure and H. Koziol (eds.), Tort and Insurance Law, Vol. 7, Springer, Wien, New York 2004, p. 358.
38. Application for compensating a research-induced damage can be subjected during the period stated by the insurer and the policyholder in the insurance contract, but the Insurance Rules state that this period can not be shorter than 5 years after the end of the study.
39. Essais cliniques, responsabilité civile et contrats d'assurance. *Bulletin des médecins suisses 40/*2002, pp. 2092-2096, Dominique Sprumont, Séverine Boillat and Hermann Amstad. On this issue, see also Liability for and Insurability of Biomedical Research with Human Subjects in a Comparative Perspective, in J. Dute, M.G. Faure and H. Koziol (eds.), Tort and Insurance Law, Vol. 7, Springer, Wien, New York 2004.
40. Benn Steil, Competition, Integration and Regulations in EC Capital Markets, Royal Institute of International Affairs, London 1993
41. See Stephen Woolcock, Competition among Rules in the Single European Market, in International Regulatory Competition and Coordination, William Barton, Joseph McCahery, Sol Piccioto and Colin Scott (eds), Clarendon Press, Oxford 1996, p. 313.
42. For more details on that conference an its follow-up, see Facing the Future Together, Conference on Research Ethics Committees in Europe, Brussels 27-28 January, 2005 http://europa.eu.int/comm/research/conferences/2005/recs/publications_en.htm