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EFFECTIVENESS OF PROTECTION OF BIOMEDICAL RESEARCH SUBJECTS UNDER INTERNATIONAL AND NATIONAL LAW

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Annotation. *The article analyses the relationship of international and national law regulating and ensuring the protection of biomedical research subjects as well as factors determining the actual effectiveness of this protection. For this purpose the article reveals reasons affecting legislation initiatives at international and European level; shows circumstances of adopting specific legal acts, their wording and compatibility. Analysing whether harmonized standards in this area ensure the actual protection of the research subjects the authors assessed the role of national legal norms and the level of legal consciousness and legal culture.*

Authors pursued the objectives of the article by analysing the main areas of biomedical research directly determining the protection of the research subjects' rights and the effectiveness of their protection such as operation of Research Ethics Committees, biomedical research liability and liability insurance. The analysis was carried out on the basis of national exam-

ples of the Baltic countries (Lithuania, Latvia, and Estonia) which were also compared to the situation in Western European countries. The article also assesses issues of the scope and effectiveness of biomedical research regulation related to the ratio of legal, ethical, and deontological norms in biomedical research.

***Keywords*:** *biomedical research, research subject, Research Ethics Committee, liability, liability insurance, informed consent.*

Introduction

During recent decades biomedical research has become one of the most regulated healthcare areas. However its particularity and fast development requires posing few basic questions on the scope, level, and nature of its regulation. First of all, at what level biomedical research should be regulated. Shall the principles of conduct be set by the professional community of medics and researchers, by governments, by international organisations or by international community? Where shall be the limit of their competence, how different levels of regulation shall correlate, and how it may affect the effectiveness of protection of research subjects' rights and legal interests?

The second group of questions concerns the nature and mechanisms of this regulation. What social norms shall regulate biomedical research: legal, ethical, or deontological? The answer needs the analysis of the new economic, social, and regulatory environment of these activities and relations.

The obvious trend of globalisation of biomedical research has a solid economical background. For example, the costs of drug development are such that products need to be marketed worldwide to meet profitability goals. According to the Tufts Centre for the Study of Drug Development the average drug R&D costs have risen from $ 231 million in 1987 to $ 802 million in 2001 and are expected to reach $1.9 billion by 2013. Global Pharmaceuticals Sales in 2003 reached $491.8 billion. According to Price Waterhouse Coopers data in order to keep levels of profitability 23-35 successful drugs per year are needed. Delay of approval costs of a US drug manufacturer constitute approximately $1.3 million per day.[1]

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 cli-

1 Lemmens, T. The Commercialization of Research and REC review in North-America. The material of conference, held on June 16-18, 2005, in Toronto "*The Regulation of Research Ethics Review*". See also Lemmens, T. Leopards in the Temple: Restoring Scientific Integrity to the Commercialized Research Scene. *Journal of Law, Medicine and Ethics*. 2004, 4: 641-657.

nical trial subjects and that the 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 these 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 speed-up the R&D process.

It is important that R&D of drug development is mostly oriented towards drug production and trade. These activities are mainly economic, related to elementary economic categories such as profit, losses, marketing. These are categories, to which such factors as the welfare of a biomedical research subject, his rights and effectiveness of their protection is rather a neutral if not to say an extraneous factor.

Individual states seeking to attract investments and competing for the market of biomedical research often set lower standards of regulatory environment. The subjects of this industry migrate to regions, which substantially or even unreasonably (*reductio ad absurdum*) lower such standards. This process is called a pursuit for more advantageous conditions at the national level or the concept of lower externalities. However, the application of lower economic standards, if it correlates with a weaker or inappropriate protection of trial subjects, endangers human rights and the effectiveness of their protection.

This is one of the reasons why individual states and international community, apart from economically focused decision-making, also develop political decision-making, which covers human wellfare and human rights protection. The basic international consensus was achieved by setting forth that human interests are above scientific or public interests; although this principle is widely accepted, it does not and cannot resolve specific questions. Therefore along with broad agreement on the need for international regulation to protect the priority of human interests, significant differences will remain over both – identification and regulation of the solution of the issue. This is especially relevant having in mind post-socialist countries of Central and Eastern Europe, which have recently become members not only of the Council of Europe but also of the European Union and are implementing agreements on regulation of biomedical research based on international consensus. While analysing such implementation, it is important not to forget that it was carried out in legal systems that did not have well-established legal traditions. Thus regulations of biomedical research were developed along with the developing contents of national laws. This determined the rise of problems not only of implementation of international requirements into national law, but also in such areas as

2 CROs provide gateway to worldwide clinical trial recruitment efforts. Impact Report. *Tufts Center for the Study of Drug Development*. 2003, No. 4 [last accessed on 30 04 2009]. <http://csdd.tufts.edu/InfoServices/ImpactReportPDFs/ImpactReportSummaryJulAug2003.pdf >.

their interpretation and application. Therefore comparative law studies on regulation of biomedical research could be a tool facilitating the identification of these problems and suggesting solutions. This vision and expectation determined the purpose of this paper: in part I, we will outline the structure and the nature of the international regulation of biomedical research in the European perspective. We are going to demonstrate the way international law affects national legal standards. In part II, using examples of research ethics committees (RECs), informed consent, liability, and liability insurance, we will analyse the importance of the national laws in the implementation of international regulation and effectiveness of the biomedical research regulation related to the ratio of legal, ethical, and deontological norms.

1. 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 committed 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] or even promoted taking into consideration health interests of these groups.[6] This research is not

3 Berkamp, L. Medical Research Involving Human Beings: Some Reflections on the Main Principles of the International Regulatory Instruments. *European Journal of Health Law*. 2004, 11: 61-69; Knoppers, B.; Sprumont, D. Human Subjects Research, Ethics, and International Codes on Genetic Research. *Encyclopedia of Ethical, Legal and Policy Issues in biotechnology*. John Wiley & Sons, 2000, p. 566–576.

4 Sprumont, D.; Pascal, A. The Nuremberg Code: Rules of Public International Law. Tröhler, U.; Reiter-Theil, S. (eds.). *Ethics Codes in Medicine : Foundations and Achievements of Codification since 1947*. Ashgate, Aldershot, 1998, p. 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 Paediatric 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 Paediatric Patients; Final Rule (21 CFR Parts 201, 312, 314 and 601).

6 For instance Directive 2001/20/EC underlines the necessity to examine drugs and vaccines with the most vulnerable group of population that is children "as their development, physiology and psychology are different from those of adults and research is needed to ensure that children later receive only the most valuable from the clinical point of view drugs".

by itself 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 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.[7]

In the early 1990s, 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 delay in making new treatments available to 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. These 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 six times in 1975, 1983, 1989, 1996, 2000 and 2008 (eight times if we

7 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.

8 D'Arcy, P. F.; Harron, D. W. G. (eds). *Proceedings of the First International Conference on Harmonization*. Brussels 1991, Queens University of Belfast.

9 Sprumont, D. Legal Protection of Human Research Subjects in Europe. *European Journal of Health Law*. 1999, 6: 25–43.

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 for medical research involving human subjects, including research on identifiable human material and data".

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. Although formal attributes of this declaration confirm that it is an ethical code, some of its provisions, by their content rather resemble mandatory norms of international law (*ius cogens)*:

"Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration".

Although this obviously conflicts with the nature of ethical norms, it is worth noticing that some steps to solve this problem are already taken. The Declaration has just 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 1980s, another international set of rules was developed by the Council of International Organization of Medical Sciences (CIOMS). The CIOMS was founded 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:

10 Declaration of Helsinki. Ethical Principles for Medical Research Involving Human Subjects. The World Medical Association. [last consulted 2009-04-30]. <http://www.wma.net/e/policy/b3.htm>.

11 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. [2005] OL L91/13.

"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 the 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 is a non binding document, related mainly to ethical justification and scientific validity of research.

This brief overview of the regulation of biomedical research at the international level shows tension between rather conservative (even prohibitive) rules and those more favourable to research. The present trend seems to go towards regulation more responding to the needs of the researchers and the sponsors, even if protection of humans 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.

On the other hand, this overview demonstrates one more important aspect, namely the absence of strict distinction between legal, ethical, and deontological norms entrenching requirements for biomedical research. This raises a practical issue of responsibility for treatment non-compliance with these norms, which determines the effectiveness of the trial subjects' protection.

1.2. In Europe

Biomedical research at the European level is regulated by both the European Union and the Council of Europe.

The Council of Europe, which was established for promoting and developing human rights and basic freedoms, has developed one of the most progressive regional human rights protection system in the world. The effectiveness of the system has especially increased after adopting 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[13] (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 hu-

12 Lemmens, T. *et al.,* CIOMS' Placebo Rule and the Promotion of Negligent Medical Practice. *European Journal of Health Law.* 2004, 11: 153-174.

13 Convention for the protection of Human Rights and Dignity of the Human Being with regards to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (adopted 4 April 1997, entered into force 1 December 1999). ETS 164. <http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm>. See also Zilgalvis, P. (ed.), European Law and biomedical research, in Council of Europe. *Ethical eye – Biomedical research*. Strasbourg. 2004, p. 166.

man 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).[14] The scope of the additional protocol is all research on a person, except epidemiological studies and research with biological material.

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.[15]

Another group of documents, which is equally important for the regulation of biomedical research at the European level, was adopted by the institutions of the European Union.

Answering the question why the EU, rather than the Member States, should take action to regulate biomedical research, the principle of subsidiarity, which was introduced into the title of the Treaty in the Single European Act, is a useful starting point:

"In areas which do not fall within its exclusive competence, the Community shall take action, in accordance with the principle of subsidiarity, only if and in so far as the objectives of the proposed action cannot be sufficiently achieved by the Member States and can therefore, by reason of the scale or effects of the proposed action, be better achieved by the Community".[16]

Amsterdam Treaty described in detail how the Community should act and whether it should act at all:

"other things being equal, directives should be preferred to regulations and framework directives to detailed measures... Community measures should leave as much scope for national decision as possible, consistent with securing the aim of the measure and observing the requirements of the Treaty. While respecting Community law, care should be taken to respect well established national arrangements and the organisation and working of Member States' legal systems".[17]

So the area of biomedical research remains the "light touch" on the EU side, which leaves rather wide space for Member States. As we shall see, although limited by minimal standards this freedom of action remains much more important to the effective protection of trial subjects' rights than it is usually considered to be.

14 Additional Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research (adopted 25 January 2005, entered into force 1 September 2007). ETS 195. <http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm>.

15 See Henriette, D. C.; Abbing R. The Convention on Human Rights and Biomedicine, An Appraisal of the Council of Europe. *European Journal of Health Law*. 1998, 5: 377-387. See also *Glass v. the United Kingdom*, Strasbourg, 9 March 2004 (Application no. 61827/00), paragraph 58 and 75.

16 Consolidated version of the Treaty establishing the European Community. [2002] OL C325.

17 The Amsterdam protocol on Subsidiarity and Proportionality. [2002] OL C 340.

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[18] (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.[19]

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,[20] "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 also has an objective to facilitate 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.

The doctrine of direct effect is a legal principle that underpins the EU law. Such supremacy of the 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.[21] One of such obligatory documents are the directives as

18 Directive 2001/20/EC of the European Parliament and 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. [2001] OL L121/34.

19 Commission Directive 2005/28/EC of 8 April 2005. [2005] OL L91/13.

20 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. [2001] OL L311.

21 Dian, D. (ed.) *Encyclopedia of the European Union*. London: Macmilan, 1998, p. 140.

stated for the first time in 1963 *Van Gend en Loos* case.[22] 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".[23] 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 with 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 choose the most proper forms and methods for incorporating the provisions of a directive.[24] 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.[25]

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.

According to the 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.

However another circumstance is no less important to the assessment of the effectiveness of the Convention: the Council of Europe is now covering virtually the entire European continent with its 47 member countries; however the Convention on Biomedicine was ratified only by 22 of them. On the other hand, the European Community, although the content of its regulatory documents in the field of biomedical research in most cases is analogical to that of the Convention on Biomedicine, has neither signed, nor ratified the Convention.

According to Article 22 of the Directive:

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22 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.

23 Desmon, D. (ed.), *Encyclopedia of the European Union*. London: Macmilan, 1998, p. 141. See also Shaw, J. *Law of the European Union*. Houndmills 2000, p. 244; Kapteyn, P. J. G. and VerLoren van Themaat. *Introduction to the Law of the European Communities*. London, 1998, p. 326.

24 Kapteyn, P.J.G.; Themaat V. *Introduction to the Law of the European Communities*. London, 1998, p. 330.

25 Favret, J. M. *Droit et pratique de l'Union européenne*. Paris, 2003, p. 333.

"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."

In this place it is noteworthy that only three old EU Member States (by 1 May, 2003) and three EU countries which joined the EU on 1 May 2004 and 1 January 2007 implemented the provisions of the Directive fully and timely. The majority of Member States had not made the necessary changes in their legislation or, at least, had not informed the Commission in time to what extent their legislation already met the requirements of the Directive.[26]

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. However the European Court of Justice and European Commission considers non communication and non conformity of national acts to directives as EU law violations.

Thus 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 advanced stage. This set of rules demonstrates a strong political will to guarantee all patients in Europe a high standard of protection in the field of clinical trials. 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.

2. National Laws Implementing International Regulation

To assess the degree of protection granted by the International laws, 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 in more detail from 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.[27]

26 <http://eur-lex.europa.eu> [last consulted 2009-04-30].

27 For an overview of those legislations, see also Gefenas, E. Central and Eastern Europe: Research-related Problems for Transition Countries. *Ethical eye: Biomedical research*. Strasbourg, 2004, p. 121–132.

2.1. Research Ethics Committees (RECs)

The 1975 Tokyo revision of the Declaration of Helsinki has 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",[28] "independent ethics committee" (IEC),[29] 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." (emphasis added).

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 universities, or the existence of a centralized or decentralized administration. Some legislation is rather detailed, while other leaves it to local or regional authorities to define the operating procedures of the REC. Several models of legislation can be identified.[30]

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 procedure to appeal 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 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

28 Paragraph 13 of the 5th revision of the Declaration of Helsinki. Edinburgh, Scotland, 2000.

29 Good Clinical Practice: Consolidated Guideline. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 1996. [last consulted April 30 th, 2009]. <http://www.ich.org/MediaServer.jser?@_ID=482&@_MODE=GLB>.

30 See Hirtle, M.; Lemmens, T.; Sprumont, D. A Comparative Analysis of Research Ethics Review Mechanisms and the ICH Good Clinical Practice Guideline. *European Journal of Health Law.* 2000, 7: 265-292.

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 *(see EU Directive Article 7)*. 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 currently 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 divided geographically: 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 a 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 the Law on Ethics of Biomedical Research No. VIII-1679 (2004-07-04 edit[31]) of 11 May 2000 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 are individuals or groups, foetuses, tissues, organs, cells and genetic material, cadavers and medical documents.

It is noteworthy that according to Article 3 of the Law Lithuanian Bioethics Committee shall however has not determined the peculiarities of the biomedical research undertaken on cadavers and medical documents. Because of this reason there are problems not only of interpretation of legal regulation of this area but also of practical application including preparation of applications for biomedical research with these objects and their evaluation.

According to Article 13 of the Law on Ethics of Biomedical Research, the Lithuanian Bioethics Committee shall be established and its composition and regulations shall be approved by the Ministry of Health.

Article 14 sets forth that Regional biomedical research ethics committees shall be formed at the universities having in place three-stage medical studies (2 out of 10 existing counties in Lithuania).

The procedure for forming and operating of regional biomedical research ethics committees as well as for solving the issues assigned to their sphere of competence is set forth by regulations of the regional biomedical research ethics committees, which shall be approved by the rector of a university subject to agreement with the Ministry of Health. Territorial boundaries of activities of regional biomedical research ethics committees shall be determined by the Ministry of Health. Implementing these provisions two regional biomedical research ethics committees are established and operate in Lithuania. The first one was established on 12 December 2001 in Kaunas County, and the second – on 1 December 2008 in Vilnius County, as a unit of the Vilnius University, Medical Faculty.

In Lithuania biomedical research can be carried out only if it is approved by the Lithuanian Bioethics Committee or the Regional Biomedical Research Ethics Committee (if the research is conducted within the attributed territory). Authorisation for bio-

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.

medical research planned to be conducted within the territory attributed to activities of more than one Regional Biomedical Research Ethics Committee shall be granted by the Lithuanian Bioethics Committee upon receipt of conclusions of both regional biomedical research ethics committees.

Permission for clinical trials of medicinal products is issued by the State Medicines Control Agency with the approval of Lithuanian Bioethics Committee and the Regional Biomedical Research Ethics Committee, to which the territory of the planned research is attributed. Conduct of biomedical research without prior approval is unlawful.

The existing assessment system of biomedical research and especially that of drugs clinical trials allows assessing in detail the documents of the planned research. However if e.g. the drugs clinical trial is conducted within a territory attributed to few regional committees protocols shall be assessed and approved by four bodies: both regional, Lithuanian National Bioethics Committee, and State Medicines Control Council under the Ministry of Health, which actually issues the permission. Although such multilevel assessment system enables to detect more potential irregularities the limits of personal responsibility within such system become vague. In the absence of division of functions between these actors duplication is also an issue.

As we can see, there is a mix between centralized and regional jurisdiction of the REC in the Baltic countries. Tasks and objectives to be met by RECs, formation of these bodies, basic requirements for membership, their funding, duty to assess risks and benefits, division of jurisdiction between these bodies are regulated at the level of law. However all other aspects of committees' operation are regulated in their own internal regulations, which often refer to various international documents: ICH-GCP, the Belmont Report, Helsinki declaration and others.

Determining requirements for RECs operation e.g. the following provisions of Operational Guidelines for Ethics Committees that review Biomedical Research[32] adopted by the World Health Organization may be used:

"These Guidelines are intended to facilitate and support ethical review in all countries around the world. They are based on a close examination of the requirements for ethical review as established in international guidelines, as well as on an evaluation of existing practices of ethical review in countries around the world."

In addition to the existing operating procedures these guidelines stipulate that:

"They do not, however, purport to replace the need for national and local guidelines for the ethical review of biomedical research, nor do they intend to supersede national laws and regulations".

So other aspects of RECs operation essential in the sense of human rights protection such as decision-making process, questions of acceptable quorum and methods (voting or consensus) used to reach a decision, which are critical to the credibility of ethics committees'; regulation of conflict of interest; requirements for assessing risk and benefit ratio remain unclear in many regulations. The ICH-GSP guideline remains vague

32 *Operational Guidelines for Ethics Committees that review Biomedical Research.* WHO, Geneva, 2000 [last consulted April 30 th, 2009]. <http://apps.who.int/tdr/publications/training-guideline-publications/operational-guidelines-ethics-biomedical-research/pdf/ethics.pdf>.

on quorum requirements remitting this to the ethics committees' operating procedures, but it does recognize that they are essential. Moreover, both decision-making processes of voting or reaching consensus are recognized as valid. This flexibility reflects the situation at the national level.

The most daunting task of the ethics committees is ensuring of continuing review or monitoring of protocols they have approved. The effectiveness of ethics review as a control mechanism of clinical trials relies on this continuing review. Arguably, monitoring or conducting continuing review of clinical trials is crucial for ensuring the protection of human subjects throughout the trial and should be one of the main tasks of an ethics committee.[33] For instance in Lithuania not a single legal act regulating these processes is published.

No less important is the fact that RECs' members often could lack the capacity and expertise to review, as they are expected to, the array of scientific and ethical elements of research protocols they review. Yet, paradoxically, the ethics committees remain, in most countries, the only bodies that actually review research protocols.[34]

All the questions considered and certain requirements for RECs in the absence of unanimous REC's regulations, Oversight and Governance system and unanimous mechanisms for biomedical research surveillance, training and qualification improvement are implemented and applied differently between laws of individual countries. Seeking assurance whether RECs meet standards of their operation, whether this ensures the protection of research subjects and their rights, a proper supervision of committees' activities is needed. In the absence of such mechanisms or in case of their ineffectiveness, the protection of research subject may appear to be in danger.

2.2. Research with Children and Incapacitated Adults

According to 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 (2) (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

33 Weijer, C. , *et al*. Monitoring Clinical Research : An Obligation Unfulfilled. *IRB : A Review of Human Subjects Research*. 1995, 152 (12): 1973–1980.

34 Hirtle, M.; Lemmens, T.; Sprumont, D. A Comparative Analysis of Research Ethics Review Mechanisms and the ICH Good Clinical Practice Guideline. *European Journal of Health Law.* 2000, 7: 265-292.

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 (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.

Neither the Directive nor the Convention contains the definitions of a minor (in other words the legal age limit between childhood and adulthood), capacity to consent and legal representatives.[35] The answer to these questions is to be found in 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. A 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. 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 pregnancy, the court may give its authorization even for a minor under 15 years old.[36] 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 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.

35 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 Detrick S. (ed.). *The United Nations Convention on the Rights of the Child, A Guide to the "Travaux Préparatoires"*. Dordrecht, Boston, London, 1992, p. 115-119. See also Veerman, P.E.; *The Rights of the Child and the Changing Image of Childhood*. Dordrecht, Boston, London. 1992, p. 17–19, 185-187.

36 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.

This brief overview of the legal age to become an adult shows some differences 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 cannot be resolved with certainty by applying the regulation of biomedical research alone.

Comparison of 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. Such a requirement is conformed to the rule of informed consent in the Directive and in the Convention. For instance, according to Article 6(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 since when it is necessary to obtain the minor's consent.[37] Could this be interpreted as denial of the child's 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 is also recognized in 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. In any case Lithuanian regulation remains the object of subjective interpretation since the age limit from which consent of a child taking part in a trial would be required is not set.

Even more discussions are raised by provisions of the Law on Fundamentals of Protection of the Rights of the Child of the Republic of Lithuania (14 March 1996, No. I – 1234). Part 2 of Article 7 of the Law seeks to protect rights of a child participating in a trial in a more secure way however it may be admitted that the actual wording of the Law entirely prohibits such trials with children:

"All types of scientific experimentation or other experimentation involving a child, that may be detrimental to his life, health, or normal personal development, shall be prohibited. This prohibition shall also apply even in the presence of an agreement by the child, his parents or other legal representatives of the child".

37 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.

Such wording of the Law does not meet international obligations of the Republic of Lithuania;[38] furthermore, it prohibits trials even in cases when a trial is potentially useful for a child as it is impossible to exclude the possibility of minimal damage in any trial.

Concerning research with incapacitated adults, it is authorized in Estonia and Latvia under similar conditions as those 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,[39] 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 in Article 18, part 3, of the Lithuanian Law on Mental Health Care (1995-06-06 No. I-924).

Analysing researches with vulnerable persons in Lithuania another important fact related to representation of persons incapable to give consent should be considered. Article 2.10 of the Civil Code stipulates that a natural person who as a result of mental illness or imbecility is not able to understand the meaning of his actions or control them may be declared incapable. The incapable person shall be placed under guardianship. Article 2.11 of the Civil Code stipulates that civil capacity may be restricted only if a person abuses alcohol, drugs, narcotic or toxic substances (guardianship shall also be imposed). Both restriction of civil capacity and declaration of incapacity shall be imposed only by court. Lithuanian Civil Law does not admit any other grounds for restricting capacity or declaring incapacity, e.g. if a person is not able to obtain civil rights and civil liabilities due to grave physical condition. These provisions also limit possibility of conducting medical trial with the person even though such trial would be necessary taking into account the peculiarity of his health condition.

The problem exists along with the mentioned above: 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 competence. This is important because with the aging of the popula-

38 Assessing this situation from the legal point of view we can see that Republic of Lithuania within the scope it restricts trials with persons unable to give consent and in case it does not amend the existing acts of national law should make a clause to the Oviedo Convention similar to one made by the Italian Government on the Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research: „The Government of Italy will not allow that a research which does not produce direct benefits to the health of the research participants be carried out on persons not able to give their consent and on a pregnant or breastfeeding woman" [last consulted April 30 th, 2009]. http://conventions.coe.int/Treaty/Commun/ListeDeclarations.asp?NT=195&CM=8&DF=6/5/2009&CL=ENG&VL=1.

39 Lietuvos Respublikos Konstitucija. *Valstybės žinios.* 1992, Nr. 33-1014.

tion, 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 existed 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 developed 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(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 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".[40]

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 20 December 2000 the Minister of health confirmed by Order 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.[41] 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 competence 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 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 of the Republic of Lithuania;

40 Dute J.; Faure M. G.; Koziol H. (eds.). Liability for and Insurability of Biomedical Research with Human Subjects in a Comparative Perspective. *Tort and Insurance Law*. Vol. 7. Springer: Wien, New York, 2004, p. 358.

41 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 cannot be shorter than 5 years after the end of the study.

- 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, 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, liability of the sponsor is limited to a 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.

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 add-

ressed 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 are 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.

Table 1[42]

	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

2.4. Effectiveness of Liability

Although the content of the considered norms setting forth the biomedical research liability and liability insurance is problematic due to incompatibility between national laws of different countries, much more problems are to be found analysing the actual effectiveness of these norms from the human rights protection perspective.

Regardless of existing international standards of liability and obligations to establish effective mechanisms of human rights protection and compensation for damage inflicted on such rights, actual human rights protection at national level firstly depends on national legal norms and national mechanisms.

Baltic countries, which seem to be practically entrenched as a fairly attractive region for biomedical researches, carried out by international researchers, have not developed such mechanisms.

42 Sprumont D.; Boillat S.; Amstad H. Essais cliniques, responsabilité civile et contrats d'assurance. *Bulletin des médecins suisses.* 2002, 40: 2092-2096. On this issue, see also Dute J.; Faure M. G.; Koziol H. (eds.). Liability for and Insurability of Biomedical Research with Human Subjects in a Comparative Perspective. *Tort and Insurance Law*. Vol. 7. Springer: Wien, New York, 2004.

Although legal sources of liability in these countries are strictly regulated by the norms of the Civil and Penal Codes as well as other special legislative provisions, they do not ensure the rights of persons undergoing medical trials. Their special provisions on liability of researchers are ineffective.

To the best of our knowledge, in those countries, since restoration of their independence in 1991 until 2005, no cases have occurred, when individuals or groups filed complaints or brought litigation against international researchers in connection with researches.[43]

Moreover - there have not been any public case, when individuals or groups filed complaints or brought litigation in front of the National or International Courts or other bodies against national researchers.

Obviously it is possible to conclude that such cases have been avoided due to professional competence of researchers, safety of drugs and other medical arrangements. However, public data alone do not allow to affirm this. One example of such data is information about an adverse drug reaction of research subjects: in 2007 State Medicines Control Agency under the Ministry of Health of the Republic of Lithuania received 134 reports about adverse drug reactions, 114 of which were evaluated as severe. Only 64 percent of the reports were received from doctors, others – from the holders of marketing entitlements.[44]

Some researchers have violated legal acts. For example on 9 June 2007 it was reported that a physician of Panevėžys hospital has applied treatment to patients using unregistered, experimental drugs without informing neither the research subjects, nor institutions, issuing permissions. It was reported that this physician hid the fact from pharmaceutical companies, which had ordered the research, that some of the research subjects died – the physician submitted to the clients signed forms of research subjects consent and X-ray pictures, which, as became obvious later, had been made several months after the patients' death.[45] Prosecution Service of the Republic of Lithuania initiated investigation of this act committed by the physician. However, public information about claims or lawsuits of victims or their representatives to authorised institutions does not exist and such cases are not known to the community of lawyers.

In principal such situation in respect to effectiveness of human rights protection encourages us to remember rudimentary categories of theory of law, such as legal culture or legal consciousness. By legal culture we mean ability of society to create effective

43 In 2005, June 16-18 in Toronto (Canada) University, Faculty of Law, workshop "The regulation and Organization of Research Ethics Review" was held. The representatives of Baltic countries stated, that in their countries no cases, when individuals or groups filed complaints or brought litigation in front of the National or International Courts or other subjects (tribunals or other forums in these countries; International organizations; Agencies that fund international researchers (e.g. the FDA in the U.S.); Agencies in the international researcher's home state that have given approval for research in these countries; Courts in an international researcher's home state, for damages and other compensation; Courts in an international researcher's home state, for enforcement of the home state's own legislation on the international researchers), have occurred.

44 The State Medicines Control Agency at the Ministry of Health of the Republic of Lithuania [last consulted April 30 th, 2009]. <www.vvkt.lt/index.php?1845716722>.

45 Ministry of Health of the Republic of Lithuania [last consulted April 30 th, 2009]. <www.sam.lt>.

measures of human rights protection and its willingness and ability to use such measures in practice, to socialize its behaviour. Legal culture encompasses the entirety of legal measures and procedures to standardize and socialize behaviour – it encompasses all legal system – legal ideas (doctrine), procedures of law making, legal norms and legal relationships, legal responsibility. However, in order to make these measures really effective, they have to be linked to consciousness and will of a certain person, legal subject, who uses the above measures. In other words, actual human rights protection is determined by two aspects: 1) whether the person knows, understands legal requirements addressed to him (permissions, prohibitions and obligations), and whether he is able to use legal measures and institutions for protection and implementation of his rights. This equals to legal consciousness and is a premise of legal culture; 2) whether the person applies such requirements in his actual behaviour; whether he actually uses legal measures to protect and implement his subjective rights. The unity of such elements constitutes premises for and determines the effective functioning of human rights protection system.[46]

Analyzing how the designated purpose can be achieved the legal functions, through which law realizes its purpose, must not be forgotten. In this case even more important than regulative is informative (educative) legal function, because it helps to inform the society about the requirements of legal behaviour and possible measures and mechanisms for defence of violated human rights. Educative legal function directly correlates with legal culture and legal consciousness, on which effective protection of human rights depends.

The above Oviedo Convention is also entrenching educative legal function. Article 28 serves this purpose. It is put as an independent - Chapter X "Public debate".

"Parties to this Convention shall see to it that the fundamental questions raised by the developments of biology and medicine are the subject of appropriate public discussion in the light, in particular, of relevant medical, social, economic, ethical and legal implications, and that their possible application is made the subject of appropriate consultation".

To sum up, it must be once more stated, that actual and effective protection of research subjects' rights is possible only if an appropriate attention is granted to national law and actions at national level. International standards, although necessary, are not always able to achieve actual effectiveness.

2.5. Nonetheless: Ethics or Law?

The analysis undertaken in the article showed that on the international level there is a problem of differentiating between legal and other social norms concerning biomedical research. Although theory of law provides a very clear division of legal norms from other social norms: from the point of view of formal attributes of legal norm (normative nature, formal definition, and general obligation covering state sanctions for their breach) the indisputable postulates of the theory of law in regulation of biomedical re-

46 Vaišvila, A. *Teisės teorija*. Vilnius: Justitia, 2004, p. 463–464.

search are treated and applied in a specific way and intensive discussions on the ratio between law and ethics in this area still go on. In certain way this discussion makes negative impact on the effectiveness of legal regulation. For instance the Law on Ethics of Biomedical Research of Republic of Lithuania, which clearly entrenches rights and duties of parties involved in biomedical research and shall be treated as a set of strictly obligatory norms, in the first article ambiguously stipulates the aim of this legal act: "This Law shall set forth requirements for and principles of the ethics ...". From the law theory point of view this provision, which is detailed by the other Articles of this law, is totally incomprehensive as ethical norms being fixed in a legal act ignoring their source and content become compulsory legal norms, the breaching of which shall impose legal sanctions. Such a situation in general confuses the whole system of norms regulating human behaviour, confuses types of norms and sets the legal (sometimes even criminal) responsibility for the conduct non-compliant with ethics.

It may be considered that treating of legal norms as non-obligatory (such are, in principal, ethical norms) partially reduces their effectiveness.

From the point of view of theory and tradition of law one of the examples to be followed by Lithuanian legislators might be the practice of the Council of Europe while designing the Oviedo Convention. The draft of this paper was for the first time published under the name of "Convention on Bioethics";[47] later in 1996 after the text was reconsidered it was specified as "Convention on human rights and biomedicine". This step is correct not only from the law theory point of view, but also in respect of the effectiveness of law: in case medical staff, sponsors and researchers treat rules regulating biomedical research as deontological (professional) or ethical norms, their effectiveness becomes significantly lower. Negative examples from global practice just confirm the rule.

Conclusions

Regulation of biomedical research in international and European law starting with the adoption of the Nuremberg Code half of a century ago still remains in a harmonization process. Analysis conducted made clear that although necessary international legal instruments do not provide an effective protection of the research subjects. Each Member State and the international community have to put more efforts so that the process of harmonization would not seem only an utopian idea. So far, the international regulation is mainly based on general principles that remain too broad and vague to provide 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 members of ethics committees. 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

47 Decision of Parliamentary Assembly of Council of Europe: Recommendation 1160 (1991-06-28) on the preparation of a convention on bioethics.

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.[48] 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 centralized 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.[49] 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 argue 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, minors, persons lacking legal capacity or research in emergency setting. Last, but not least, the more detailed regulation of Research Ethics Committees operation is needed including but not limiting to the supervision of the content of their activities and issues of committees' members' responsibility. It would be useful to apply the same standards everywhere across 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

48 Steil, B. *Competition, Integration and Regulations in EC Capital Markets.* London: Royal Institute of International Affairs, 1993.

49 Woolcock, S. Competition among Rules in the Single European Market. Barton W., *et al.* (eds). *International Regulatory Competition and Coordination*. Oxford: Clarendon Press, 1996.

law, without mentioning the issue of constitutional law. The law-ethics ratio in biomedical research is still problematic: the importance of ethics should be appreciated however its "quasi-legal" claim confuses the whole system of legal norms. This undoubtedly also affects the efficiency of research subjects' protection.

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 deliver 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 of submitting an application to the REC and the Drug agency. These documents present some similarities, and it may prove an interesting move to harmonize these forms in a near future. The forms being harmonised it would suppose uniform requirements for research and protection of research subjects at least in the Baltic countries, make easier to exchange experience and enable RECs members to work together with the same procedures, allow us to expect higher professionalism and potentially more effective protection of research subjects. 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 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 interpretation and implementation of those norms. This could be organized by the RECs themselves or by the controlling authorities. In addition, these bodies should be more proactive at national levels: in certain cases providing information and training on ensuring rights of research subjects may prove to be more effective than the specification of existing rules. This shall not be forgotten also.

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TARPTAUTINĖS IR NACIONALINĖS TEISĖS VAIDMUO UŽTIKRINANT VEIKSMINGĄ ASMENŲ, DALYVAUJANČIŲ BIOMEDICININIUOSE TYRIMUOSE, APSAUGĄ

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Santrauka. *Straipsnyje analizuojamas tarptautinės teisės ir nacionalinės teisės santykis reglamentuojant ir užtikrinant biomedicininiuose tyrimuose dalyvaujančių tiriamųjų apsaugą, taip pat veiksniai, kurie lemia šios apsaugos realų veiksmingumą.*

Straipsnyje nagrinėjami klausimai, lemiantys tiriamųjų asmenų apsaugą: kokiu lygiu biomedicininiai tyrimai turi būti reglamentuojami (medikų ar tyrėjų profesinių bendruomenių, nacionaliniu lygiu sprendimus priimančių asmenų, tarptautinių organizacijų ar tarptautinės valstybių bendrijos), kokia turėtų būti šių subjektų kompetencijos takoskyra, kaip šie reguliavimo lygiai turėtų būti susiję, ir kokios normos – teisės, etikos ar deontologinės – šį darbą turi atlikti? Atlikta analizė rodo, kad atsakymai į šiuos klausimus priklauso nuo egzistuojančios biomedicininių tyrimų socialinės, reguliavimo ir, ypač, nuo ekonominės aplinkos. Plėtojant šią mintį, straipsnyje pabrėžiamos biomedicininių tyrimų kaip komercinės veiklos sąsajos su ekonominėmis kategorijomis, pelno siekimu ir praradimų minimizavimu, parodoma, kaip ekonominis tyrimų aspektas daro įtaką biomedicininių tyrimų srities reglamentavimo turiniui.

Ieškant atsakymų į iškeltus klausimus taip pat nagrinėjamas biomedicininių tyrimų tarptautinis reglamentavimas. Pradedama Niurnbergo kodeksu, kurio formuluotės, nepasitelkiant kitų teisės aiškinimo metodų, kai kurių vis dar aiškinamos kaip besąlygiškai draudžiančios tyrimus su negalinčiais duoti sutikimo asmenimis. Analizuojant vėlesnius dokumentus, tokius kaip tarptautinės harmonizavimo konferencijos (ICH) priimtos konsoli-

duotosios geros klinikinės praktikos taisyklės (GCP), pasaulio medikų asociacijos Helsinkio deklaracija, CIOM priimti dokumentai, daroma išvada kad tarptautiniu mastu vis dar jaučiama įtampa tarp labiau konservatyvių ar net draudžiančių ir tyrimams labiau palankių normų. Nėra pakankamai aiški takoskyra tarp biomedicininius tyrimus reglamentuojančių teisės, etikos ir deontologinių normų, nuo kurios tiesiogiai priklauso ir tiriamųjų teisių apsauga. Europos lygmenyje vertinama Europos Tarybos Ovjedo konvencija, taip pat su biomedicininiais tyrimais susiję Europos Sąjungos direktyvos: jų tikslai, nuostatos, įgyvendinimas valstybėse narėse. Nors progresas, padarytas harmonizuojant biomedicininių tyrimų reglamentus, yra akivaizdus, o politinė valia kiekvienam Europoje tiriamam asmeniui garantuoti tą patį apsaugos lygį – tvirtą, realų tiriamųjų apsaugos veiksmingumą iš dalies kvestionuoja praktika. Šiuo atveju vertinti Baltijos valstybių – Lietuvos, Latvijos ir Estijos – nacionaliniai pavyzdžiai biomedicininių tyrimų srityse, nuo kurių tiesiogiai priklauso tiriamųjų asmenų teisių apsauga ir jų gynybos efektyvumas. Tai nacionalinių tyrimų etikos komitetų veikla, reikalavimai vaikų ir negalinčių duoti sutikimo asmenų, jos atsakomybės dėl biomedicininių tyrimų ir draudimo institutai, atsakomybės veiksmingumas.

Palyginus nacionalinius šių valstybių reikalavimus biomedicininiams tyrimams su tarptautine praktika arba reikalingais kitose vakarų Europos valstybėse, daroma išvada, kad asmenų, dalyvaujančių biomedicininiuose tyrimuose, apsauga nacionaliniu mastu, nepaisant minimalių tarptautinių standartų, išlieka nepakankama.

Reikšminiai žodžiai: *biomedicininiai tyrimai, tiriamieji asmenys, tyrimų etikos komitetai, atsakomybė, atsakomybės draudimas, informuotas sutikimas.*

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