Research Ethics System in Latvia: structure, functioning, and problems

El sistema de ética de la investigación en Letonia: Estructura, funcionamiento y problemas

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ABSTRACT: *The paper attempts to provide an updated and holistic description of the research ethics system in Latvia and discuses the problems in its structure and functioning. It is based on the data gathered in an empirical study of RECs in Central and Eastern Europe in 2008 and it is structured according to the integrated framework proposed by Hyder et al. First a short outline of the historical development of the ethics review system in the 1990s is given, then the issues of general social, political and economic background and the resultant enabling conditions, as well as the national and regional strategy of ethical review are reviewed. Next, the discussion turns to institutional commitment, the factors influencing the quality of review, and ethically relevant aspects of investigators' behavior. The main conclusion is that current developmental conditions are not too favorable for research ethics review; despite the overall progress, several crucial enabling conditions are not in place yet.*

KEIWORDS: *research ethics committees, developmental conditions, enabling conditions, structure, functioning, problems*

RESUMEN: *Este artículo ofrece una descripción actualizada y global del sistema de ética de la investigación en Letonia y analiza los problemas en su estructura y funcionamiento. Se basa en los datos obtenidos en un estudio empírico de 2008 sobre los comités de ética de la investigación en el Centro y Este de Europa y está estructurado de acuerdo con el marco integrado propuesto por Hyder et al. En primer lugar se ofrece un breve panorama del desarrollo histórico de los sistemas de revisión en la década de 1990; luego se examina el trasfondo social, político y económico, así como las condiciones de puesta en marcha a las que dieron lugar, y las estrategias nacionales y regionales de supervisión ética. A continuación se pasa a discutir el compromiso institucional, los factores que influyen en la calidad de la supervisión, y los aspectos éticamente relevantes del comportamiento de los investigadores. La conclusión principal es que las actuales condiciones de desarrollo no son muy favorables al ejercicio de la ética de la investigación; a pesar de los progresos logrados, aún no se han implementado ciertas condiciones cruciales de puesta en marcha.*

PALABRAS CLAVE: *comités de ética de la investigación, condiciones de desarrollo, condiciones de puesta en marcha, estructura, funcionamiento, problemas*

Introduction

In order to give a holistic description of the structure and functioning of Latvian RECs system, it is necessary to take in account the social, political, and economic conditions that are influencing it. The relation between economic development and research ethics has been analyzed by several authors, two of whom are major sources of inspiration for this article. One of them is Lithuanian bioethicist Eugenijus Gefenas, (Gefenas, 2004, 2009). The other is Adnan Ali Hyder and his colleagues, who emphasize the influence of developmental and other conditions on the main goals of human research ethics. Their approach is based on idea that „Attempts to describe the individual elements of research ethics and the interaction among them are challenging in the absence of a coherent conceptual framework" (Hyder, 2009, 862). In order to overcome these difficulties, they propose the use of an integrated framework for research ethics systems consisting of six domains: development, enabling conditions, national/regional strategy, institutional commitment, characteristics of research ethics review, and investigator's conduct (see *Figure 1*).

LEMATA, año 2 (2010), nº 2, 55-69 ISSN 1989-7022

Recibido:2009-11-13
Aceptado: 2010-01-8

DILEMATA, año 2 (2010), nº 2, 55-69 ISSN 1989-7022

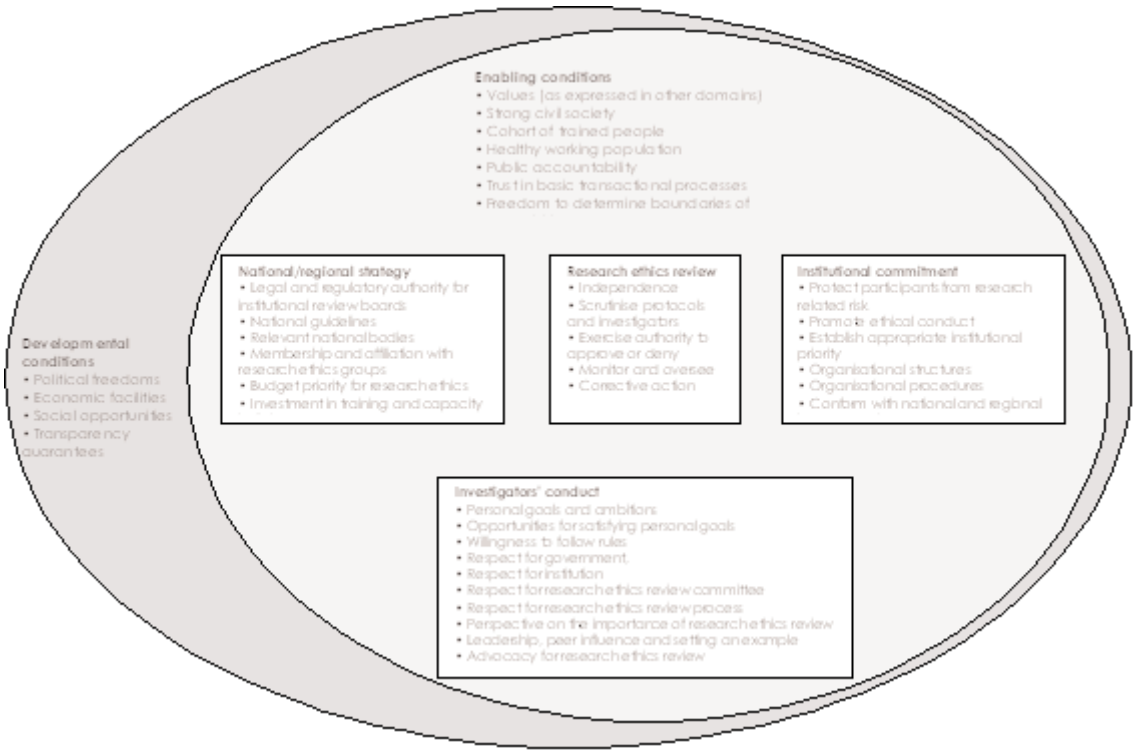

Figure 1: Relations between domains (with constituting elements) in Hyder *et al's* framework.

As far as the available information allows, the task of this article is to describe the structure and evaluate the functioning of Latvian system of research ethics review in terms of Hyder *et al's* framework, and to indicate the most problematic elements and issues in the process.

First, however, it is necessary to say a few words about the research of the Latvian system of RECs, which constitutes an empirical basis of this article. It is a part of larger comparative study of Ethics Committees in Central and Eastern Europe, conducted in 2008 within the framework of *Advanced Certificate Program in Research Ethics in Central and Eastern Europe*.[1] One source of data was the review of publicly available information: internet home pages of Latvian RECs and related institutions, printed publications and reports, as well as normative documents – statutes, laws and regulations that govern the establishment and functioning of RECs. Attempts were also made to contact these institutions directly, but they didn't turn out to be very fruitful. Another source of data was a questionnaire developed in cooperation with the colleagues from the *Advanced Certificate Program* for the purpose of collecting detailed and up-to-date information on research ethics committees in CEE countries. The questionnaire focused on such issues as number and types of currently operating RECs, history of their establishment, legal provisions, accountability and accreditation, fees for review, annual budget and payment, composition, membership and training, workload and the procedure of issuing approvals. It was distributed among the seven of Latvian RECs that were known at the time (two more were "found" later). Only three of seven questionnaires were returned and one of the new-found committees handed in a presentation covering some part of the questionnaire issues.

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1. Chronological development of REC's system in Latvia

As it is noted by Eugenijus Gefeneas the main reason behind establishing research ethics committees (RECs) was "the willingness of CEE researchers to take part in multi-centre clinical trials" (Gefenas, 2004, 121). The first research ethics committees that could meet the formal requirements of ethical review accepted in developed countries were founded in CEE countries in late 1980s and early 1990s, "predominantly in teaching hospitals and therefore came to resemble the institutional review boards operating in the USA" (Gefenas, 2004, 121).

The development of ethics review system began after Latvia restored national independence on May 4, 1990. The first committee was founded at the Latvian Institute of Cardiology in 1992 and was then called Ethics Committee of Clinical and Experimental Research (in 1999 it was reorganized and in 2007 given its present name – EC for Clinical-Physiological Research, Drug and Pharmaceutical Product Clinical Investigation of Scientific Institute of Cardiology at University of Latvia). The second one was established four years later in 1996 at Riga Stradins University by the RSU Senate decision. Both committees started working in absence of any local legal acts for establishment and functions of RECs. The subject matter is first addressed not until the 1997 *Law on Pharmacy*, which states that it is within the scope of competence of the Minister of Health to "approve the model by-law for establishment of the medicinal products clinical trials ethics committees and the membership of such committees" (Ch. III, Section 6.7.). This was done in 1998, when *Ministry of Welfare By-law No. 199* "On Procedure of Staff Harmonization for Ethics Committees for Drug and Pharmaceutical products Clinical Trials" (now replaced by *Ministry of Health Model by-law No. 15/10* "By-law of Ethics committees for Drug Clinical Trials") was issued.

In contrast to the first two, a third committee was mentioned in the legislation before its actual establishment. *Law on Medical Treatment*, adopted in 1997, addressed the operation of a national body: "The Central Medical Ethics Committee shall operate in accordance with Cabinet regulations and it shall examine ethical issues of biomedical progress relating to social problems. Members of the Central Medical Ethics Committee shall be approved by the Cabinet upon recommendation from the Minister for Health" (Section 15.). A few months later, in the January of 1998 the committee was established by the *Cabinet Regulation No.9*. Other REC's were established after the main laws were in place. In total, there are 9 research ethics committees that are currently known to be operating in Latvia. But, before engaging a more detailed discussion about the whole system, let us first examine the political, economic, and social context of the ethical review in terms of Hyder's integrated framework.

2. Development, enabling conditions and national strategy

The first of six domains in the integrated framework is that of developmental conditions. Hyder and colleagues borrow Amartya Sen's model of development (Sen, 1999), stressing that "the five basic freedoms, that Sen describes as being constitutive of development are part of a necessary foundation of any research ethics system" (Hyder, 2009, 862). Latvia shares most of its developmental characteristics with other Central and Eastern European (CEE) countries, especially with the neighboring Baltic Countries – Lithuania and Estonia, – which allows experts to make similar conclusions about all three.

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According to European Bank for Reconstruction and Development (EBRD), in the period since 1989-90 CEE countries have established democratic systems with great rapidity. Since 1991 all elections have been free and fair, there have been no coups, so the general consensus is that all these countries and Latvia among them, now are "functioning democratic states meeting – among other things – the European Union's Copenhagen criteria on democracy, respect for human rights, protection of minorities and, … the rule of law" (Cviic, 2006, 12). On the other hand, the future of political, economic, and legal development has been put into question because of "chronic instability" of government: party coalitions ruling the country are fragile and politically weak, thus the average life span of Latvian government is only 16 months.

In the classification of World Bank Latvia is placed among the middle-income economies (World Bank). Experts agree that Latvia and other eight new EU member states have "transformed themselves into dynamic transition economies… and been successful in attracting foreign direct investment, re-training and improving the skills of their labor forces and [..] these measures have enabled the integration of these countries into the EU framework" (Strasser, Kutenicova, 2006, 8). Yet in spite of overall success and continued general improvement of life conditions, Latvia's GDP *per capita* in 2008 was 14,000 €, which is just 55.7% of EU average (Eurostat, 2008). Another problematic factor is a sharp economic recession – after the rapid increase by 11.9% in 2006 and 10.2% in 2007, country's GDP has decreased by almost 20% in 2009, which has forced government to make severe budget cuts in January and June, and ask for financial aid from International Monetary Fund and European Commission. Meanwhile, the current official unemployment is 18.4 % and it is expected to grow.

The transparency guarantees, defined by Sen as the freedom to deal with one another under guarantees of disclosure and lucidity, are not always in place. In many cases, the public is locked out of the participating in reviewing financial and business agreements, even when decisions involve spending public money or making policy decisions. On the other hand, both the efforts of Corruption Prevention and Combating Bureau and NGO "Transparency International Latvia – *Delna*" have contributed much to reinstatement of such guarantees. Still, due to the insufficient level of transparency the level of corruption in public sector is relatively high, which negatively affects the social opportunities. Latvia's score in the *Corruption Perceptions Index* is 5.0 out of 10.0 points, which is 8th worst among EU countries (Corruption Perceptions Index, 2008). That, however, represents a 1.6 point improvement since 2001.

Protective security is ensured by the Ministry of Interior of Latvia, which supervises state police, security police, fire and rescue service, border guards and other offices. In recent budget cuts, the Ministry has lost 22% of the original funding, thus raising justified concerns about the impact on its operative capacity. Hopefully these concerns will not prove right over the next few years.

Developmental conditions give rise to the second domain in Hyder *et al's* framework – the enabling conditions. The turbulent period of economical and political changes has left a major impact on the ethical climate in Latvia and other post-Soviet countries – a shift of values during a short time has resulted in instability and relativity of both moral and legal norms. As it is put by Lithuanian sociologists Irayda Jakusovaite and Vaida Bankauskaite, „the traditions in democracy in these countries are weak and mistrust in the country's legal system is common. Newly adopted laws are not capable of changing the patterns of people's behavior immediately, despite their rhetoric to do so" (Jakusovaite, Bankauskaite, 2007, 424). The rise of western standards in medical and research ethics was simultaneously contradicted by tradition of hierar-

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chical paternalism, inherited from Soviet medicine, and pragmatic selfishness of the newly introduced free market economy. Thus, current moral standards represent an odd mixture of not yet rooted new values and not yet extinguished old traditions. Hopefully with the arrival of a new generation of medical specialists who have received an appropriate ethical education, moral norms will acquire proper authority, becoming fundamental constituents of everyday practices.

Similarly, to other CEE countries, one of the reasons behind ethical problems in Latvia is lack of civil society activities. One of the conclusions of the study on the civil society in Latvia is that "Although the law provides ways for being involved in policy development, only a small proportion of residents and non-governmental organizations are involved in policy development with local governments, ministries and the Parliament. There are few positive examples of advocacy. Each unsuccessful attempt dissuades from further involvement" (Vilka, Strupiss, 2004, 67).

Indicators of human capital are the cohort of trained people and healthy working population. Regarding the first, it appears that the proportion of students in tertiary education in 2008 was 5.5% of the population, which is higher than the EU average. The problem thus is not the quantity, but the quality of educated specialists: "results of the *FICIL labor market study 2008* clearly showed that workforce quality in Latvia requires immediate attention and is a critical aspect for the country's economic growth and welfare." (Greiskalns, 2008, 10). Regarding the population health, the major indicator is average life expectancy. In 2009, it was estimated to be 72.3 years, which is seven years below EU average (UNDP, 2009). The main causes of earlier mortality are noncommunicable diseases and lifestyle factors. 2006 survey of the economically active population (aged 15 – 64) indicated that substantial alcohol abuse is "a very prevalent risk factor in Latvia, associated with many health problems" (Pudule *et al*., 2007, 7). Smoking and excess weight are other risk factors – 47% of men and 18% of women are daily smokers, and 45% of the respondents are overweight or obese.

In response to the increasing demands by EU institutions, as well as local media and NGOs expressed for public accountability the access to the government information is improving and cooperation is taking place between state institutions and civil society organizations. Despite some successful cases of policy making and implementation, the overall accountability has hardly improved over the years because "a latent conflict exists between increasingly accountable administrative activities and continuously non-transparent political decision-making" (Tisenkopfs, 2002, 2). This has resulted in widespread distrust in basic transactional processes in particular, and in politics in general which, in turn, has created an air of disillusionment in democracy as such and raised nostalgia for authoritative rule.

The freedom to determine the boundaries of personal risk is defined by the Latvian constitution, which includes all basic human rights, and Latvian legislation regarding participation in research, which is harmonized with EU laws and regulations. Thus, as far as person is autonomous and informed about the foreseeable risks, this person is free to make his or her decision whether or not to engage into risky practices under consideration.

Sufficient enabling conditions, in turn, create a receptive environment for the third domain in Hyder et al's framework – a national and regional strategy for research ethics. Basic features of RECs and their legal regulation and relation to relevant national bodies are illustrated in the *Figure 2* below.

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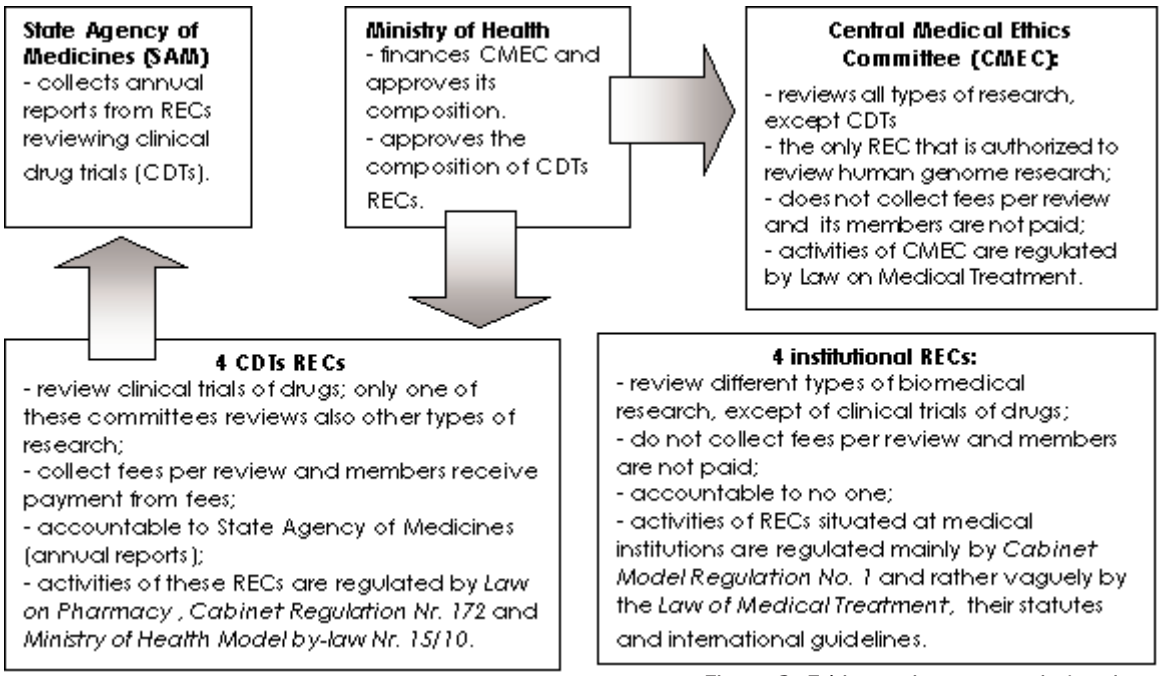

Figure 2: Ethics review system in Latvia.

CMEC occupies a special position among the committees and is governed by specifically designed law – Cabinet Regulation No. 9 "Statutes of Central Medical Ethics Committee", issued in 1998 and amended in 2003 and 2009 to introduce the changes in its membership. The functions assigned to CMEC are following: (1) to "evaluate the compliance of new medical technologies, biomedical research involving human subjects (henceforth – biomedical research) with the norms of medical ethics" (Article 4.5), and (2) to "evaluate the compliance with principles of ethics in genetic research, creation of genome data base and the activities of the chief processor" (Article 4.11).[2] Besides reviewing research protocols, the committee also has to consult governmental, municipal, medical and other institutions about the compliance of regulations issued by those institutions to the norms of medical ethics; facilitate the inclusion of medical ethics in the study programs of social medicine, psychology and communication; develop draft laws and other regulations regarding the ethics of biomedical progress; initiate the revocation of medical certificates in case of breach of ethical norms; cooperate with institutions interested in the ethics of biomedical progress (both Latvian and foreign); issue resolutions regarding research and biotechnologies of both national importance and international scale; educate the population, advise on the ethical issues of biomedical progress, and consult ethics committees reviewing biomedical research.

Other Latvian RECs can be divided into two large groups according to the field of their activity. The first group consists of those RECs that review clinical trials of drugs and pharmaceutical products. They are regulated by *Law on Pharmacy*, which states that "clinical trials of medicinal products, involving humans as subjects of the investigation, may not occur if the permission of a clinical medicinal product investigation ethics committee has not been received" (Section 26). The same requirement is expressed in *Cabinet Regulation No. 172* (Article 39) regarding the conduct of clinical trials and non-interventional trials. With this new regulation, which implements the *EU Clinical Trials Directive 2001/20/EC*, these RECs have become much more independent. Prior

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to its issuance after receiving the opinion from CDTs RECs, research protocols had to be submitted also to the State Agency of Medicines to receive the final approval. Now, according to the regulation, "The sponsor may submit the application simultaneously to the Ethics Committee and the State Agency of Medicines," (Article 69) and the trial can start only after the first gives a favorable opinion and the second has issued the authorisation. Decisions of clinical drug trial REC's (as well as their activities in general) are not overseen by SAM, but these committees are obliged to report to it every case of negative assessment of research protocols. Also, according to the *Model by-law No. 15/10* (Ch. II, Par. 4.18), they are obliged to annually submit to the SAM the list of all reviewed applications for drug clinical trials and drug administration surveillance trials.

The second group of RECs, reviewing all other kinds of research appears to be regulated by *Cabinet Model Regulation No. 1* (issued in 1998 and still in force), which is issued according to the *Law on Medical Treatment*. According to the law, these are RECs functioning within medical treatment institutions as "advisory bodies established for resolving problems of medical ethics" (Section 13). They are not specifically defined as research ethics committees but as "medical ethics committees" that "shall examine ethical matters related to the activities of medical practitioners and new medical technologies" (Section 14). Other regulations are their own statutes and international guidelines.

As one can see, Latvian legislation on ethical review in some areas of research is much more elaborate than in others. Particularly, laws for CDTs RECs contain clear and strict requirement that clinical drug trial can begin only after receiving approval of ethics committee. The same can be said about laws for genetic research too. Legislation for other kinds of research, in contrast, is unspecific and vague. As a result, there is imbalance in the force of the decisions – the ethics committee's opinion is legally binding in the case of CDTs, while for other kinds of studies the opinion is just a recommendation. The situation is especially peculiar with CMEC, whose decisions about genetic research are legally binding, while decisions about other kinds of research are not.

Another aspect of this situation is that some types of human research, for example, genetic research is reviewed very thoroughly by two institutions – Genome Research Council, and the Central Medical Ethics Committee, – while some others, such as sociological, public health or anthropological research, are not reviewed at all.

Latvian RECs contain 7 – 13 members, and again differences in size are determined by what kind of trials they review. Before the Statutes amendment of 2009, the CMEC was the largest committee in Latvia, consisting of 14 members. Now it is downsized to 12 – a chairperson and 11 members. In the current composition of CMEC Latvian National Human Rights office is not represented anymore because it was closed in 2007, and instead of two now there is just one representative of Latvian Professional Medical Persons Organizations Union. Besides the ones mentioned, the committee includes representatives of following institutions: Ministry of Health, Riga Stradins University, State Institute for Experimental and Clinical Medicine, Council of Science of Latvia, Nurses Association, Pharmacists' Association, Disabled Persons Association, Pensioners' Federation and Evangelical Lutheran Church of Latvia. No explanation is provided why exactly these institutions were selected for representation in this relevant national body.

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Model by-law No. 15/10 requires that CDTs RECs must consist of at least 9 members; the largest one is REC of the Latvian Institute of Cardiology consisting of 13 people. According to the law, among them should be at least 2 professionals without medical educational. Data from the publications and questionnaires revealed that such professionals are journalists, police officers, biologists, lawyers, academics, representatives of the government Ministries, of NGOs and of private enterprises. Other legal requirements are that 2 members must be independent of the institution where trial-related activities are actually conducted and all of them must be adequately qualified and experienced to be able to assess the scientific and ethical aspects of the clinical and drug administration surveillance trials, and that both sexes must be represented.

RECs dealing with other kinds of research are required by *Cabinet Model Regulation No. 1* to include at least 6 members. In practice, they consist of 7 – 9 members, and that of Riga Stradins University is the largest. Besides medical professionals, these committees also include representatives of religion, engineers, parliament members, and diplomats. The only trained ethicist works in REC of Riga Stradins University.

Budget and payment can be very sensitive topic in low-income and middle-income countries. For example, when a representative of REC for Clinical Trials of Drugs and Pharmaceutical Products of P. Stradins Clinical University Hospital was approached to fill in the questionnaire about the composition and functioning of the committee, the first response was positive. But as soon it was revealed that the questionnaire includes financial issues too, any further cooperation was declined on the grounds that "one should not count money in another's pocket". In contrast, REC of the Latvian Institute of Cardiology did not see any problem in revealing its annual budget, which is between 3000 and 4000 Ls (€ 4270 – 5690) per year.

The annual budget of CMEC paid from the budget of Ministry of Health is Ls 5000 (€ 7114) which is barely enough to cover for rent and office expenses, thus, members' work is not compensated. CDTs RECs are financing themselves from the fees that vary from € 14 for review of changes in protocol to € 640 for assessment of international multi-centered clinical trial application and pay salaries to the members. RECs situated in institutions have no official budget, material and technical operation is ensured by the host institution. According to requirement of *Cabinet Model Regulation No.1*, neither the work of chairperson, nor a member is compensated. It can be concluded, thus, that research ethics is definitely not a budget priority in Latvia.

Research revealed that in low-income and middle-income countries the well-intended requirement for no pay to institutional REC members can in fact decrease the quality of review: when asked about the main problems in functioning of the committee, in one of the returned questionnaires it was noted that the lack of material reinforcement, on par with the fact that members are quite often very preoccupied with their paid jobs, is leading to lack enthusiasm and low work motivation.

The issue of investment in training and capacity building of RECs members is also problematic – laws and regulations do not even address this issue leaving it entirely up to committees themselves. REC of State Agency for Tuberculosis and Lung Diseases indicated in the questionnaire, that their capacity building activities consist of "self-education, materials prepared by the colleagues, and materials available on the internet." At the Latvian Institute of Cardiology REC, attendance of high-level international courses, seminars, and conferences was indicated. Among the members of RSU committee is a well known author and a professor of humanities who is teaching Medical and Research Ethics, but little is known about capacity building activities of

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other members. Representatives of the other RECs have been noticed attending seminars and conferences related to ethics review.

The national strategy for research ethics distinguishes between clinical drug trial review and review of other types of research. Another of its features is that CMEC is seen as the central and the most important element of the whole system. A newly amended version has added to the list of its tasks another very important function: besides the tasks mentioned above, CMEC also has to "coordinate and methodically supervise the operation of ethics committees reviewing biomedical research…"[3] (Article 4.9) However, instead of being the strongest link that holds the system together and makes it work effectively, in reality CMEC is the weakest one. Due to the lack of financing and motivation of its members, it is not able to accomplish many of its tasks.

An examination of legislation and practices of RECs functioning in Latvia indicates a lack of any general strategy, showing rather ill-considered attempts to implement international practices in response to the needs of particular types of research, such as clinical drug trials and genome research. Some of the important aspects, such as financing, affiliation, and qualification of RECs members, as well and training are described too vaguely, some of them, such as accreditation and audit are omitted altogether. Lack of proper legislation and adequate financing system has effectively weakened the system as a whole, rendering many functions assigned to the key element of the system – Central Medical Ethics Committee – unrealizable in practice. Thus, to discuss the problems of national strategy for research ethics largely means to discuss the lack of thereof.

3. Institutional commitment, quality of review and investigator's conduct

Due to the lack of direct, comprehensive, and reliable information, first three issues in the fourth domain in Hyder's framework – institutional commitment – can currently be described only by making inferences from the laws, guidelines, and statutes of the RECs. Thus, regarding conformity to the national legislation, it is indicated in the statutes of the committees that they are functioning according to the *Law on Medical Treatment*, and/or the *Law on Pharmacy*, as well as to the list of international declarations on research ethics and guidelines on good clinical practice.

According to Hyder *et al.*, the priority that institutions give to the responsibility for ethical review can be judged by appropriateness of the structures and procedures for review and emphasis on ethical conduct within the institution. As it was noted when discussing national laws and guidelines in Chapter 2, organizational structures dealing with ethical review in medical and educational institutions are "medical ethics committees". The Cabinet Model Regulation No. 1 (issued in 1998 and still in force) indicates that among the tasks of such committees is "to evaluate the compliance of the new medical treatment technologies to the ethical norms and to report the outcome to the administration of the respective institution." (Article 4.3) Organizational procedures of these committees are also described in the *Model Regulation No. 1*. Committee members elect one of them to be a chairperson whose duties are to compose the agenda and organize the documentation and process of review. Committee meetings are gathered, prepared, and protocoled by the secretary. The quorum is 2/3 of the members; meetings are open for public, unless the issue is related to the professional conduct or the privacy of patient, in which case interested parties are invited

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and meeting and it is closed. The final decision is reached by majority vote and if the chairperson has the casting vote. Decisions are sent to the interested parties within three days, and can be appealed within two weeks.

Organizational procedures for the clinical drug trial committees are described in *Model by-law No. 15/10*. These committees must include at least 9 members, and are lead by the chairperson who is preparing the agenda, organizing the meetings and all other activities. The meetings are closed unless it is decided otherwise; decisions are taken if more than 1/2 of committee members are present by a simple majority of vote and chairperson has the casting vote.

All biomedical human research, including student research, has to undergo ethical scrutiny. Although review of student research is not addressed in law, it is required either by regulations on student's research activities as in Faculty of Biology of University of Latvia, or by regulations on defense of student's thesis as in Riga Stradins University. However, legislation does not require reviewing non-biomedical human research, (such as psychological, sociological or anthropological studies) if it takes place outside the clinical settings, so these studies are reviewed only if the researcher voluntarily decides to submit the project to the REC. Accordingly, the level of protection from research risks varies depending on the type of research – participants have more protection in biomedical human studies and less protection in non-biomedical studies.

It can be concluded that basic structures and procedures are in place, which means that the ethical review is assigned certain priority, but it has not reached the optimal level yet. Also, promotion of ethical conduct in research is not mentioned in statutes of either kind of RECs, which leads to the conclusion that the function of Latvian ethics committees is rather seen as safeguarding against misconduct, not the promotion of ethical conduct.

Another important aspect of institutional commitment is quality of the review. First component of its components – independence of committees – is ensured in both legislation and statutes of RECs, therefore formally they are completely independent. On the other hand, current system of financing where the fees for the review of clinical drug trials are paid directly to the committees raises substantiated concerns about the possible conflict of interest. The fact that some clinical drug trial committees were particularly unwilling to reveal any information about their financing only increases these concerns.

The second component is the quality of scrutiny. *Model by-law No. 15/10* on clinical drug trials contains the standard list of criteria, such as scientific significance, balance of risks and benefits, qualification of personnel, quality of equipment, as well as review of informed consent sheet, research protocol, and investigator's brochure. *Model Regulation No. 1* on ethics committees does not provide any such criteria, but the statutes of the institutional committees refer to the common standards for good scientific practice and protection of research participants. Quality of scrutiny can also be related with the workload of Latvian RECs. The number of annually reviewed protocols is not big, ranging approximately between 15 – 30 protocols per year. Meetings of the committees are either monthly or depending on necessity. Normally committees have enough time to thoroughly scrutinize and debate the submitted protocols. The only known exception is the REC of Riga Stradins University which has much bigger workload: 400 – 450 protocols per year. Approximately 4/5 of them are unsophisticated protocols of student research, for which the common practice is to distribute among the members of committee who then prepare the decisions. If no

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complications are found, voting takes place without debate, which allows having more time for debating the complex and problematic protocols. The precise number of approved protocols is known only regarding clinical drug trials. According to the annual report of State Agency of Medicines, in 2008 approval was given to 88 protocols – in comparison to 85 protocols in 2007 (State Agency of Medicines, 2008, 16). Although the cases of disapproved protocols are reported to SAM, when they were contacted, they refused to reveal this number because of "ethical reasons," One wonders what would be the ethical reasons for a state institution to withhold basic statistics thus breaching the requirement for transparency and public accountability, spelled out in its own code of ethics. Exactly how many other kinds of research protocols do or do not receive approval is not known because official statistics of this kind simply do not exist. The information about approved protocols gathered during our research is not complete – some RECs agreed to cooperate, some did not. Such data allows just for a very general conclusion that apparently most of the submitted protocols get approved either straight away or after researchers have amended them on request of the RECs.

Cabinet Regulation No. 172 on clinical drug trials requires that "Both the risk threshold and the degree of distress have to be specially defined and constantly monitored." (Article 31.6) The function of monitoring clinical drug trials is assigned to Clinical Trials Department SAM. Also, according to *Model by-law 15/10* CDT RECs can "apply to SAM with suggestion to suspend the research either temporarily or permanently" (Article 5.4) Legislation on other kinds of research does not contain requirement for monitoring, thus the international guidelines, such as *Declaration of Helsinki* (2008), can be applied here: "The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events." (Article 15.)

The final domain in Hyder et al's framework is that of investigators' conduct. Unfortunately, no research has been conducted in Latvia to study the aspects of investigators' conduct therefore this domain can be outlined very roughly – as a product of other elements in the model. As it was noted earlier, many of the developmental and enabling characteristics are common for Central and Eastern European countries, thus the observations of colleagues from other countries can be applied to Latvian situation as well.

Investigators' personal goals and ambitions, as well as the opportunities for satisfying them, are strongly influenced by the economic conditions. As Eugenijus Gefenas has put it, "researchers in the region have a relatively stronger incentive to conduct clinical trials proposed by pharmaceutical companies because benefits offered in the transition societies are relatively much higher than in Western countries. For example, the payments received by the researchers in remuneration for conducting a clinical trial could very well exceed their regular salaries, especially if we add such hidden types of remuneration as the reimbursement of expenses for overseas conferences and the like" (Gefenas, 2004, 124).

Investigators' respect for government and willingness to follow rules is undermined by lack of trust in basic transactional processes and rule of law in general, because high-profile corruption scandals provide multiple examples of state officials and politicians breaking the law in what Christopher Cviic calls "an unprincipled struggle for power combined with personal enrichment" (Cviic, 2006, 12). This, in turn, has negatively influenced Latvian researchers' respect for ethics review committee and research ethics review process: "For example, there is anecdotal evidence that in some CEE

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countries ethical approval is still being obtained "retrospectively" (that is after the experimental part of the research project had already been finished) or a REC meeting is not actually taking place but rather the secretary of the "paper" committee collects the signatures of its members" (Gefenas, 2009, 128). Another equally anecdotal practice would be "probing" for which of the available clinical drug trial RECs would be the best to submit the research protocol and receive approval. On the other hand Gefenas stresses that after the recent developments in legislation and research ethics infrastructure the occurrence of such severe breaches of regulations in new EU member states is very unlikely.

Some idea of what could be investigators' perspective on the importance of research ethics review can be drawn from one of the returned questionnaires, where it was indicated that among the main problems in functioning of the REC is investigators' vague understanding of what is the nature of ethical review procedure. Of course, such incompetence cannot be generalized to describe all Latvian researchers, many of whom have received very good ethical training; however, it seems to be quite common. Perhaps that is also why the other problem indicated by the same committee was lack of contact with educational institutions.

Yet another problem is the widespread misconception about ethics being vague and incoherent, something more connected with one's moral intuition than with the reasoning and argumentation. Equally widespread is the perception that ethical review is a burden and unnecessary complication that is hindering the research. At the foundation of both misconceptions is the lack of information about contemporary research ethics, which is a well-reasoned and methodical assessment of the ethical aspects of scientific research, designed to foster responsible conduct, thereby being an integral part of good scientific practice in general, and especially of research involving humans.

Finally, no information is available regarding investigators' advocacy for research ethics review, peer influence, and setting a positive example. And – similarly – nothing in particular can be mentioned about the cases of research misconduct because there are no public scandals either. It can be concluded thus that the discourse of research ethics in Latvia is still in very early stage of development.

Conclusions and suggestions

Despite the radical social, political, and economic changes that took place since the collapse of Soviet Union in last two decades, Latvia can still be characterized as a medium-income country. It means that the developmental conditions for research the ethics review are not as favorable as in more developed countries – material incentives of both RECs and the researchers are one of the most serious obstacles in achieving a better quality of review.

Current developmental conditions are the reason for absence of several crucial enabling conditions such as authority of moral values, developed mechanisms of civil society, and a climate of transparency and public accountability. Among the main problems resulting from that is scarcity, incompleteness and, sometimes, complete lack of up-to-date information regarding RECs and their work. The fact that two RECs were "discovered" almost accidentally when reporting the preliminary results of the comparative study speaks for itself. Also, unwillingness to cooperate with researchers expressed by some RECs and related institutions has lead to an important secondary

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conclusion: more often than not even the most justified inquiries about the work of RECs system are perceived not as a part of transparency policy and normal public relations, but as intrusive curiosity or masked attempt to inspect and report possible misconduct.

Another problem is the absence of clear and well-planned strategy for research ethics that would help to establish the priority of ethical review not just formally, but also in practice. Such strategy is needed to increase transparency and accountability of RECs system by collecting and publishing information about its structure and operations, and to amend vague and incomplete legal regulations regarding the procedures of audit, qualification, and training of REC members.

Revision is also needed for the current system of financing that has proved inadequate in so many ways. Firstly, due to the lack of proper funding CMEC – a national body which plays a key role in the whole system – is unable to perform most of its functions, including the newly assigned task of supervision of other RECs. Secondly, in case of CDT RECs the fees for review are paid directly to the RECs thereby creating a constant threat to the independence of the review. Thirdly, as it was indicated in questionnaire received from one of the institutional RECs, lack of material reinforcement causes low work motivation and enthusiasm, as well as makes it difficult to ensure the presence of all members at the committee meeting because most of them are very busy in their paid jobs. Abovementioned factors are problematic not only in and of themselves, but also because they negatively influence investigators' respect for research ethics committees and the process of ethics review, as well as their willingness to follow the rules of good conduct.

It must be noted that the criticism towards current state of affairs, expressed in this article, should not be understood as an attempt to dismiss the tremendous progress and positive change that Latvia has achieved in the field of human research ethics. After regaining the national independence, Latvia has successfully established and continually developed a system of RECs that would implement the international requirements for research ethics review. Therefore, this article constitutes an attempt to fill in at least some of the vast informational gaps and to assess the complex challenges associated with structure and functioning of Latvian research ethics system against the background of the most relevant social, political, and economic factors. Hopefully the factual information, as well as the criticism and suggestions expressed here will help to promote change and further improvement.

Acknowledgments

I am very grateful to my colleague Signe Mežinska, with whom we gathered and performed primary analysis of the information about Latvian research ethics system. I am also greatly indebted to my colleagues from the *Advanced Certificate Program in Research Ethics in CEE Countries,* in particular to Martin Strosberg, Eugenijus Gefenas, and Andres Soosaar who provided their thoughtful insights and suggestions for the current article.

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Notes

1. Currently two more articles on the results of the study are being prepared. First one describes historical and structural aspects of ethics review systems in Baltic States (Estonia, Latvia and Lithuania). It is called "20 Years of Human Research Ethics Committees in the Baltic States" and is already submitted for publication into *Developing World Bioethics*. The second is analysing differences in legislation and lack of equivalence in review of the human research in Baltic States.

2. *Cabinet Regulation No. 692* "Procedure of Genetic Research" (2004) reinforces this requirement by stating that in order to commence genetic research "favorable assessment of Central Medical Ethics Committee regarding compliance with principles of ethics" (Section 2.2.) must be received.

3. It is important to note, that amendment of 2009 of the Statutes of CMEC is the first example of the term "ethics committees reviewing biomedical research" is actually used in the language of Latvian law. Law on Medical Treatment refers to them as "medical ethics committees", while Law of Pharmacy refers to them just as "ethics committees".

Dilemata, año 2 (2010), nº 2, 55-69 ISSN 1989-7022