

# Draft Final Report

## Provision of Support for Producing a European Directory of Local Ethics Committees (LECs)

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Contractor

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# Contents

## Foreword

### I. Introduction

- A. Professional scope
- B. Geographical scope
- C. Aim
- D. Methodology
- E. Deliverables

### II. Medical Research and the Development of Research Ethics Committees

- A. Historical background
- B. From ethics to law
- C. Tasks of the committees

### III. Countries' Profiles

- A. EU Member States
  - 1. Austria
    - a) Historical background
    - b) Legal framework
    - c) Current situation
    - d) References
  - 2. Belgium
    - a) Historical and legal background
    - b) Discussion
    - c) References
  - 3. Denmark
    - a) Historical background
    - b) Legal framework
    - c) References
  - 4. Finland
    - a) Legal framework and current situation
    - b) References
  - 5. France
    - a) Historical background and legal framework
    - b) Translation into action and discussion
    - c) Conférence nationale des CCPPRB and Avis n° 79 of the CCNE
    - d) References
  - 6. Germany
    - a) Legal framework
    - b) Historical background

- 
- c) References
  - 7. Greece
    - a) Historical background, legal and institutional framework
    - b) Current practice
    - c) Discussion
    - d) References
  - 8. Ireland
    - a) Historical background and legal framework
    - b) Current situation
    - c) References
  - 9. Italy
    - a) Historical background and legal framework
    - b) Current activities
    - c) References
  - 10. Luxembourg
    - a) Legal framework
    - b) Current situation
    - c) References
  - 11. The Netherlands
    - a) Historical background and legal framework
    - b) Current situation
    - c) References
  - 12. Portugal
    - a) Historical background and legal framework
    - b) Comments
    - c) References
  - 13. Spain
    - a) Historical background and legal framework
    - b) Comments
    - c) References
  - 14. Sweden
    - a) Historical background and legal framework
    - b) References
  - 15. United Kingdom
    - a) Legal framework
    - b) Historical background
    - c) Composition of research ethics committees and procedures of ethical review
    - d) Regional multi-centre research ethics committees
    - e) Discussion and comments
    - f) References
  - B. EU new Member States
    - 1. Cyprus

- a) Legal regulations
- b) Historical background and local institutions
- c) References
2. Czech Republic
  - a) Legal regulations
  - b) Historical background
  - c) Public awareness and perception in the scientific community
  - d) References
3. Estonia
  - a) Legal framework
  - b) Historical background
  - c) Current situation
  - d) References
4. Hungary
  - a) Historical background and legal framework
  - b) Practice of ethical review
  - c) References
5. Latvia
  - a) Legal and institutional framework
  - b) Historical background
  - c) Current situation
  - d) Reference
6. Lithuania
  - a) Legal framework and institutions
  - b) Historical background and current situation
  - c) Reference
7. Malta
  - a) Legal regulations
  - b) Current situation
  - c) Reference
8. Poland
  - a) Legal framework
  - b) Current situation
  - c) References
9. Slovakia
  - a) Historical background and legal framework
  - b) References
10. Slovenia
  - a) Legal framework
  - b) System of ethic review
  - c) Reference

---

### C. Candidate countries

1. Bulgaria
  - a) Legal and governmental regulations
  - b) Reference
2. Romania
  - a) Legal regulations and current situation
  - b) References
3. Turkey
  - a) Legal framework
  - b) Historical background and current committees' system
  - c) References

### D. Associate countries to the 5<sup>th</sup> and 6<sup>th</sup> Framework Programmes

1. Iceland
  - a) Legal framework and relevant institutions
  - b) Current activities
  - c) References
2. Israel
  - a) Legal framework and ethical review system
  - b) References
3. Liechtenstein
  - a) Legal situation and ethical review
  - b) Reference
4. Norway
  - a) Legal framework of ethics committees' system
  - b) Current situation
  - c) References
5. Switzerland
  - a) Historical background
  - b) Legal framework
  - c) Ethical review procedures of biomedical research on human beings
  - d) References

## IV. General Findings

- A. Establishment, affiliation and independence
- B. Local competence
- C. Competence for different kind of research on human beings
- D. Competence for ethical review and scientific assessment
- E. Membership
- F. Staff

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G. Education

H. Public awareness

I. Interaction between Local Ethics Committees and national institutions

J. Procedure for Multi-Centre Trials

## **V. Conclusions and Recommendations**

## **VI. Appendixes**

Appendix 1. Database of European Local Ethics Committees

Appendix 2. Bibliography

Appendix 3. List of Experts

Appendix 4. Questionnaire

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## Foreword

Will follow

## I. Introduction

In the dialogue between science and society in the field of medicine and medical research, hardly any other institution is as characteristic as the establishment of ethics committees. The ethics committees' decision-making process is especially significant in the area of the transition from the traditional reflection on the medical action's moral appropriateness to current developments in biomedical ethics. The term of ethics committees itself, however, is both ambiguous and multi-faceted. There are, at least, three distinctive types of ethics committees.

Firstly, at a local or regional level, there are committees, whose mandate is to examine the research projects, involving research on human beings; most commonly these institutions are called (research) ethics committees. The second type of committees, which are also established on a local level and are widespread both in Europe and in the United States of America, are so-called "clinical ethics committees"; these kind of committees are mandated to counsel and advise not only on research-related issues, but also and especially on treatment-related decisions. In this context, decisions on the choice of therapy, as well as the questions on the limitation of the therapy are of special significance. *Last*, but not least, there are national ethics councils, whose prime task is to counsel and advise governmental bodies on certain legislation questions regarding biomedical issues. Recently (but as early as 1983 in France – Conseil Consultatif National de l'Éthique (CCNE)), national ethics councils were rooted as permanent institutions and they are now also mandated to provide advice on moral issues in the entire field of biomedicine.

All the three above-mentioned types of councils or committees have several common characteristics. One of them is the fact that all ethics committees operate in the field, or at least part of the field, of health care and biomedical research, whenever decisions, involving moral differentiation of good and bad are at stake. Another common feature is that all ethics committees are established as bodies with the task to form judgments at a level, which goes beyond the individual, yet at the same time narrower than that of the entire group of those concerned: The number of members of all ethics councils and committees is as optimal as the face-to-face debate is possible at all times during the discussions. Finally, the primary goal for all ethics committees is to protect human beings in the context of research, health care and biomedical progress.<sup>1</sup>

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<sup>1</sup> Beside that there are also committees dealing with the welfare of animals, especially in research.

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However, there are also significant differences as the short description indicates, which will not be elaborated on here.<sup>2</sup>

#### *A. Professional scope*

The object of the study is the (Research) Ethics Committees (ECs), i.e. only the first of the three types mentioned above. In the context of this study “ECs” means all institutional and local or regional bodies, which are responsible for the ethical evaluation of research projects involving human beings. We have also contacted national ethics committees in order to have a broader picture of the national system: We have learnt whether national ethics councils have legitimacy and how they use their competence to supervise activities of local ethics committees, or if they are only legitimised to give advice or have no control at all over EC’s work. Ethics committees at the national level are especially important in those countries, where they act as the central research ethics committee or as an appeal institution.

#### *B. Geographical scope*

The target countries of the study are the EU Member states: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Portugal, Spain, Sweden, UK; the EU new Member states:, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Malta, Poland, , Slovakia, Slovenia; the EU candidate countries: Bulgaria, Romania, Turkey and associated countries to the 5<sup>th</sup> and 6<sup>th</sup> Research Framework Programmes: Iceland, Israel, Liechtenstein, Norway and Switzerland.

Therefore, the scope of the report is aiming to collect the reliable information about the situation and the background of research ethics committees in 33 countries.

#### *C. Aim*

The main aim of the report is to gather information about research ethics committees, to set certain criteria and to analyse ECs’ activities. Thus, this European report is to be seen as a first step to:

- to provide (as complete as possible within given restraints of resources) a directory of European ethics committees (ECs),
- to analyse the similarities and differences among the European ECs,
- to analyse the main challenges and difficulties in the functioning and activities of these committees,

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<sup>2</sup> Byk, Mémeteau 1996, Kettner 2002, Fuchs 2002.

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- to compare the findings/ analysis on European ECs with the available relevant information from the USA, Japan, and India,
  - to provide examples of excellences among European ECs,
  - to draw recommendations for possible cooperation among European ECs and improvements in their activities,
  - to make suggestions for further studies and activities.

Since the landscape of ethics committees is permanently changing, the establishment of a complete list of all relevant committees is nearly impossible. Besides, in some countries there is no clear procedure for ECs' accreditation and the exact number of the existing committees is therefore not known. Nevertheless, the detected amount of ECs in Europe was much higher than expected. One of the reasons of such an outcome (David?) is that there is a tendency to establish ethics committees in each country's hospital and sometimes – *ad hoc* committees for a specific clinical trial. Another reason is the mixed function of clinical and research ethics committees, as is observed, for instance, in Italy.

#### *D. Methodology*

Various sources were used with the purpose of collecting relevant information on the work, mandate and the problems of ECs in a rather short period of time: the existing national surveys, legal texts, articles from journals, working papers and handbooks, material from the world-wide web. Additionally, in each country of interest relevant experts have been contacted, who had provided valuable information on ECs (including contact information and legal background). The idea was also to obtain some insight information from the members of ethics committees, members of their staff, and experts in the field of ethical review of research and in the field of medical law.

Due to reasons of time restriction, the Directory of Ethics Committees is not comprehensive and cannot be acknowledged as complete. However, it could be a part of discussion among representatives of local ethics committees from different countries whether a comprehensive directory is feasible and if it is really needed at all.

#### *E. Outline*

Following some general remarks on the historical background of the research ethics committees' establishment, the process of legislation regarding ethical review and the tasks of the committees, the third part of this report contains each of the countries' profiles, where an overview is provided of the committees' system in each

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target country and the relevant literature is listed, concerning ethical review of research on human beings in that country. The countries' reports are followed by a chapter on the general findings. The final chapter summarises the conclusions and recommendations.

The Report is accompanied by several Annexes. The most important annex (Annex 1) is the Database of European Ethics Committees. The database contains the 818 identified ECs and presents the address, affiliation and some other statistical data of each EC that was available.

Another annexe is the List of identified and used Literature (Annex 2).

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## II. Medical Research and the Development of Research Ethics Committees

A principal goal of European policies in the field of medical research and clinical trials is the protection of human subjects, who participate in clinical trials. Since the General Assembly of the World Medical Association in Tokyo in 1975, the institution and the work of research ethics committees are seen as the essential means to ensure protection. Meanwhile these committees are also seen as the guarantors of high scientific quality and protectors of researchers and their institutions. The Directive on Good Clinical Practice, which must be implemented in national law of each EU Member state, states that clinical practices involving human subjects need the approval of local ethics committees. This will certainly have a significant impact on the procedures of the multi-centre trials, especially at the international level. However, it is not yet really clear, how and in what sense these new regulations will influence the role of ethics committees in the future. One of the reasons for this future uncertainty is the current unawareness of the existing differences among the European committees with respect to their mandate, composition, legal status and functions.

To understand these differences it is not only necessary to be aware of the cultural diversities, but also to note in general the different historical backgrounds in medical research ethics.

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### *A. Historical background*

On the occasion of the 20<sup>th</sup> anniversary of the scientific ethical committee system in Denmark Povl Riis described the general historical background as follows:

“The history of the scientific ethical system has long-reaching roots, even in that part of the events familiar to me from personal experience. In accordance with the concept of the duality of scientific ethics, science and ethics, the committee system also has two parallel roots.

One is clinical science, i.e. the emergence of patient-centred science in the 20<sup>th</sup> century. The other is the rediscovered visibility of non-tangible values after the Second World War’s violation of fundamental human rights. [...] In its systematic form, clinical science is no more than about 100 years old. [...] Today we can ascribe the innovation of the methodological umbrella term to two basic principles: one that all evaluation is based on comparisons, the other that the pattern of pathological and life processes constantly varies. In order to take the two principles on board, new tools were taken into the service of medical science. Notions like control groups, drawing lots, blinding of both trial patients and investigators, and the use of placebo preparations were introduced. The new

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methodology necessitated some break with the traditional patient/doctor relationship, wherein dwelt the illusion of a tailor-made investigation and treatment regime for the individual patient. [...]

The second root from recent history was an acknowledgement of the necessary validity of fundamental, non-tangible values – for the patient-doctor relationship, too, particularly in trial situations. This turned into a showdown with paternalism, placing the emphasis on the right of self-determination instead. The requirement for truth imposed on information increased at the same time as the issue was taken up with the medical atrocities of the concentration camps. All this led to both the 1948 Geneva Declaration and the 1st Declaration of Helsinki from 1964. [...] But for a young generation of clinicians interested in research, these initiatives were not sufficient, as judged from the level of hands-on science. The enthusiasm of young doctors led to a revivalist-style initiative, which in turn led to the World Medical Association asking myself and two of my Nordic colleagues, Erik Enger from Norway and Clarence Blomquist from Sweden, to write a new 2nd Declaration of Helsinki.” (Riis 2001)

In some countries state authorities, international and intergovernmental organisations also played a significant role in establishing the important principles to regulate functions and activities of the research ethics committees. For example, in 1974 the US Congress launched the National Commission for the Protection of Biomedical and Behavioural Research; in 1990 the Council of Europe initiated the preparation of the Convention on the protection of human rights and dignity in the sphere of Biomedicine and medical research. Both initiatives resulted in the formulation of important principles for the work of research ethics committees.

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Another considerable example of international co-operation is the Sixth Framework. The current 6th Framework Programme (FP6) established an ethical review of any proposals submitted for funding under FP6 rules. FP6 projects that involve sensitive ethical issues (research on human embryo's, human embryonic cells, human foetal tissues, research on children or persons unable to give consent, use of sensitive personal data, including genetic data; research on non-human primates, etc.) are automatically subject to an ethical review by independent external experts. The ethical review above requires that projects fulfil the national legal and ethical obligations of the country where the research is performed (approval of relevant national authority) and that FP6 rules are fulfilled, including ethics requirements. Therefore while respecting the principle of subsidiarity established in the Treaty, the Commission ensures that research funded under the Framework Programme is in compliance with fundamental ethical principles agreed by Member States as signatories to FP6.

Regardless the ethical review system adopted in FP6, if we come back the work of research ethics committees, at both national and international level, several issues need still to be explored. As for the ethical assessment of research protocols, there

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is a clear need to have a balance between the risks and burdens in such experiments and the interests of the community to obtain new means for therapy, as well as for the development in medical research. We should consider that drugs and medical products are only approved and accepted on the global markets if they meet the requirements of good clinical practice and are approved by the competent research ethics committee. And finally the EU membership aspiring Eastern and Central European countries had reasonable incentives to co-ordinate their legal system and policy-making process with the ones in the EU Member States; as well as the Council of Europe Member States agreed on the necessity to develop their own ethics committee system.

The plurality of roots and the difference in the countries' historical backgrounds resulted in a diversity of a system of research on human beings ethical review. However, the protection of human beings is generally considered as a basic and universal principle. Therefore, initiatives to find common standards were started. Another reason for the need to harmonize the ethics review mechanism resulted from the increased international collaboration in the field of medical research. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in the words of Marie Hirtle, Trudo Lemmens and Dominique Sprumont, is "a consultative structure set up between the European Union, Japan and the United States, and a number of observers including Canada, Australia, New Zealand and South Africa. It works towards providing, among other things, the ICH Harmonised Tripartite Guideline – Guideline For Good Clinical Practice (hereinafter ICH-GCP guideline). The ICH-GCP guideline sets an international ethical and scientific quality standard for drug trials that involve human subjects. The main objective of the ICH-GCP guideline is to facilitate the acceptance of clinical data collected in other countries by these harmonized standards. This should simplify drug approval procedures for research sponsors and could ultimately help to avoid duplicating studies and decrease delays and costs. The approval of the ICH-GCP guideline in May 1996 indicates that the European Union, the United States and Japan are politically committed to harmonizing their regulations. Almost four years after their adoption, we are aware that at least the European Union, Japan, Switzerland, South Africa and Canada either have reviewed their relevant Good Clinical Practice guidelines or applicable regulatory systems, or are committed to do so. The ethics review system of the US has required fewer amendments to conform to the harmonized guidelines. In New Zealand, Interim guidelines based on a preliminary version of the ICH-GCP guidelines were adopted in 1996. The ICH-GCP is becoming the international standard for clinical drug trials involving human subjects." (Hirtle, Lemmens, Sprumont 2000, 265-266)

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### *B. From ethics to law*

Although there have been some legal efforts to regulate medical research since the beginning of the twentieth century, the first institutional review boards and research ethics committees research protocols reviews did not appear before the 1960s and 1970s. Interestingly enough, the first such kind of initiative came not from the state authorities, but was initiated by the research institutions and the World Medical Association. When the research funding organisations and the professional journals enhanced their requirements for the researchers to acquire the official approval for their research from institutional review boards and local research ethics committees, the scientific community's self-commitments to the golden standard of good clinical research had to be anyhow institutionalised. Some European governments, for example the Danish, acknowledged the need to establish the complete system of ethics committees. In other countries, for example France, the establishment of local research ethics committees (*Comités Consultatifs de Protection des Personnes dans la Recherche Biomédicale* (CCPPRB)) became a law (1988) only after some institutions – such as the national medical research institute INSERM and some university hospitals – had already taken steps to set-up national and local ethics committees with a diversity of tasks. In Germany, the Chambers of Physicians and the universities' medical faculties had taken the initiative to establish the committee system and until 1995, when the fifth revision on the *Drug Act* was endorsed, opinions have been divided between those, who preferred the existing self-regulatory system and those, who argued in favour of legal regulation from higher authorities. Most of the legal regulations by the *Länder* empowered the chambers of physicians to decide on all actual questions concerning the detailed tasks, the membership and the procedural rules of the ethics committees. In Belgium the implementation of the European Directive on Good Clinical Practice brings with it the necessity of the first national regulation for the work of research ethics committees. However, in the UK, for example, traditionally there are no laws for research ethics committees: the existing committees are working according to the clear governmental guidelines and decrees.

### *C. Tasks of the committees*

The idea of the Tokyo-Version and the following versions of the Helsinki-Declaration of the World Medical Association was to phrase the binding rules for “biomedical research involving human subjects”. The above-mentioned European Directive is subjecting only the clinical trials. In some of the present study's target countries, legal regulations cover only the area of drug research and research on medical products. In that sense, for instance, in Germany the same committee, which approves or disapproves of the clinical trials for pharmaceutical research, is also responsible to give an advice to a medical doctor, who is also conducting other research on human beings. However, some regional Chambers of Physicians rules

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differ: for some “research on human beings” includes epidemiological studies and for others not.

The loi Huriet in France is the paradigm for a law, which covers research on human beings in a very broad sense. It makes explicit the fact that not only medical doctors and pharmaceutical firms, but also the cosmetics industry and psychologists, who do research on human beings, have to present their research proposals to a competent CCPPRB. However, since 1988 there is an ongoing discussion about the status of Phase 4 studies, as well as the procedure in research with human biological material.

The Edinburgh Version of the Helsinki Declaration added the following: “The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events.” (§ 13) This obligation for the researcher is also mentioned in the European Directive on Good Clinical Practice. It is an open question how this monitoring function could be translated into the daily work of the committees and what it should comprehend. Since the debate between John Robertson and Robert Levine, which was launched in the USA during the 1980s, there is an ongoing discussion if the committees could enhance their functional effectiveness by sending members to the sites when research is conducted for ability to check the compliance or if those measures of ongoing control should be restricted to the special cases, where a non-compliance is expected.

It seems that in those countries, where a system of monitoring ongoing trials is generally foreseen by law, this opportunity was never translated into practice. The effectiveness of such a monitoring system, which is focused on special cases and serious adverse events, depends mainly on the competence and experience of the members of the ethics committees.

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### III. Countries' Profiles

#### A. EU Member States

##### 1. Austria

###### a) Historical background

“Until the early 1980s, pertinent legislation was essentially nonexistent. That situation attracted a substantial volume of clinical research to Austria, because other countries had begun to heavily regulate such activities.

Austria's Ministry of Health (MoH) soon reacted to what it perceived as its overly liberal climate, passing the Austrian Medicines Act in 1984. The law required that a sponsor must obtain a positive opinion from a government advisory body (the cumbersome Drug Advisory Board, or “*Arzneimittelbeirat*”) before initiating most clinical trials. Though well intended, that regulatory process proved exceedingly inefficient and unpredictable, stifling both industry-sponsored and investigator-initiated clinical research. Very quickly, the international clinical trials community shunned Austrian research centres, which resulted in the loss of many industry-related jobs.” (Eichler, Druml 1998)

After 1996, when Austria became a full member of European Union, a new medical act was established and Austria was one of the first EU Member States to fully incorporate the EU's Good Clinical Practice (GCP) guidelines of 1990 into national law.

###### b) Legal framework

Clinical trials in Austria are regulated by two main legal documents. The *Act on Pharmaceutical Products* (*Arzneimittelgesetz*, AMG) regulates all matters regarding drugs, while the *Act on Medical Products* (*Medizinproduktegesetz*<sup>3</sup>, MPG) is subject to those products (besides drugs), which are used in the context of diagnosis or therapy (e.g., an electrocardiograph). The two regulations, besides addressing different sorts of products, essentially coincide in the procedures for handling clinical trials and for the activities of the ethics committees<sup>4</sup>.

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<sup>3</sup> The English translation of the relevant passages – as well as the law's titles themselves – given in this text, by no means is official. The author has taken the liberty to translate the text where necessary

<sup>4</sup> Thus this text will therefore focus on the AMG, giving the corresponding norm of the MPG in parenthesis where applicable

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According to § 2 a (1) AMG clinical trial is a “...*systematic evaluation of pharmaceutical product being administered to a subject and aiming to discover or verify its effects, identify adverse reactions, analyse its absorption, distribution, metabolism and excretion in order to establish its efficiency and safety.*” [The corresponding provision of the MPG is laid down in § 3 (2)].

In this provision, there is no differentiation between clinical research and non-clinical biomedical research. The same rules apply whether the subject is a patient subjected to non-standard therapies or a healthy test person.<sup>5</sup>

In order to conduct a clinical trial sponsor or main researcher has to obtain the opinion of the responsible ethics committee as specified in § 40 (3) AMG [§ 77 (1) MPG]. Note that for the trial to commence, the opinion must not necessarily be positive.

According to the § 2 a (5) AMG, an ethics committee is “...an independent body, composed of medical experts, experts from other fields and lay persons, charged with the task to assess if the subject’s rights and integrity are preserved.” [A similar although slightly different definition is given in §3 (9) MPG]

The committee must contain at least one jurist, one medical practitioner – not involved in the research project, - one member of the local nursing staff, one advocate of patient’s rights and one person, who has expertise in the field of ethics or who is involved in pastoral duties [§ 40 (2) AMG and § 58 (2) – with a slightly different make-up of the committee– respectively].

The ethics committee has to assess, among others, the scientific qualification of the principal researcher, the suitability of facilities and persons involved, the scientific merit of the proposed project, especially the benefit/risk relationship, the recruitment process of subjects, and the conduct of informed consent [§ 41 (2) AMG]. The law contains provisions on insurance [§ 32 AMG], protection of special groups [§§ 42-44 AMG], informed consent [§§ 38-39 AMG], and handling of data.

Prior to the amendment of the AMG in 1993, only clinical trials conducted in hospitals had to be evaluated by an ethics committee, with the result, that some drugs were admitted without an ethics committee giving its opinion. Since 1993 § 40 (1) AMG commits the governors [*Landeshauptmann*] of the Austrian territories [*Länder*] to establish ethics committees for clinical trials outside of medical institutions in their territory [§ 58 (1) MPG].

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<sup>5</sup> Q.v Erwin Bernat, *Landesbericht Österreich in Deutsch/Taupitz* [Hrsg.], *Forschungsfreiheit und Forschungskontrolle in der Medizin : zur geplanten Revision der Deklaration von Helsinki*, 2000, Berlin, Springer, S. 8.

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Austria has not signed the *Convention on Human Rights and Biomedicine*.

c) Current situation

In 1997 the Ethics committee of the Medical Faculty in Vienna took the initiative to create a Forum of ethics committees. Actually it provides a list with 32 ethics committees, registered with the Forum and which use and accept the forms, distributed by Forum. Some of them are regional committees as for example the *Ethikkommission des Landes Niederösterreich*, the *Ethikkommission des Landes Oberösterreich*, as well as their counterparts in Kärnten and Salzburg. Others are linked to huge hospitals and one was established by the Association for Clinical Pharmacology (*Österreichische Arbeitsgemeinschaft für Klinische Pharmakologie und Therapie und Institut für Hypertoniker*). Among others, the procedures for multi-centre trials are discussed at the Forum of ethics committees. There is a strong tendency to find agreements on mutual recognition, but contradictory votes are also registered in the protocol and there is no fixed procedure on how to handle this situation.

d) References

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## 2. Belgium

a) Historical and legal background

Belgium's regulations on matters of biomedical research are well established, if somewhat convoluted. The first norms on pharmaceutical issues (still in force today to some extent) date back to 1885. Since then a number of additional laws and

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decrees in biomedicine were enacted, but none of them provided clear regulations for research on human beings in a comprehensive way.

Different relevant norms have been introduced based on the Royal Decree Nr. 78 from 10 November 1967 on the Conduct of Medical Professionals, the Law on Medicinal Products from 25 March 1964, and the Royal Decree from 3 July 1969 regarding the Registration of Medicinal Products. Furthermore, following the European directive 91/507/EEG, the term “Good Clinical Practice” has been introduced into Belgian law by amending (5 December 1992) the Royal Decree from 16 September 1985 (Decree on the Norms and Rules in Trials on Medicinal Products intended for Human Use) which refers to the 1992 version of the Helsinki Declaration. The Act on es obliges (since an amendment in 1999) every hospital to have a local ethics committee (Art 70ter). These committees have a supporting function regarding ethical aspects of hospital care and a counselling role regarding protocols on research on human beings and human material. The *National Council of the Order of Physicians* also passed some professional legislation<sup>6</sup>, containing deontological rules pertaining to medical research and the obligation to ask for the opinion of an independent committee for medical ethics. Lastly, some international rules such as regulation 2001/20/EG apply to Belgian law.

As the *Advising Committee for Bioethics in Belgium* defined, due to the multitude of applicable, but not quite suitable for the subject norms, the Belgian system of ethics committee looks as a “normative polyphony”<sup>7</sup>. It voiced the opinion that there should be a uniform act on biomedical research issued in order to regulate all legal ambiguities, resulting from this polyphony.

Not quite following the letter of this recommendation, but obeying its spirit, on 24 December 2002 Belgian Parliament amended the Law on Medicinal Products (LMP) from 25 March 1964 by adding the Art. 6bis. This provision empowers the King, after being advised by a scientific committee he has appointed, to issue rules on the general conditions under which clinical trials may be conducted (Art. 6bis § 1 LMP). These rules shall specifically be aimed at the protection of a special interest group, the design of clinical trials, the responsibilities of a researcher, the follow-up procedures, etc.

Without infringing on the aforementioned rules, each proposal for a clinical trial has to obtain the positive evaluation of an ethics committee (Art. 6bis § 2 Clause 2 LMP). In this context, the committee is responsible for: the protection of the participant’s rights, security and well-being; it has to act as a public guarantor for

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<sup>6</sup> Nationale Raad van de Orde van Geneesheren „Code van de Geneeskundige Plichtenleer“, 1993.

<sup>7</sup> Q.v. Raadgevend Comité voor bio-ethiek van België “Advies Nr. 13 van juli 2001 betreffende experimenten met mensen”, 2001, S. 10.

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those rights by giving its opinion on the protocol, the competence of the researchers and the facilities used; and, finally, to evaluate the validity of informed consent and the methods used to obtain it (Art. 6bis § 2 Clause 3 LMP).

In agreement with the *Advising Committee for Bioethics in Belgium*, the King is responsible to issue rules on the composition and procedures of ethics committees (Art. 6bis § 2 Clause 1 LMP).<sup>8</sup>

Belgium did not sign the Convention on Human Rights and Biomedicine.

## b) Discussion

The position of the *Advising Committee on Bioethics* was provided as an answer to the question of two experts and members of the research ethics committees, who complained about the possibility of a researcher choosing a committee that might accept his protocol. The advising committee seemed to be divided on the appropriateness of normative polyphony and the need to intensify the control over the activities of ethics committees. The discussion is continuing after the amendment of the law.

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<sup>8</sup> Our research did not yield such rules. They probably will be issued in form of a Royal Decree in the near future if they have not been issued yet.

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### 3. Denmark

#### a) Historical background

Danish experts have been involved in the preparation of the Second Declaration of Helsinki, which was adopted in Tokyo in 1975. The Danish Association of County Councils, universities, scientific health research and professional organizations were

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involved in the discussion on the establishment of independent ethics committees, as required by the Declaration. A consensus was reached and the first official report on the Danish system of ethics committees was issued in March 1977. Since then Denmark has the system of regional ethics committees (7 later 8) with the representation of all relevant disciplines and a lay component. This system was fixed by law in 1992. It is a most important innovation that it created a lay majority in all of the committees.

## b) Legal framework

Since 1992 biomedical research is governed by the *Law on a Scientific Ethical Committee System and the Handling of Biomedical Research Projects* (Act no. 503 of 24 June 1992 and amended in 1994, 1996 and 1997. It is abridged as *LSEC* in this text). Furthermore, the *Danish Central Scientific Ethical Committee* has issued guidelines on biomedical experiments in November 2000, which are primarily addressed to the regional scientific ethical committees, aiming to guide and structure their evaluation of the research projects.

In the context of LSEC biomedical research on live-born human individuals, human germ cells intended to be used in fertilisation, human fertilized eggs, embryos and fetuses, tissue, cells and genetic materials from humans, fetuses and the like, and deceased persons must be notified to the competent regional committee pursuant to Part 2 Sect. 6 of the LSEC.

Without the committee's approval the project may not be initiated (Part 2 Sect. 7 LSEC), projects permitted may not be substantially changed without the permission of the committee and the committee may itself require the researcher to modify the project.

The above said is also valid if biomedical research (as defined above) is an integral part of a bigger project. If the project includes medical clinical trials, the committee has to submit its scientific ethical evaluation to the Danish Medicines Agency which has to give the final decision on the initiation of the project (Part 2 Sect. 7 Subs. 3 LSEC).

If the regional committee is not able to reach a decision on a given project or reaches the conclusion that the project raises fundamental questions, the regional committee must delegate the case to the *Danish Central Scientific Ethical Committee* (Part 2 Sect. 7 Subs. 4 LSEC). The scientist, whose project has been refused by the regional committee, has the right for appeal to the *Danish Central Scientific Ethical Committee* under Part 3 Sect. 12 LSEC.

There was a special provision, regulating the research on fertilized human eggs and germ cells intended for use in procreation, which has been repealed by later

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amendments. According to this provision, the research was only to be carried out if it aims at the improvement of IVF-treatment and if both, the regional committee and the *Danish Central Scientific Ethical Committee*, approved the project. The committees may monitor projects they have approved and may also demand the submission of the final report with the scientific results.

According to LSEC's Part 1, the local committees consist of at least 7 members, who are appointed for a period of 4 years (reappointment is possible only once). If the local situation warrants it, the number of committee members may be increased to 9, 11, 13 or 15.

The committees are appointed by the county councils, which may, if necessary, establish more than one committee in the region. Several councils may also opt to appoint the same committee. Depending on the committee's size, the Danish Medical Research Council must nominate 3 to 7 members of the regional committees. The regional committees may draft their own rules of conduct, which must be approved by the *Danish Central Scientific Ethical Committee*.

The *Danish Central Scientific Ethical Committee* is set-up by the Minister of Research and Information Technology and consists of two members from each regional committee, plus two appointees by the Ministers of Research and Health respectively. The LSEC has no requirements concerning the committee (regional and central) members' professions. The central committee drafts its own rules and regulations, which have to be agreed by the Minister of Research and Information Technology.

According to the Part 3 Sect. 8, the evaluation process, carried by the regional committees (as well as the central committee, where appropriate), has to ensure 1) that the risks, posed by the implementation of the certain project, have been carefully considered and are not either in themselves or in foreseeable benefits of an unjustifiable proportion, 2) that the rules of informed consent (especially where the subject is not able to consent itself) are observed and that the persons involved are also entitled to withdraw their consent at any time, 3) that the patients are also properly informed about the researchers' (possible) relationship with private financial interest, 4) that the project conforms with the standards of good scientific practice and 5) that there is a sufficient reason to perform the research. The above-mentioned Guidelines of the *Danish Central Scientific Ethical Committee* elaborate further on this.

The regional committees are financially supported by the respective county councils. Private companies and hospitals have to pay a fee for the evaluation, which is decided on by the respective council. However this may not exceed the cost of the evaluation process. The expenditures of the central provisions are to be covered by the Ministry of Research and Information Technology. The LSEC contains

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provisions on the payment for committee's members in Part 5 and refers to the Danish law on local authorities for further details.

Denmark has signed the *Convention on Human Rights and Biomedicine*. The treaty entered into force on 1 December 1999.

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## 4. Finland

### a) Legal framework and current situation

In Finland medical research is governed by the *Medical Research Act* (MRA, Statute No. 488/1999), which entered into force on 1 November 1999. The *Medical Research Decree* (MRD, Statute No. 1999) further elaborates on the matter stating, among

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others, the conditions for consent. Lastly, the National Agency for Medicines issued the *Regulation on Clinical Trials on Medicinal Products in Human Subjects* (Regulation 1/2001 from 4 April 2001), explicitly stating the requirements for conduct of clinical trial in Finland and referring to the Helsinki-Tokyo Declaration and GCP Instructions of the EU.

The MRA states that medical research means research involving an intervention in the integrity of a person, human embryo or human foetus for the purpose of increasing knowledge of the causes, symptoms, diagnosis, treatment and prevention of diseases or the nature of disease in general.

While including embryos and fetuses into the application frame, the act does not itself give a definition of research, just defining medical research as a special kind of research.

The act states that no trial may commence without a further favourable opinion of the competent ethics committee (Sect. 3 MRA). If the research plan is altered, the committee has to be notified and may, if necessary, deliver a new opinion. When a negative opinion is given, the researcher may appeal to the same committee, which in turn has to also get the opinion of the Sub-Committee on Medical Research Ethics (TUKIJA) of the National Advisory Board on Health Care Ethics (Sect. 3 MRA and Sect. 2 MRD), which is an integral institution of the Ministry of Social Affairs and Health. The same rules are applicable if the clinical trial “requires a national opinion to be delivered” (Sect. 17 MRA). This provision aims at multi-centre international trials. Multi-centre research at a national level will be evaluated by the committee of the district, in which the principal researcher is working<sup>9</sup>.

According to Sect. 1 MRD, only ethics committees of the relevant hospital district may be considered for the evaluation. The ethics committees of other institutions, private or public, may not deliver such an opinion.

The MRA requires each hospital district to have at least one ethics committee (Sect. 16 MRA), but those committees must not necessarily be separate institutions - instead, districts may also form joint ethics committees. The committees are appointed by the relevant hospital in that district and are registered by provincial state offices (Sect. 20 MRA). The committees must comprise of one chairperson, at least six other members, one of them acting as a deputy chairperson (Sect. 18 MRA). Besides medicine, at least two other professions must be represented. Two of the committee members must be lay persons. The Act also contains procedural rules for decision-making and minimum quorum. Sect. 19 MRA refers to the

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<sup>9</sup> Q.v. Halila, Ritva “National Ethics Committee in Finland” in EMEA Workshop „Ethical considerations in clinical trials”, S. 117.

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Administrative Procedure Act (APA, Statute No. 598/1982) for disqualification of committee members (regulated in Sect. 10 and 11 APA).

The committee has to give a reasoned view on whether the intended research is ethically acceptable or not. Therefore, it has to take into account (according to Sect. 17 MRA) if the project conforms to the MRA and MRD, data protection legislation and relevant international rules (which of them are binding in Finland). By considering the conformance with the MRA, the committee must pay special attention to the balance of gain and benefit (Sect. 4 MRA states that the research subject's interests should always be primary with regard to any benefit for science or society), as well as to the rules of informed consent (Sect. 6 MRA), and the requirements regarding the vulnerable groups (Sect. 7 to 10 MRA).

The aforementioned *Regulation on Clinical Trials on Medicinal Products in Human Subjects* further elaborates on these topics.

Besides the MRA, there is a decree on animal experimentation, making it necessary to have an institutional committee for animal experimentation in any institute conducting such research.

At present, Finland has 21 hospital districts and 30 ethics committees. An unknown number of institutional ethics committees at different universities, research institutes and psychological departments are performing evaluations of projects, which are not covered by recent Finnish legislation (as for instance, surveys and questionnaires). According to Salla Lötjönen, these ethics committees resemble the ethics committees of hospital districts in composition and size.

Finland has signed the *Convention on Human Rights and Biomedicine* on 4 March 1997, but the Parliament has not yet ratified it.

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## 5. France

### a) Historical background and legal framework

The French law from 20 December 1988 created a regulation for the protection of persons who make themselves available for biomedical research. This law provides regulation for the research on human beings, who demand the institution of advisory committees, and grant these *Comités Consultatifs de Protection des Personnes dans la Recherche Biomédicale* (CCPPRB) a central role. The law is known under the title „*Loi Huriet*“ as it was introduced by Claude Huriet (Sénateur Honoraire, Président de l’Institut Curie, Paris) and Franck Sérusclat. This law put an end to the unregulated practice of biomedical research which was bemoaned by many sides, among these the CCNE (Avis N° 2), i.e. the French National Bioethics Committee.

The law demands that biomedical research should only be conducted under the direction and control of a physician who can prove appropriate experiences, under technical and material terms, which take into account the scientific preciseness and the security of the persons on trial, as well as following detailed conditions of the informed consent. In advance of the realization of a biomedical research project the statement of an authorized CCPPRB must be provided as well.

The article L209-18 of the code of public health constitutes the task of the CCPPRB to the effect that it should include the conditions of the legal validity of the research considering the protection of the persons, in particular the overall relevance of the project, the adequacy of the pursued aim and the therefore employed means, the qualification of the researcher, the protection of the participants, the modalities of the information of probationers, the modalities to get the approval, and the precaution in case of a compensation by the sponsor in the case of research without direct individual profit for the person. Therefore, the French law does not only relate to drug-testing, but to every research project involving human beings. There are no explicit regulations concerning the possible use of body material, which was produced at an earlier date. Otherwise research on human beings is understood in a wider sense so that epidemiological studies, as well as psychological studies, are concerned.

For all these research projects involving humans, the researcher is asked to present the project to a CCPPRB licensed in this region for a statement.

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More than one committee can be established in one region. In principle, there is the possibility of competence extension of one committee to other regions, if the conditions cannot be fulfilled for a legal functioning committee in that region. This provides at least in some regions a certain option for the researcher. Mostly, the CCPPRB are accommodated in hospitals and university-clinics, but in a few cases through the government regional authority for health and social affairs (DRASS).

For the CCPPRB independence and the diversity of professional background are called for. The demand for independency is underlined by the possibility of a withdrawal of the licence of a committee by the health minister as far as the independency is not preserved. The annulment of the accreditation with reference to the composition is also possible. The nomination occurs through the DRASS (*Direction régionale des affaires sanitaires et sociales*) in the name of the prefect of the concerned region. Following its designation, a committee must have twelve members (Titularmitglieder?) and as many proxy persons, where eight categories are to be differentiated. Four persons, of whom at least three are doctors, who have qualifications and experiences in the area of medical research, one general practitioner, two pharmacists, of whom at least one is working at a hospital, one female or male nurse, one person who is qualified through his or her expertise concerning ethical questions, one person who is qualified through his work in the social field, one person who is warranted to have the title psychologist, and one person, who is qualified in the field of the jurisprudence.

According to this pluri-disciplinary composition, the appointing authority has a list, which sizes suggestions out of the eight categories of responsible organisations.? With regard to the first category, these are the big regional and national biomedical research facilities (*directeurs D'UFR, directeur général de l'INSERM*), with regard to the general practitioners it is the chairmen of the Councils in the Department of the medical profession (*ordre des médecins*). The pharmacist is also suggested through their registrar organisation, as well as through the director of the teaching hospitals, the nurses through the director of care institutions and regional directors for social affairs, the ethicist through the headmaster of the academy, the representatives of the social dimension through the consumer-, family and patient-association, the psychologists through the responsible professional association and care institutions and the legal experts through the president of the upper court and the bar association.

A membership in more than one CCPPRB is impossible (*Code de la santé publique, Art. R. 2013*). The membership is honorary, although the refund of costs and special allowances are not barred.

There is often an accentuation on the only deliberative role of the CCPPRB, with a hint to the remaining responsibility of the sponsor and the researcher. In the case of a negative statement a research project cannot be taken up for the following two

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months under threat of punishment, so at least with regard to this the vote of the commission has direct judicial consequences.

b) Translation into action and discussion

Also in the scientific community as in the public there was great attention paid to the *Loi Huriet*, which has led to extensive revisions through different constitutional institutions. The statement of the deputy Jean-François Mattei from 1994 to the Prime Minister seems of special importance as well as the Rapport d'Information from Claude Huriet in the name of the commission of *Affaires Sociales* of 2001. More evaluations and reports are mentioned here(?).

The report of Mattei makes the difficulties, related to the wide field of application which is a subject of discussion. Many scientists involved are not familiar with the medical research applications beyond drug research. Mattei names insecurity dealing with biological material<sup>10</sup>, with the psychology and the behavioural research, as well as the research field of the cosmetic industry. Besides, he sees the demand for the establishment of a committee in the field of the military research on human beings. Mattei voted for the retention of a wide field of application under the introduction of a few necessary differentiations, which in some parts did occur. Mattei describes the area wide assembly of the committees in the year's 1991- 1994.<sup>11</sup> Those committees, which do not have an available office, would have difficulties to abide the respite of 5 weeks for their vote. The biggest problems concerning the realisation of the new laws does the report ascribe to the different responsible administration authorities, who are also blamed for the difficulties concerning the development and mode of operation of the CCPPRB.

The criticism of Mattei was met by various steps of the legislation. The law from the 25<sup>th</sup> July 1994 gives strength to the obligations of the promoter in the cases where the biomedical research causes strong negative results. The law from the first of July 1998 established the AFSSAPS (*Agence française de sécurité sanitaire des produits de santé*). The AFSSAPS is the proper authority for the statement of the committee if the research deals with medical products, drugs or cosmetic products, as named in the article L793-1 of the *Code de la Santé Publique*. Only in some cases the addressee is still the health minister. The new authority is, at the same time, the addressee for the statements of the promoters (sponsor) about the eventuation of serious side effects.

The report of Claude Huriet from 2001 puts once again the question of the area of application of the law to discussion, as well as the pluralism of the composition of

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<sup>10</sup> „Les essais cliniques sur le matériel biomédical ne sont visiblement presque jamais déclarés dans le cadre de la loi Huriet : » (p. 4)

<sup>11</sup> „A l'heure actuelle, toutes les régions, à l'exception de la Réunion, de la Guyane et de la Guadeloupe, disposent d'au moins un comité. » (p. 9)

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the committee, and the question of the regulation of the finances. Huriet has made an extensive survey of the committees and their work. He evaluated a questionnaire, which was answered by nearly every committee. Besides, he made extensive interviews with the representatives from all the organizations involved. The results of Huriet can still be used for the description of the current functioning of the CCPPRB in France.

With respect to the differentiation, which was introduced through the law of 1998, it arose for the protocols, which fall in the spheres of competence of the AFSSAPS that their promoters are mainly industrial. The other protocols which fall in the spheres of competence of the DGS and which are not a medical product or drug studies, but physiological, psychopathological, epidemiological, genetic and other studies the promoters are mainly institutional (hospital centres, INSERM, CNRS and others). Medical drug studies make up 78% of the research projects, other medical product studies make up 10%, basic research makes up 9%, and the psychological research makes up 3%. The assignment of cosmetic products causes problems throughout the statistics, as well as in the practice of the committees. One of the conclusions which Huriet draws from questioning the participants of the committees is that providing an overview covering the positioning and votes up to the present met by the different committees would be useful. Through this a judgment practice, after the pattern of the common law ( p. 34), could be developed.

Huriet discusses the question of absences from meetings of committee members under the keyword of pluralism. It must be distinguished between re-nomination not carried out in the case of resignation from the seat and the non-appearance of actual members. One can describe this phenomenon precisely according to the eight categories of members. While Huriet estimates the presence of experts in biomedical research, as well as pharmacists as sufficient and also the presence of nurses as relatively high, he estimates the presence of general practitioners and of non-medical professions as unsatisfactory. Because of the raised data of attendance it seems as if the principle of pluralism is not fully respected. Therefore, Huriet also refers to the estimation of the Île-de-France by the DRASS. Huriet refers in his analysis of the causes in particular to procedural problems concerning the nomination and difficulties of motivation. Both causes are connected with the practice of nomination, where the willingness to enduring participation is not considered enough and with the fact that too little information about the practice of work is given. A lot depends on information given ahead. Quote:

*“Certaines démissions semblent pouvoir s’expliquer par un déficit d’information initiale concernant tant le rôle des comités que la charge de travail qui incombe aux membres.”* (p. 42)

Further problems seem to occur concerning those members, who hold the status of a proxy – (“substitution”) member. The lack of remuneration is also named as a

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cause for the high number of absences. Huriet points at the special difficulties for freelancers.

One can attribute the high number of vacancies and the slow moving practice of re-nomination guides back to the difficulties to which the DRASS is exposed. First of all, the list of participating organizations is extremely long , and secondly some of these institutions (*Récteur de l'Académie, Conseils départementaux de l'ordre des médecins*) obviously co-operate insufficiently.

Huriet assumes that one should unconditionally hold on to the principle of pluralism. Regarding the operating method of the committee, Huriet describes a heterogeneity of activities. It seems important for him to point out that a practice of consultation has been established in the work of these committees, for which there had not been a designation in the *Code de la santé publique*. In many cases the scientists turn to the responsible committee in advance with the request for advice concerning the formulation of their application. Questions occur which are brought up by the consultation over the methodology of a research project which many times exceed the capacities of the committee. Finally, Huriet observes that the practice of positive statements under the condition of the conveyance of additional information, as it is designated in the *Code de la santé publique* L200-12-1, is continuously increasing (*Avis favorable 59 %*, *Avis défavorable 2 %*, *Avis favorable sous réserves 39 %*). As well as the request for additional information by the committee, also the practice of amendment on the part of the applicant has increased considerably. Different committees have mentioned with regret the practice of researchers submitting incomplete protocols with the intention to complete them later by amendments towards the reporter Huriet. It also occurs to be important for Huriet concerning the practice of the CCPPRB to mention that the large state research institution (INSERM, *Assistance publique – Hôpitaux de Paris* (AP-HP)) has established committees localized in their own institutions for quality evaluation which are partly regarded by these institutions as a virtual CCPPRB.

Different committees, as well as the reporter Huriet, describe and analyse the danger related to the fact that the legally founded geographical principle of responsibility implies no certain CCPPRB so that it could result in a Gault-Millau of CCPPRB. While the members of the committees point out that it is well known that in some committees it is easier to achieve a positive vote than in others, Huriet in his analysis of the number of issued statements discovers that it clearly declined in the case of the Île-de-France where the choice of 14 committees exist in a certain period, but stayed constantly for some committees while for some it even rose. Because of the partly mentioned institutional proximity of the researcher and the committee, Huriet discusses the suggestion that the evaluation and statement should not be performed by committees, which are located in the same institution where the project is to be carried out.

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In alignment with another analysis of the work of the administrative bodies and the interrogation of the other participating organizations, Huriet reports a number of suggestions. Besides a couple of advices which relate to the realisation of research (precise definition of research without direct use and of research with direct use, standard of the number of amendments) he gives concrete suggestions for reformatory measures for the commissions. Regarding the CCPPRB's legal status, Huriet questions the legal term of a *personnalité juridique*. This status is not sufficient to negotiate with the large research institutions and with the administration at eye level. Huriet, therefore, suggests the foundation of a public national institution which should have the function of a roof over the CCPPRB. Besides the partnership in dialogue with the research organizations and the administration, it's task would be the distribution of funds. At once Huriet stresses that this umbrella organization should not be a central committee but play the role of a central organ of service. With regard to the finances, Huriet suggests a greater transparency as the first step of reform. The possibility of the committees to act as a consulting authority towards the researcher should explicitly be stressed to dispel the doubts of different participants in the CCPPRB that this practice endangers an objective statement concerning the submitted protocols. Regarding the composition of the CCPPRB, Huriet suggests abolishing the distinction between nominal members and proxy members. An in-advance-information for members should be provided to permit them to win motivated persons who are aware of their future tasks. In view of the complexity of the new formulation of questions expressed in the committees and to guarantee the efficiency of the pluralism, it appears to be necessary to regularly organize continuous courses (extension studies) for the members of ethics committees (p. 86). The *Conférence nationale des CCPPRB* could be entrusted with the co-ordination and realisation of these continuous courses. As the income of the fixed charges for the submission of research protocols have until the present time been used insufficiently, it should in future be possible to pay specific expenses with them as they occur under the members of ethics committees (e.g. to compensate the loss of earnings as a result of functioning as an expert and for functions in meetings). Huriet's report names in particular physicians, pharmacists and lawyers who are in private practice. Finally, the committees should be given information about the results of the research projects which they had to examine. It is especially unfortunate that this does not happen to-date, since this would provide an important source for the improvement of the statements' quality. Concerning the nomination of members, the DRASS should be supported by the suggested official institutions, insofar as it can co-ordinate the suggestions for candidacy. The *Conférence nationale des CCPPRB* should obtain a more significant role: Besides the achievement of a deepened dialogue between the committees and education, as well as the advanced training (extension studies) of members the report also plans a consulting role for the autonomous organisation of the financial administration which should win an increasing autonomy from the DGS.

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c) Conférence nationale des CCPPRB and Avis n° 79 of the CCNE

At present the CCPPRB of Lille provides an on-line forum, for the discussion of questions inside the National Conference of CCPPRB and outside. One of the problems is the implementation of the European Directive on Good clinical practice on the national consequences. In September 2003 the National Advisory Committee for Ethics in Life Sciences and Health Care (CCNE) published an opinion on the transposition of the directive in national law. The opinion focuses on the balancing of benefits and risks and on consent procedures. The structure and effectiveness of CCPPRB (CPPR) is not discussed.

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## 6. Germany

### a) Legal framework

The legal situation in Germany regarding research ethics committees is quite complicated.

There are three different sets of provisions (one regulation and two acts) dealing with the different types of research on human beings and ethics committees' role in it. Moreover, there is professional law, issued by the *German Medical Association* and implemented by the medical associations in the German federal states.

The most relevant article for the work of German ethics committees<sup>12</sup> is the *Act on Pharmaceutical Products* (*Arzneimittelgesetz*, AMG). The AMG deals with pharmaceutical products<sup>13</sup> and provides rules on the conduct of clinical trials in §§ 40-42 AMG.

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<sup>12</sup> 67 % of the research proposals, evaluated by German ethics committee, fall under the framework of the AMG. Q.v. Hansjörg Just “Die öffentlich-rechtlichen medizinischen Ethik-Kommissionen in Deutschland – derzeitige Struktur und Arbeitsweise, so wie Perspektiven der zukünftigen Entwicklung.”, [http://www.ak-med-ethik-komm.de/struktur\\_main.html](http://www.ak-med-ethik-komm.de/struktur_main.html), S. 8.

<sup>13</sup> Defined as „matters and mixtures of matters“ destined to (1) “heal, alleviate, prevent or discern diseases, ailments, suffering or bodily damages”, to (2) “analyse the constitution,

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According to AMG § 40 Sect. 1, 2<sup>nd</sup> sentence, clinical trials may only commence if there is a prior positive vote by an ethics committee<sup>14</sup>. If no such vote is given, the trial may only commence if the competent authority (the *Federal Institute Federal Institute for Drugs and Medical Devices* BfArM as indicated in § 77 Sect. 1 AMG) does not gain, say within a period of 60 days. § 40 AMG also contains rules on matters as informed consent, special groups of trial subjects, the qualification of the researcher, pharmacological and toxicological assessment, insurance etc. All these criteria also constitute to the parameters of evaluation by the ethics committees. In § 41 the rules for clinical trials on persons who may benefit from the experimental treatment are laid down. In certain cases a clinical trial may be conducted on these persons without their (if not against their) explicitly stated will.

The second act with some relevance for research ethics committees is the *Act on Medical Devices (Medizinproduktegesetz, MPG)*. Medical devices— broadly speaking – are those instruments and devices used in a medical context, which are not covered by the AMG.<sup>15</sup> The rules for clinical trials with medical devices are given in §§ 19-24 MPG. Pursuant to § 17 Sect. 6 clinical trials using a medical device may only commence when they have been notified to the competent authority (the authorities being located on the level of the federal states) and have been approved by an ethics committee. Again, the trial may also begin if the authority did not issue written disapproval within 60 days. In contrast to the provisions of the AMG, the ethics committees responsible for the evaluation of trials with medical devices are not to be registered by the federal states but by the BfArM.<sup>16</sup> § 20 Sect. 8 contains some rules regarding the composition and make up of these committees.<sup>17</sup> Pursuant to this section they have to be independent, interdisciplinary, and must contain at least five members. Some of them have to be medical experts, some have to be lay members (non-medical professionals). The committee may only be registered by the BfArM if it notifies that institution about their procedures and fees.

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the condition und the functions of the human body and mind”, to (3) “substitute agents or bodily fluids produced by the human or animal body”, to (4) “fend of and dispose of etiologic agents, parasites or intruding substances” and to (5) “modify the constitution, the condition und the functions of the human body and mind” in § 1 Sect. 1 AMG.

<sup>14</sup> This provision further defines, that the committees have to be established according to the law oft the federal states. For a complete list q.v. [http://www.bfarm.de/de/Arzneimittel/klin\\_pr/klin\\_pr\\_faq/ListeEK\\_Landes-behoerde.pdf](http://www.bfarm.de/de/Arzneimittel/klin_pr/klin_pr_faq/ListeEK_Landes-behoerde.pdf).

<sup>15</sup> A more exact and comprehensive definition is given in § 3 MPG. But it is far too lengthy and convoluted to be cited in this context.

<sup>16</sup> For more information also see [http://www.bfarm.de/de/Medizinprodukte/klin\\_ethik/index.php](http://www.bfarm.de/de/Medizinprodukte/klin_ethik/index.php).

<sup>17</sup> Q.v. [http://www.bfarm.de/de/Medizinprodukte/klin\\_ethik/index.php?more=ethikkom.php](http://www.bfarm.de/de/Medizinprodukte/klin_ethik/index.php?more=ethikkom.php) for a complete list of those committees.

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The last generally binding set of rules is the *Regulation on the Protection from Ionising Radiance (Strahlenschutzverordnung, StrlSchV)*. It deals *inter alia* with medical research involving human subjects to be exposed to ionising radiance. The preconditions for the acceptability of such clinical trials are even stricter than those in the AMG and MPG. With regard to the role of ethics committees, the rules are quite similar nonetheless. Pursuant to § 23 StrlSchV the researcher needs to apply for permission to the *Federal Office for Radiation Protection (BfS)* before he may conduct medical research of that sort. In contrast to the rules laid down in the AMG and MPG, the trial must be approved explicitly from the start. One of the requirements (§ 24 Sect. 1 No. 2 StrlSchV) for the BfS to comply with the request is that an ethics committee has to issue an opinion (not necessarily positive according to the StrlSchV) regarding the research-plan. According to § 92 StrlSchV an ethics committee responsible for that kind of research evaluation must be independent, interdisciplinary and registered at the BfS<sup>18</sup>. To be registered, the committee must be composed of at least five persons, containing medical professionals as well as lay persons, must have issued written rules of procedure and has to notify the BfS of their mode of operation. Their opinions have to take into account legally, as well as ethical aspects and must be published in written form within three months after the application of the researcher.

All three sets of rules detailed above deal with multi-centre trials. In the case of the AMG, the opinion of the ethics committee responsible for the region (federal state) in which the main-researcher is located, is binding. No further opinions are required.<sup>19</sup> According to § 20 Sect. 7, 2<sup>nd</sup> sentence, the vote of just one ethics committee is enough to fulfil the preconditions of the MPG in the case of multi-centre trials. § 92, 3<sup>rd</sup> sentence StrlSchV delineates, that in the case of multi-centre trials, the vote of one committee is sufficient.

Besides the three legal codices mentioned above, there is the *Stemcell Act (StZG)*. Although this law contains rules on the participation of ethical deliberation in administrative procedures, it does not deal with *local* ethics committees. The StZG introduces *acentral* committee that has some part in the decisions of proposals for the import of human embryonic stem cells into Germany.

Another set of rules which bears upon the work of ethics committees in Germany is the *(Model) Professional Code of Conduct of the German Medical Association* (abbreviated as MPCC hereafter). Although that normative text is in two senses less legally binding than a law or decree, its influence on the work of ethics committees is quite important nonetheless. First, as it originates from professional law, the Code just

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<sup>18</sup> Q.v. [http://www.bfs.de/bfs/dienstleitungen/med\\_forschung/strlschv/ethikkomm.html](http://www.bfs.de/bfs/dienstleitungen/med_forschung/strlschv/ethikkomm.html) for a complete list of those ethics committees.

<sup>19</sup> Q.v. the BfArM's guidelines for clinical trials online under [http://www.bfarm.de/de/-Arzneimittel/klin\\_pr/klin\\_pr\\_faq/index.php#I](http://www.bfarm.de/de/-Arzneimittel/klin_pr/klin_pr_faq/index.php#I).

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addresses physicians, being in no way binding for other people (even for other medical professionals). While that lessens the legal force of the code in some way, the practical repercussions of that reservation are quite limited. As physicians are the main conductors of clinical trials, other medical professionals playing but secondary parts, the code practically applies for almost all biomedical research. The second restriction of its legal force comes from the fact that it is just a model. The *German Medical Association* has just given a guideline for the design of codes of conduct for the medical associations of the federal states. This construction stems from the different legal nature of the German Medical Association and the Medical Associations in the federal states<sup>20</sup>. But even this objection does not bear much practical force as the resulting codes divert from the model code only in minor detail. For the sake of practicability, we therefore refer to the provisions of the MPCC of the *German Medical Association* on biomedical research instead of citing the codes of the 16 federal states. In § 15 Sect. 1 MPCC the physicians are obliged to let themselves be counselled by the ethics committee of the states medical association or an ethics committee situated at an university's medical department when conducting biomedical research. The definition of biomedical research used in this code entails also research conducted on human gametes and foetal tissue but excludes purely epidemiological studies.<sup>21</sup> The physician does not need an approval by the ethics committee, but is only required to avail himself of advice on legal and ethical matters pertaining to the planned research.

This slight difference in function, compared to the role of ethics committees in the context of AMG and MPG, has led to some legal frictions in the past. As the MPG only requires an ethics committee to be registered (pursuant to the requirements set out in § 20 Sect. 7-8 MPG) to conduct the evaluation of clinical trials, there is no

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<sup>20</sup> Whereas the medical associations in the federal states are empowered to enact some functions of public law and therefore have the status of public bodies, the *German Medical Association* acts as an umbrella organisation meant to coordinate the activities and rules of the medical associations in the federal states but without public law functions and corresponding public body status. Nevertheless the *German Medical Association* fulfils vital functions and even provides a central commission concerned with somatic gene-therapy and acting as obligatory advisor to local ethics committees involved in such cases according to Sect. 3.1.4 of the *German Medical Association's* guideline on *Gene-transfer into Human Somatic Cells*; q.v. <http://www.bundesaerztekammer.de/30/Richtlinien/Richtidx/Gentransferpdf.pdf>.

<sup>21</sup> In that regard the Conduct Code of the Medical Association of Baden-Württemberg differs from the model code of the German Medical Association, as it entails also epidemiological studies according to § 15 of the *Professional Code of Conduct of the Medical Association of Baden-Württemberg*, q.v. <http://www.aerztekammer-bw.de/20/arztrecht/05kammerrecht/bo-neu.pdf>. There are also other instances in which the codes of conduct of the medical associations differ among the federal states from the model code of conduct of the *German Medical Association*.

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stricture against private ethics committees (opposed to public ones) to operate in this context. However, the MPCC only refers to public ethics committees which led to claims that the situation constituted an unfair restriction of the private ethics committees' activities. The concerned parties went to court claiming, that the legal situation infringed on their freedom of professional activities as no one would obtain a vote by a private ethics committee if that vote only accounts for the requirements of § 20 Sect. 7 MPG but not for those laid down in the code of conduct for the states medical association, whereas the vote of an public committee (registered according to § 20 Sect. 7-8 and being competent to carry out consultations according to the conduct code) cover both votes.<sup>22</sup> The concerned court decided, that, although the public committees may give votes in both respects, they may not give an opinion that encompasses the counselling being required by professional law *and* the evaluation required by the MPG *in the same act*. In particular, they have to issue two different acts. This is grounded in the different natures of professional advice for physicians on the one hand and evaluation of research projects having the nature of legal approval on the other. The first is mainly for the benefit of the medical professional helping and guiding him in his work and decision processes, the second aims at the protection of rights and interests of the research subjects. That having been said, the private ethics committees are not disadvantaged with regard to the evaluation following § 29 Sect. 7 MPG as even public committees have to issue two different opinions. The court decided further, that the exclusion of private ethics committees from the counselling pertaining to the codes of conduct does not infringe on their professional freedom, as it is well within the Medical Association's competence to limit these tasks to institutions of their own choosing.

That regulation poses another question of some legal relevance which has not yet been decided by German courts: Must a physician planning to conduct research on human embryonic stem cells (HESC) apply for counselling according to the code of conduct, separately from her proposal to the *Central Ethics Committee for Stem-Cell Research*? As mentioned above, that issue has not yet been decided by a German court. As far as we know, all of the first four applicants who proposed to import HESC let their research projects be evaluated by the competent local ethics committee. If they should ever go to court in the future, we would expect the decision to follow the legal ideas put forward in the above-mentioned case. The decision of the *Central Ethics Committee for Stem-Cell Research* on the allowance of stem cell import is similar to the vote of a local research ethics committee regarding clinical trials in two important aspects. It has the legal character of admittance (in contrast to counselling) and its central aim is to protect the interests of some third party instead of just giving guidelines and ethical advice to the researcher. Insofar as the vote of the *Central Ethics Committee for Stem-Cell Research* differs from the

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<sup>22</sup> For a comprehensive description of that case q.v. Taupitz, Jochen, MedR 2003, Heft 12, S. 109-118.

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counselling required by the code of conduct in the same manner as the positive vote according to § 20 Sect. 7 MPG differs from it. Therefore, it is to be expected that a court deciding on that matter in the future will require the researcher to obtain both votes.

Besides the different regulatory layers discussed above, another practical level exists in Germany. Even researchers which do not fall under the above-mentioned norms (like those conducting psychological research with human beings or just using data) are well advised to let their projects be evaluated by the universities ethics committees. Otherwise, they may face serious problems by trying to publish their results in the acknowledged scientific journals. Also research grants may prove problematic as the DFG and other institutions are not likely to fund any project that does not comply with the established standards of ethics. In practice almost all research on German universities is reviewed by ethics committees and most researchers are eager to obtain the advice of their colleagues.

Germany has not signed the Convention on Human Rights and Biomedicine.

#### b) Historical background

The complexity of the legal framework in Germany can be understood by reviewing the background of the development of the committee system. After the Second Declaration of Helsinki, the German Science Foundation (DFG) took the initiative to establish an ethics committee to review integrated projects (*Sonderforschungsbereich*). On the local and regional level medical faculties and the Chambers of Physicians followed this example. The committees at the medical faculties, as well as the committees at the Chambers of Physicians, established a working group (*Arbeitsgemeinschaft Medizinischer Ethikkommissionen*) with the task of exchanging information inside Germany as well as at the European and international level. The committees were entitled to provide an advice in all research with human being projects. The legal framework on the federal and regional level was not established until the 1990s. The relevant amendment to the AMG dates from 1995. However, the scope of the mentioned acts is limited and regulates only parts of ethics committees' activities.

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## 7. Greece

### a) Historical background, legal and institutional framework

The Greek legal framework does not explicitly provide us with normative provisions for the local research ethics committees. The only norms we were able to identify are quite vague and do not seem possible to properly implement.

In 1978 the Greek Ministry of Health, Welfare and Social Security issued a decree (A2/OIK 3061/5-6-78), which required anyone applying for the public research grants together with the grant request to also submit a positive vote of an ethics committee. According to our information, this requirement, seems, not to have taken an effective root.

Another chronological legislative text, relevant to the research ethics, is the Ministerial Decision issued in 1984 (Ministerial Decision A6/10983/1/2.12.1984). This decision<sup>23</sup> provides the requirements for safeguarding the parties involved in research. It follows the principles put forward in the Declaration of Helsinki.

One more relevant legal document on biomedical research is Law 2071 (from 1992) regarding “the modernization of the Greek National Health System”. Section 47 para 5 thereof, among others, provides the concept of informed consent for protecting patients’ rights. Before 1992, patients were only protected by the more general legal norms such as the Greek Constitution, civil and criminal codex, etc. But Law 2071 does not mention research ethics committees in itself. It just provides further parameters on how to measure the acceptability of clinical trials and biomedical research in general.

The most recent law regarding the biomedical research was enacted in 1997. This law established the National Bioethics and Deontology Committee<sup>24</sup> and envisages that the future Ministerial Decision will specify the terms and conditions for application of new experimental methods and clinical trials and will also provide procedural regulations. To our knowledge, this decision has not yet been put forward. The National Drug Organization (EOF)<sup>25</sup> is the body entitled to review pharmaceutical research and market approval for drugs.

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<sup>23</sup> We were not able to receive an English translation of this text and can therefore provide only broad outlines of its content

<sup>24</sup> Which according to our interpretation is synonymous to the National Bioethics Commission

<sup>25</sup> For more information about this institution please view [http://www.eof.gr/Profile\\_en.htm](http://www.eof.gr/Profile_en.htm).

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Greece signed the *Convention on Human Rights and Biomedicine* on 4 April 1997. The Convention entered into force on 1 December 1999.

b) Current practice

Given the actual institutional settings, the Board of Directors of the National Drug Organization (EOF) has the function of a central research ethics committee. “This Board consists of 13 members of the following specialities: medical doctors, pharmacologists, lawyers, economists and one judge.” (Garranis-Paradatos, dalla Vorgia 2000, 444). The function of the local committees are divided between the Board of Directors of the hospital where the clinical trial shall take place and a Hospital Ethics Committee if the hospital has one.

c) Discussion

Problems concerning the work of ethics committees in Greece are rarely addressed. The number of local ethics committees still seems to be quite insignificant.

d) References

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## 8. Ireland

a) Historical background and legal framework

According to the *Control of Clinical Trials Act* (No. 28/1987 from 22 December 1987, further – CCTA) clinical trials fall under the authority of the Irish Ministry of Health. Clinical trial is defined as “the conducting of a systematic investigation or series of investigations for the purpose of ascertaining the effects (including kinetic effects) of the administration of one or more substances or preparations on persons where such an administration may have a pharmacological or harmful effect” (Sect. 6 Subs. 2 CCTA). The act explicitly rules out trials, which constitute a part of medical qualification/training (Sect. 6 Subs. 2 b CCTA), research on the nutritional effect of substances recognised as normal dietary constituent (Sect. 6 Subs. 2 c CCTA), and most significant the administration of untested substances or

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preparations in the course of medical treatment, as far as they are primarily intended to serve the welfare of the recipient (Sect. 6 Subs. a 2 CCTA).

Any person attempting to conduct the clinical trial, has to apply to the Minister of Health for permission (Sect. 3 Subs. 1 CCTA). The *Irish Medicines Board* takes care of these matters<sup>26</sup>. The permission may be granted, refused or granted, but subjected to modifications (Sect. 4 Subs. 1 (i)-(iii) CCTA). Permission granted, according to Sect. 6 Subs. 2 (i) CCTA, may be revoked by the Minister according to Sect. 7 CCTA if s/he is of the opinion that the conduct of the trial is deviating from the permission or should for other reasons not continue.

Each research proposal has to identify the ethics committee, which will be responsible for the evaluation of the project (Sect. 3 Subs. 1 (c) CCTA). The Minister may, as part of his decision on the proposal (but before the final decision is made), approve or disapprove of the nomination of the ethics committee, chosen by the researcher. If the Minister is satisfied with the nominated committee, the committee has to give its opinion on the justification of the trial and the circumstances, under which it is proposed to be conducted (Sect. 8 Subs. 2 CCAT). If the trial is approved, the decision has to be communicated to the Minister in writing by the applicant. The committee may not give a positive vote until it is assured that the risks to be incurred by participants would be commensurate with the objectives of the trial (Sect. 8 Subs. 2 CCAT).

In making this judgement the committee has to consider a list of criteria, given in Sect. 8 Subs. 3 CCAT, among others: the qualification of the researchers and staff involved, the extent to which the health of the participants of the research is monitored during an after trial, the objectives of the proposed trial, protection of identity and confidentiality of data, as well as payments, rewards and inducement offered and given to the participants. The whole process of decision (including the committees vote) has to take place within twelve weeks after the application (Sect. 4 Subs. 1 CCAT). If the applicant on its own accord amends the proposed clinical trial, the Minister as well as the responsible ethics committee has to agree to the amendments (Sect. 5 Subs. 2 CCAT).

The Act does not provide criteria for composition or procedural rules of ethics committees, besides stating in Sect. 3 Subs. 1 (c) and Subs. 2, that the Minister has to approve members and their relative qualification. The composition of the committee may only be changed with the approval of the Minister (Sect. 8 Subs. 5 CCAT). The Minister of Health is empowered to issue regulations to implement the provisions of the Act (Sect. 17 CCAT) including procedural rules for ethics committees and the like.

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<sup>26</sup> For more information q.v. <http://www.imb.ie/inner.asp?nav=2,82&pos=1&num=2>.

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Ireland signed the *Convention on Human Rights and Biomedicine* on the 4 April 1997. The convention has not yet been ratified by Parliament.

b) Current situation

According to our information, received from the Irish Council of Bioethics, there are approximately 52 research ethics committees in Ireland and no central institution for LECs. Most of them are located in hospitals and universities. Whilst most of them comply with the Helsinki Declaration, each Ethics Committee defines its own standard operating procedures and appoints its own members.

Local committees use their own application forms and have different requirements. There are no established procedures for multi-centre trials and no institution for appeal.

Responding to the EU Clinical Trial Directive, The Department of Health and Children published their proposed legislation in September 2003. A central authority shall be established with the responsibility for funding, auditing and potentially disbanding research ethics committees, to consider clinical trial research protocols. This proposal complies with the requirement for a 'single opinion' from a Member state in multi-centre and multi-clinical trials. There is no intention to extend the system to other areas of biomedical research.

c) References

Department of Health and Children (2003). *Public Consultation on Implementation of 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 Relation to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use.* /OJ No. L. 121, 01.05.2001, p. 34–44). <<http://www.doh.ie/pdfdocs/clintria.pdf>> 1 December 2003.

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## 9. Italy

a) Historical background and legal framework

In Italy the research ethics committees were establishment but not based on legal norms. Instead, they arose spontaneously from local initiatives. *Comitato Nazionale per*

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*la Bioetica* felt responsible for filling the gaps of legal regulations and offering advice and guidance regarding the constitution of committees: in February 1992 it published a statement *I comitati etici*, which was followed by a *decreto ministeriale* with the purpose of incorporating the EC directive 51/507 on good clinical practice guidelines.

In 1997 the existing European guidelines, regulating the drug trials, were adopted by the decree of the Italian Ministry of Health (*Ministerio della Sanità, Decreto Ministeriale 15 luglio 1997, Recepimento delle linee guida dell'Unione Europea di Buona Pratica Clinica per la esecuzione delle sperimentazioni cliniche dei medicinali, Gazzetta Ufficiale della Repubblica Italiana, Roma, 18 Agosto 1997*).

Since the European guidelines left many questions of details and procedures open and did not cover biomedical research, the statement of the national committee still had important effects, where multiple tasks for ethics committees were listed. Ethics committees should not only evaluate the proposed research on human beings, but also give ethical consult in clinical practice, promote awareness of ethical issues in medicine, train experts who work in the field of health care and are dealing with moral questions as well as discuss problems, initiated by the advances in medicine. The increasing workload of reviewing research projects as well as the diversity of tasks and demands caused many difficulties, which were further elaborated on in the second statement of the *Comitato Nazionale per la Bioetica*.

#### b) Current activities

In the meantime other associations were launched for harmonizing and streamlining the procedures of ethics committees, which are evaluating medical research. The *Società Italiana per la Bioetica e I Comitati Etici* (SIBCE) sees its principle area of responsibility in the promotion of awareness of moral issues in medical research. The *Federazione Nazionale dei Comitati di Etica* (FNaCE) was founded in 1995 and defined its tasks as the promotion and co-ordination of the work of ethics committees. It plays an important role in all training programmes for members of ethics committees. For the increasing number of multi-centre clinical trials and their supervision, the *Comitato Etico Nazionale per la Ricerca e per le Sperimentazioni Cliniche dei Medicinali* is also important.

In April 2000 the *Comitato Nazionale per la Bioetica* initiated the consultations on the current state of ethics committees in Italy. The importance of training for ethic committees' members is emphasised at the very beginning as the guarantee for safety, well-being and respect to persons. The committee also proposes to split the committees: in future one body shall be responsible for research (*commissione per la Ricerca Biomedica*) and the other for clinical and other medical questions (*comitato per la Bioetica*).

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Currently there are 289 local ethics committees in Italy (*Comitati di Etica*: CE or CdE), which activities are facilitated by the FNACE's prepared flow charts.

c) References

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## 10. Luxembourg

### a) Legal framework

With the Law of 28 August 1998 on hospital establishments (*Mémorial: Journal Officiel du Grand-Duché de Luxembourg, Part A, 18 September 1998, No. 78, pp. 1564-1672*) the Grand Duchy recast two earlier laws on hospitals, viz. the Law of 29 August 1976 on hospital planning and organization and the Law of 31 July 1990 aimed at assuring hospital services in accordance with the country's needs. New elements include Chapter 9, Secs. 24 and 25 which mandate the activities of hospital ethics committees and research ethics committees.

Following the opinion 2/96 of the Commission consultative *Nationale d'éthique pour les sciences de la vie et de la santé* section 24. (1) requires every hospital and every specialized hospital establishment "shall be equipped, either individually or in association with one or more hospitals or specialized hospital establishments, with a hospital ethics committee." Their task is to provide assistance in decision-making-processes and to prepare guidelines to be followed within the hospital wherever ethical issues are involved.

Section 25 reads as follows: "No trial, study, or experiment may be carried out on human beings with a view to furthering biological or medical knowledge unless the project has been submitted beforehand for the opinion of a research ethics committee. The research ethics committee shall consist, in addition to a majority of persons competent in medicine, pharmacy, biology, or chemistry, of persons competent in ethical, social, or legal matters. The members of the committee shall be appointed by the Minister of Health.

The organization and working procedures of the research ethics committee may be the subject of Regulations of the Grand Duke. The research ethics committee shall issue its opinions entirely independently. If and to the extent that the opinion of the research ethics committee is not favourable to the project or makes it subject to conditions or restrictions deemed unacceptable by the research sponsor, the latter may not disregard the opinion without having first referred it to the Minister of Health, whose decision shall be binding for the research sponsor and the investigator. Neither the opinion of the committee nor the decision of the Minister of Health shall exempt the research sponsor or investigator from his liability. The sponsor or, failing that, the investigator, shall take out an insurance covering his liability and that of all parties involved".

### b) Current situation

Neither the on-line researching through the web pages of Luxembourg hospitals nor the on-line information on the research institutions in Luxembourg nor the recent

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literature could provide us with details on how the new hospital law and the regulations concerning research ethics committees are translated into practice.

### c) References

Luxembourg (1998). *Law of 28 August 1998 on hospital establishments. (Mémorial: Journal Officiel du Grand-Duché de Luxembourg, Part A, 18 September 1998, No. 78, pp. 1564-1672)* Lux.99.001. <<http://www3.who.int/idhl-rils/frame.cfm?language=english>> 1 December 2003.

Commission Consultative Nationale d'Éthique pour les Sciences de la Vie et de la Santé (1999). „Avis 2/96 sur les comités d'éthique hospitaliers. Recommandations de la CNE à l'égard de la mise en place éventuelle CEH au Luxembourg et des modalités gouvernant celles-ci.“ *Journal International de Bioéthique* 10/5: 71–72.

Commission Consultative Nationale d'Éthique pour les Sciences de la Vie et de la Santé (1997). „Rapport annuel 1995.“ *Journal international de bioéthique* 8/4: 107–109.

Commission Consultative Nationale d'Éthique pour les Sciences de la Vie et de la Santé (1992). „Avis concernant la brevetabilité des inventions biotechnologiques.“ *Journal international de bioéthique* 3/4: 262–265.

Paediatric Rheumatology International Trials Organisation, PRINTO. *Formulaire d'information et de consentement pour une personne participant à une recherche biomédicale: enfant avec bénéfice individuel direct.* <[http://www.printo.it/file\\_pdf/CF\\_Luxemburg.htm](http://www.printo.it/file_pdf/CF_Luxemburg.htm)> 1 December 2003.

## 11. The Netherlands

### a) Historical background and legal framework

The legal framework for the work of ethics committees in the Netherlands is quite explicit. According to the *Medical Research Involving Human Subjects Act (WMO)* every activity involving persons being subjected to medical treatment or being required to behave in a certain manner, is considered as medical research and therefore is subject to revision by an ethics committee.

Most forms of research may be supervised by a local committee; local committee could be established if the following conditions specified in Sect. 15 Subsect. 2 *WMO* are met: 1) the committee must include at least one doctor, persons with expertise in law, research methodology and ethics as well as person, possible to review the protocols explicitly from the research subject's position; 2) the local committee must have standing orders (structural guidelines); 3) these orders must state the area of the committee's activities, the procedures for the committee's activities, and have to make adequate provisions for co-operation with further experts in order to ensure the adequate review of submitted protocols; 4) lastly,

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there must be a reasonable expectation that the number of submitted protocols will exceed a certain ?.

When all of those requirements are met, the local committee is a subject to the recognition by the *Centrale Commissie Mensgebonden Onderzoek (CCMO)*. CCMO has mandate of the central review organisation, as well as the direct authority to supervise certain areas of research (for example gene therapy and xenotransplantation). The committee's approval of the submitted protocol is necessary to launch the research project. If the supplicant does not agree with the committee's decision, s/he, as well as any other interested party, may lodge an administrative appeal against the decision under Sect. 23 *WMO*. The *CCMO* is the competent authority in charge of reviewing those appeals.

The *WMO* entitles the local committees to charge supplicants a fee to cover its expenditures.

All decisions have to be notified to the *CCMO*. The committees are obliged to issue a report of its activities, which has to be made available to the public by the *CCMO*.

The *CCMO* itself is composed of at least thirteen members nominated by the Dutch Minister of Health and appointed by Royal Decree (meeting the same rules of composition mentioned above) and is empowered to issue standing orders of operation subject to the approval by the Minister.

The *WMO* (Sect. 3-6) also specifies the terms under which medical research is permissible at all. Research on persons, who have not reached the age of 18 years, is not permitted, except for those cases where there may be a direct benefit for the subject or the risk of participation is negligible. Those cases have to be handled directly by the *CCMO*. Research on persons is not permissible if the research subject has an actual or legal relationship with the researcher or the party recruiting the subject may influence the results of research. Sect. 6 of the *WMO* spells out the conditions of informed consent, containing *inter alia* provisions on representation and research in emergency situations.

Besides the *WMO*, there are other legal documents relevant to clinical trials and local ethics committees. The most important among them is the *Temporary Decree regulating obligatory insurance for medical research involving human subjects*, actual from 1 December 2002 (replacing the previous relevant decree from 5 July 1999), the *CCMO Directive concerning the review procedure for multi-centre research (Multi-centre Research Review Procedure Directive)* from 1 January 2003 and the Directive on organisation and working procedures for medical ethics committees, meant to enter into force on 1 January 2004 and containing, amongst others, provisions regarding the make-up, independence, decisional procedures and funding of the local ethics committees.

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b) Current situation

Compared with other double-stringed ethics committee systems, the Dutch system has a quite strong centralised power. With the strong position of the CCMO it could be stated that the Dutch system functions under the delegation of power from the government. The CCMO is also responsible for the national training course for members of ethics committees. The network of Dutch local ethics committees has established the Dutch Association of Medical Ethics Committees.

c) References

Agt, F. M. van; Dekkers, W. J. M. (1998). „Ethici en de proportionaliteit van wetenschappelijk onderzoek met mensen.“ *Medisch Contact* 53/7: 239–240.

The Central Committee for Medical Research Involving Human Subjects (CCMO) (2002). Directive of the Central Committee for Medical Research Involving Human Subjects (CCMO) pursuant to section 24 of the Medical Research Involving Human Subjects Act (WMO), concerning the review procedure for multicentre research (Multicentre Research Review Procedure Directive). <<http://www.ccmo.nl>> June, 11 2001.

Groot, M. G. de; Epenhuysen, L. S. van (1997). „Ethici in toetsingscommissies. Personen met deskundigheid op het gebied van de ethiek?“ *Medisch Contact* 52/7: 225–226.

Kloot, H. H. van der (1992). „Institutional Ethics Committees in the Netherlands.“ *HEC (HealthCare Ethics Committee) Forum* 4/3: 209–217.

Noach, E. L. (1995). „Ethische beoordeling van bioedische experimenten in Nederland.“ *Verhandelingen (Koninklijke Academie voor Geneeskunde van België)* 57/1: 157–182.

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## 12. Portugal

a) Historical background and legal framework

In Portugal clinical trials are governed by decree no. 97/94 (DL 97/94) issued by the Ministry of Health on 9 April 1994. In the framework of Portuguese law, the concept of “clinical trial” covers any “...*systematic study involving medicine to be conducted on human beings, with the purpose of investigating or checking the effects and/or studying their absorption, distribution, metabolism and excretion, in order to determine their effectiveness and safety.*” (Art. 1 Subs. 2 DL 97/94).

In order to perform clinical trials, the would be researcher has to obtain the approval from the responsible administrative organ of the institution, in which

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research is to be conducted, as well as the assent of the institutions' ethics committee (Art. 7 Subs. 1 DL 97/94). Any institution, whether private or public, may house an ethics committee, but those institutions who do not, may not conduct clinical trials at all.

Reviewing the proposed trial, the ethics committee takes into account the researcher's scientific qualification and clinical experience, the technical and support conditions in which the trial shall be conducted and the appropriateness of the protocol to the objectives of the trial with special attention to the foreseeable risks and benefits. The committees' responsibility does not end with the beginning of the trial. It is in charge of monitoring the execution, with special consideration given to ethical aspects and the security and integrity of the subjects. In the context of monitoring, the committees are empowered to suspend and even revoke a prior positive vote, thereby suspending or stopping the trial (Art. 18 DL 97/94).

Regulations regarding the composition, powers and mode of functioning of ethics committees are relegated (pursuant to Art. 8 Subs. 3 DL 97/94) to a further decree having been issued on 10 May 1997 as DL 97/95.<sup>27</sup> DL 97/94 does not contain any provisions regarding budgeting or the admissibility of charging fees for the committee's work.

DL 97/94 provides rules for obtaining consent (Art. 10 DL 97/94), informational requirements (Art. 9 DL 97/94), confidentiality (Art. 11 DL 97/94) and insurance (Art. 14 DL 97/94).

The approval of the ethics committee and administrative body of the institution, as well as the beginning of the trial should be communicated to the *Instituto Nacional da Farmácia e do Medicamento (INFARMED)* by the trials' promoter as specified in Art. 7 Subs. 5 DL 97/94. A special body of this institution, the National Centre for Pharmacovigilance, also being in charge of the statutory follow-up concerning such trials, notifies trials to the *INFARMED*.

In addition to the national regulation discussed, Portugal is a signifier to the *Convention on Human Rights and Biomedicine*, the convention having entered into force there on December 1<sup>st</sup> 2001.

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<sup>27</sup> We were not able to locate an English translation of DL 97/95. For specifics relating to DL 07/95 we therefore have to defer to the résumé given by Monteiro/Andrade/Costa/Pereira in Deutsch/ Taupitz [Hrsg.], *Forschungsfreiheit und Forschungskontrolle in der Medizin : zur geplanten Revision der Deklaration von Helsinki*, 2000, Berlin, Springer, S.150-154.

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b) Comments

Our research suggests that the explicit provisions laid down in DL 97/94, are largely “law in books” and do lack translation into practise. One of the reasons for such a situation is the insufficient time resources of the committee’s members, who, besides their obligations to the committee’s are medical personnel. Another reason is the absence of provisions on financial compensations for the committee and thus most of the job, which could be done by the supporting staff, is considered by the committees’ members themselves.

c) References

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- Martino da Silva, R. (1993). „Avis sur les greffes d'organes et de tissus (1991).“ *Journal international de bioéthique* 4/2: 154–155.
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- Monteiro, Sinde et al. (2000) [Andrade, Costa; Costa, Faria; Dias Pereira, André Gonçalo]. „Country Report Portugal.“ In: Deutsch, Erwin; Taupitz, Jochen (Hgg.). *Forschungsfreiheit und Forschungskontrolle in der Medizin. Zur geplanten Revision der Deklaration von Helsinki [= Freedom and Control of Biomedical Research. The Planned Revision of the Declaration of Helsinki]*. Berlin; Heidelberg; New York; Barcelona; Hongkong; London; Mailand; Paris; Singapur; Tokio (Veröffentlichungen des Instituts für Deutsches, Europäisches und Internationales Medizinrecht, Gesundheitsrecht und Bioethik der Universitäten Heidelberg und Mannheim, 2): 149–154.
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### 13. Spain

#### a) History background and legal framework

The rules for clinical trials and the role ethics committees play therein are specified in Royal Decree 561/1993<sup>28</sup> (RD 561/1993) issued on 16 April 1993. In accordance with the regulations already given in the Medical Act (*Ley del Medicamento* from 20 December 1990 abbreviated as LM hereafter) the research ethics committees have to approve every research protocol prior to the trials' beginning. These committees have to be established in every public or private hospital or health centre intending to perform research involving human subjects.

The committees have to be accredited by the local authority in charge of health care (Art. 64 Abs. 1 LM as well as Art. 39 RD 561/1993).

The committees' scope of evaluation is not restricted to ethical or legal aspects. They also have to take into account aspects of purely methodological and scientific

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<sup>28</sup> Information regarding the legal situation in Spain has been kindly provided by Mr. Carlos Maria Romero-Casabona.

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nature as well as the equilibrium of likely risks and gains. The committees' functions are spelled out clearly in the above-mentioned Royal Decree:

- “1. They will evaluate the suitability of the medical protocol in relation to the objectives of the research, its scientific efficiency (the possibility of reaching valid conclusions, with the less possible exposition of subjects) and the justification of the risks and previewed annoyances, weighted in function of the expected benefits for the subjects and the society.
2. They will evaluate the suitability of the research team for the aimed trial. It will take into account its experience and research capacity to carry the study forward, paying attention to its care duties and commitments previously acquired in relation to other research medical protocols.
3. They will evaluate the written information about the features of the trial that will be given to the possible subjects of the research, or failing that, to their legal representatives, the way that such information will be given and the type of consent that is going to be obtained.
4. They will test the foresight of the compensation and treatment that will be offered to the subjects that take part, in case of injury or death that could be attributed to the clinical trial, and of the insurance or indemnification to cover the responsibilities specified in article 13.2.
5. They will know and evaluate the reach of the compensations that will be offered to the researchers and the subjects of the research for their participation.
6. They will make the follow-up of the clinical trial from its beginning until to receive the final report” (art. 42, RD 561/1993).<sup>29</sup>

The committees themselves, as well as their members, have to be independent (Art. 64 Abs. 1 LM) and – probably as a function thereof – do not receive any payment for their work.

The committees have to consist of at least seven members, containing a lawyer and one layperson, the rest being recruited from medical professions and the nursery staff. ( Art. 41 RD 561/1993 and Art. 64 Abs. 3 LM).

## b) Comments

Except for accreditation there seems to be no centralized supervision of the local ethics committees' work. Besides, Spanish legislation also lacks any explicit regulations on multi-centre clinical trials.

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<sup>29</sup> This is an unofficial translation provided by Mr. Carlos Maria Romero-Casabona.

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- Spain (1993). *Real Decreto 561/1993, de 16 de abril, por el que se establecen los requisitos para la realización de ensayos clínicos medicamentos. Título I. Consideraciones Generales y Principios Básicos*. <<http://www.juridicas.com/base-datos/Admin/rd561-1993.t1.html>> June, 12 2003.
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- Spain (1993). *Real Decreto 561/1993, de 16 de abril, por el que se establecen los requisitos para la realización de ensayos clínicos medicamentos. Título IV. Del Cumplimiento de las Normas de Buena Práctica Clínica y de las Inspecciones de Buena Práctica Clínica*. <<http://www.juridicas.com/base-datos/Admin/rd561-1993.t4.html>> June, 12 2003.
- Tato, F. (1998). „Regional Clinical Research Ethics Committees.“ *Methods and Findings in Experimental and Clinical Pharmacology* 20/Suppl. A: 15–18.

### 14. Sweden

#### a) Historical background and legal framework

There are at least three different regulations in Sweden, dealing with clinical trials: the *Medicinal Products Act* (*Läkemedelslag*, SFS 1992: 859), the Decree on Medicinal

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Products (*Läkemedelsförordning*, SFS 1992:1752) and the *Medical Products Agency's Code of Statutes* (*Läkemedelsverkets föreskrifter och allmänna råd om klinisk läkemedelsprövning*, LVFS 1996:17 being abridged as LVFS in this text)<sup>30</sup>.

Speaking in terms of normative hierarchy, the act is the most specific but has the lowest rank. As far as can be established, the LVFS is based on the *Decree on Medicinal Products*, which in turn refers to the *Medicinal Products Act*. Clinical trials are mentioned in § 13 of the *Medicinal Products Act* and § 10 of the *Decree on Medicinal Products*. The LVFS refers to the *Medicinal Products Act* regarding the definition of legal terms used (Part 1 Sect. 3 LVFS) but also states a definition for clinical trials of medicinal products in Part 1 Sect. 4: “...*clinical trial of medicinal products [is] any systematic study of the effect of medicinal products on humans, both patients and volunteer subjects, with the purpose of discovering or confirming the efficacy of the medicinal product and/or of identifying any side-effects and/or studying its absorption, distribution, metabolism and excretion so that the safety of the product can be guaranteed...*”

Pursuant to Part 2 Sect. 1 LVFS the Medical Products Agency (MPA) is responsible for issuing the authorisation for clinical trials. If a multi-centre trial is proposed each participating centre has to apply separately in addition to the complete application (Part 2 Sect. 2 LVFS).<sup>31</sup>

Part 3 Sect. 1 of the LVFS states that the responsible investigator of a proposed trial shall apply for authorization at the competent regional ethics committee. The trial may not commence before the approval of the ethics committee has been granted.

The ethics committees act as advisory body for the MPA and has to evaluate the design of the trial prior to its start. This examination has to cover scientific feasibility, ethical aspects, patient information and informed consent. The regional ethics committee may delegate the task to a local regional ethics committee (Guidelines relating Part 3 LVFS). Regarding to the composition of the committee, the LVFS states in Part 1 Sect. 4: “...[an] ethics committee [is] an independent committee consisting of both medical scientific expertise and laypeople..”, stating further, that: “...[its] responsibility is to ensure that patient’s rights, well-being, safety and integrity are respected and that the trial otherwise is appropriate and possible to conduct at a particular location...” The ethics committee is not responsible for monitoring a trial of which it has approved.

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<sup>30</sup> Only the third regulation was available in English during the production of this report, thus in no means this presentation can claim the throughout overview of Swedish documents, since the lack specific of language skills

<sup>31</sup> This is applicable only if each of the multi-centre trials are conducted only in Swedish facilities. If the trial is run in different EU countries, the task is delegated to the European Agency for Evaluation of Medicinal Products. C.v. <http://www.mpa.se/eng/regulatory/index.shtml> .

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The LVFS provides no further norms for composition or mode of conduct of ethics committees. There are provisions relating to information and consent (Part 8 LVFS), Insurance (Part 9 LVFS), handling of data (Part 16 LVFS) and various other issues.

The LVFS declares the Declaration of Helsinki to be applicable for clinical trials conducted in Sweden.

Sweden signed the *Convention on Human Rights and Biomedicine* on 4 April 1997. The Swedish Parliament has not yet ratified the convention.

## b) References

Medical Products Agency (1997). *Medical Products Agency's Provisions and Guidelines on the Clinical Trials of Medicinal Products*; adopted 15 November 1996. LVFS 1996: 17. <[http://mpa.se/eng/lvfse/LVFSe\\_1996-17\\_2.html](http://mpa.se/eng/lvfse/LVFSe_1996-17_2.html)> 19 June 2003.

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Nilstun, Tore (1992). „Forskningsetiska kommittéer bör ändra praxis. Fokusera på svårbedömda projekt, motivera beslut.“ *Läkartidningen* 89/8: 581–582.

Standing Conference of National Ethics Committees <Sweden> (1994). „Troisième réunion des Comités nationaux d'éthique. Stockholm, 8–9 avril 1994.“ *Journal international de bioéthique* 5/3: 245–246.

## 15. United Kingdom

### a) Legal framework

The legal framework in which research ethics committees in the United Kingdom operate can be described as two layered. The one layer consists of “hard legislation” governing medical treatment and related matters, like the law concerning capacity to consent. Another example of those “hard laws” is provided by the *Human Fertilisation and Embryology Act* (HFE) and the Code of Practice issued by the *Human Fertilisation and Embryology Authority* (HFEA) on its ground. The code of practice

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prescribes (Part. 11.6) each research project governed by the HFE to be evaluated by a properly assigned ethics committee prior to its commencement.<sup>32</sup>

But the greatest part of the regulations governing research on human subjects falls into the category of “soft law”. Although it may be questioned if they constitute legal norms in the strict sense of the word, they are nevertheless in effect quite binding. This is the case mainly for two reasons: First of all the vast majority of research studies take place within the context of the National Health Service.<sup>33</sup> Thus researchers’ compliance with established standards of ethical conduct is guaranteed by their researchers’ contracts. While there is also a small amount of private medical research, the General Medical Council (the authority which is charged with the registration of doctors) would require the same conditions to be fulfilled in these cases. Moreover, none of the reputable journals would publish results that were obtained from a study, which was not properly evaluated beforehand.

Therefore, research projects that do not receive the approval of a research ethics committee are not illegal in the first place but face serious problems of funding and the publication of results. Furthermore, the lack of approval may be grounds for latter civil actions by participants of the trial if anything goes wrong or may even be attacked by public law remedies in some cases.<sup>34</sup> The UK fields a vast number of Ethics Committees at the local level, as well as some central committees responsible for certain kinds of research.<sup>35</sup>

The United Kingdom has not signed the Convention on Human Rights and Biomedicine.

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<sup>32</sup> These regulations apply to England and Scotland uniformly.

<sup>33</sup> Q.v. John W.G. Blackie and Andrew Horne, “Country Report United Kingdom” in Erwin Deutsch/ Jochen Taupitz “Freedom and Control of Biomedical Research”, Berlin, 2000, S. 209.

<sup>34</sup> Q.v. J. Montgomery, “New Law Needed for Better RECs”, 1992 (78) Bulletin of Medical Ethics S. 34 – 35; T. Mander “The Legal Standing of Local Research Ethics Committees”, 1996 II Med Law International S. 149 ff.

<sup>35</sup> E.g. the *Gene Advisory Committee* for genetic studies, the *United Kingdom Xenotransplantation Interim Regulatory Authority* for xenotransplantation. Both bodies have to approve of research proposals within these topics and also advise local ethics committees in such matters. Another example is the *Clinical Research Committee of the Royal College of General Practitioners* which has to evaluate all drug trials in the primary care sector in the community. Q.v. John W.G. Blackie and Andrew Horne, “Country Report United Kingdom” in Erwin Deutsch/ Jochen Taupitz “Freedom and Control of Biomedical Research”, Berlin, 2000, S. 212.

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b) Historical background

The system of ethical review is well established in the UK since the mid-1970s when the first informal committees began to form. Originally formed as an effort of self-regulation within the medical community the system became stricter, when the *Department of Health and Social Security* required local research ethics committees to be set up, where there had been none before<sup>36</sup>. The guidelines issued by the department clarified that it was the responsibility of the *National Health Service* (NHS) to approve of research projects but that it had to take the opinion of the relevant local research ethics committee (LREC) into account. Whereas the committees were said to normally be organised on a health district basis, it was also stressed that they are not in any sense management arms of the District Health Authority. Nevertheless, the District Health Authority is named as the body in charge of establishing the LREC in those regions where none existed before.<sup>37</sup>

c) Composition of research ethics committees and procedures of ethical review

The *National Health Service's* guidelines also provide some criteria for the composition and procedure of LRECs. The committees should have eight to twelve members hailing from different professions thus allowing for a reasonable range of experience in science, medical practice and other matters related to health care including the ethical implications. Members should be drawn from both sexes and from a wide range of age groups. The members should include members of the hospital medical staff, the nursing staff, general practitioners and at least two laypersons.<sup>38</sup> It is also stressed that, although the members should be drawn from groups with an interest in and a connection to health care issues, they do not act as the representatives of their respective groups. Whereas the guidelines provide for laypersons being members of the LRECs, the definition of layperson seems to be somewhat of a controversy in the UK. The laypersons are often drawn from quite a narrow scope of society, being lawyers, theologians and the like and their participation in the decision-making process seems to be hampered by information being provided in too scientific a form.<sup>39</sup> The department's guidelines also contain

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<sup>36</sup> Department of Health and Social Security, "Local research ethics committees", London 1991. A similar guideline with certain variations was issued for Scotland: Department of Health and Social Security, "Local research ethics committees", Edinburgh, 1992.

<sup>37</sup> Department of Health and Social Security, "Local research ethics committees", London 1991, Chapter 2.1, S7.

<sup>38</sup> Department of Health and Social Security, "Local research ethics committees", London 1991, Chapter 2.4 and 2.5, S. 7.

<sup>39</sup> John W.G. Blackie and Andrew Horne, "Country Report United Kingdom" in Erwin Deutsch/ Jochen Taupitz "Freedom and Control of Biomedical Research", Berlin, 2000, S. 211.

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broad outlines for working procedures, periods of appointment, confidentiality, criteria of evaluation, as well as some advice on legal liability of committee members.

Another guideline with some impact on the work of LRECs in the UK is issued by the *Royal College of Physicians*<sup>40</sup>. Although just professional law and not universally binding even for medical professionals, these guidelines have gained a wide recognition. A number of further guidelines also have some degree of influence<sup>41</sup>.

The diversity of different standards and norms in the field and the further differences of interpretation the RECs apply to these standards lead to a very heterogeneous practice in the evaluation of research practices as some surveys published in the *Bulletin of Medical Ethics* may indicate. This situation is not only somewhat ambiguous from the perspective of legal consistence but also poses a problem in cases of multi-centre studies. There has been a move towards a more centralised system of ethical review<sup>42</sup>, which was furthered by a recommendation *Royal College of Physicians* issued in 1996. This recommendation put forward the ideal that multi-centre-studies should be dealt with by central committees while confining the LRECs to those issues that can only be assessed locally.<sup>43</sup>

#### d) Regional multi-centre research ethics committees

In 1997 the *National Health Service* published a guideline<sup>44</sup>, which required each of the English regions to set up one Multi-centre Research Ethics Committee. Similar arrangements were being made for Scotland, Wales and Northern Ireland. In England the *Central Office for Research Ethics Committees* (COREC) is authorised by the Department of Health, to deal with matters regarding the development and operational systems of research ethics committees including the training of

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<sup>40</sup> Latest version: Royal College of Physicians „Guidelines on the practice of ethics committees in medical research involving human subjects“ Third Edition, 19996.

<sup>41</sup> For some of them, like the minimum code of conduct established by the General Medical Council or the United Kingdom Central Council (the nurses' registration authority) q.v. Horner, JS “Criteria for Decision Making in Local Research (Ethics) Committees”, *Public Health*, 1993 (107), S. 403-411 for more detail.

<sup>42</sup> Which has already taken place in certain areas, q.v. footnote 4.

<sup>43</sup> Department of Health, “Ethics Committee Review of Multi-Centre Research Consultation Paper (London 1996).

<sup>44</sup> National Health Service Executive, “Ethics Committee Review of Multi-Centre Research”, HSG(97)23, April the 14<sup>th</sup> 1997. This document, as well as HSG (91)5 dealing with the establishment of local research ethics committees, was replaced by: Department of Health, “Government Arrangements for NHS Research Ethics Committees”, July 2001.

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members of ethics committees. Specifically they have to manage the Multi-centre Research Ethics Committees<sup>45</sup>.

e) Discussion and comments

Differences aside there seem to be some commonly recognised features that characterise the practice of ethics committees in the UK. The focus of the LRECs' work may be summarised as evaluating a projects efficacy, tolerability and acceptability as well as its use and dissemination of findings<sup>46</sup>. All of these aspects are in a way part of the projects ethical appropriateness. But there is a consensus that LRECs have to evaluate the scientific soundness of a protocol as well as its ethical aspects. This stems from an interpretation of unscientific research as also being unethical<sup>47</sup>. However, it is also very important to emphasize again the role of research ethics committees. It is not their role to authorise research, that part is left to the health authorities. Their role is to advise and thus help the researcher while protecting the dignity, rights, safety and well being of all actual or potential research participants.<sup>48</sup>

After the establishment of regional ethics committees and with regard to the implementation of the European Directive on Good Clinical Practice there is an ongoing debate in the United Kingdom concerning the balance of power between the local and the regional level. On the one hand, there is hope for streamlining the process of review by strengthening the regional level whereas, on the other hand, some people claim that the local level of review is the only one that is able to protect the subjects of clinical trials.

Besides COREC ethic committees in the UK they have built up a non-governmental organisation: AREC, the Association of Research Ethics Committees is an independent, self-governing body of local and multi-centre Research Ethics Committees, including their members and administrators. AREC provides meetings and training for members of Research Ethics Committees.

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<sup>45</sup> For more information q.v. <http://www.gqp22.dial.pipex.com/index.htm>.

<sup>46</sup> John W.G. Blackie and Andrew Horne, "Country Report United Kingdom" in Erwin Deutsch/ Jochen Taupitz "Freedom and Control of Biomedical Research", Berlin, 2000, S. 216.

<sup>47</sup> John W.G. Blackie and Andrew Horne, "Country Report United Kingdom" in Erwin Deutsch/ Jochen Taupitz "Freedom and Control of Biomedical Research", Berlin, 2000, S. 225.

<sup>48</sup> Q.v. Ian Kennedy and Phil Bates „Research ethics committees and the law" in Sue Eckstein [ed.] "Manual for Research Ethics Committees", Centre of Medical Law and Ethics, Kings College London, 6<sup>th</sup> edition, Cambridge, 2003, S. 16.

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## B. EU new Member states

### 1. Cyprus

#### a) Legal regulations

Currently there are two laws relevant to the biomedical research. Law No. 150 (I)/2001, issued on recommendation of the *Panyprian Medical Association* in 2001, established the Cyprus National Bioethics Committee (CNBC). Amongst others, CNBC is authorised to establish local research ethics committees, which would be mandated to review biomedical research projects in Cyprus. Law No. 31 (III)/2001 integrates the *Convention on Human Rights and Biomedicine* (Oviedo Convention), which was signed on 30 September 1998 and entered into force on 1 July 2002.

According to the Art. 16 Sect. 3 of the Oviedo Convention, Law No. 31 (III)/2001 establishes that any biomedical research project should be approved by the CNBC or any competent body to which the CNBC has delegated that task.

#### b) Historical background and local institutions

On the local level research, ethics committees were functional already before the above-mentioned legislation: the Bioethics Committee of the Institute of Neurology and Genetics, the Scientific Committee of the Panyprian Medical Association, the Medical and Scientific Advisory Board of the Karaiskakio Foundation and the Medical Research Ethics Committee of the Bank of Cyprus Oncology Centre. All of these committees work on the principles detailed in the Declaration of Helsinki and the European GCP Guideline.

#### c) References

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### 2. Czech Republic

#### a) Legal regulations

The system of local ethics committees in the Czech Republic has developed since 1990, when Martin Bojar, then Minister of Health, established the Central Ethics Committee as an advisory body, simultaneously recommending the establishment of

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local ethics committees in the major health care facilities.<sup>49</sup> But those (approximately 20) ethics committees did not gain any degree of legal recognition until 1997, when the Drug Act (No. 79/1997) delegated the review of research projects to them. The committees' approval is a requirement for the enactment of biomedical research in the Czech Republic.<sup>50</sup> In 1999 the Ministerial Decree was issued, providing the rules for Good Clinical Practice in the context of clinical trials. Finally, in 2000 another Act (No. 123/2000 on medical devices) delegated the authority to review and approve projects on the clinical evaluation of medical devices to the local ethics committees.

The Czech Republic yet lacks regional ethics committees that could evaluate projects taking place at smaller institutions, which cannot house their own ethics committee<sup>51</sup>.

The Czech Central Ethics Committee does not act as a body of appeal for the decisions of the local ethics committees. Instead, it continues to function as an advisory body, occasionally, depending on the esteem granted to it by the current Minister of Health, practising this mandate.

The Czech Republic has signed the *Convention on Human Rights and Biomedicine* on 24 July 1998. It entered into force on 1 October 2001.

#### b) Historical background

As described by Czech medical and research ethics experts, LECs in the Czech Republic worked beyond any legislation for many years and their survival was based on, *first* – enthusiasm of LECs members and their willingness to fulfil their moral duties; and *second* - support from the pharmaceutical companies, which were in need of LECs approvals for their research.

#### c) Public awareness and perception in the scientific community

According to the answers to our questionnaire, many Czech researchers perceive LECs as an unavoidable evil. It also seems that the public, in general, has no strong

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<sup>49</sup> Q.v. Jiří Šimek et. al. "Ethics Committees in the Czech Republic" in J. Glasa "Ethics Committees in Central & Eastern Europe" p. 170.

<sup>50</sup> As we could not obtain an English translation of the aforementioned act our information on the exact details are somewhat vague (we neither know anything about the committees composition nor the legal procedures) and also a bit outdated (2000).

<sup>51</sup> Q.v. Jiří Šimek et. al. "Ethics Committees in the Czech Republic" in J. Glasa "Ethics Committees in Central & Eastern Europe" p. 171.

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interest in their activities, neither does mass media nor the official institutions. Thus, employment with LECs is not recognised and there is no education for members of LECs provided.

#### d) References

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### 3. Estonia

#### a) Legal framework

The provisions for conduct of clinical trials in Estonia are laid down in Chapter 3 of the Medicinal Products Act (MPA).<sup>52</sup> According to the act, clinical trial is: “...*the use of a medicinal product in humans...in order to collect information on the effect, side effects, absorption, distribution, metabolism, excretion, efficacy and safety of the medicinal product*”<sup>53</sup> (§ 13 Subs. 1 MPA).

Clinical trials in Estonia may be conducted by a doctor, dentist or veterinarian in their respective area of specialisation (§ 13<sup>2</sup> Subs. 1 MPA). Every trial, not just those conducted on human beings, must have the approval of a medical ethics committee<sup>54</sup> for clinical trials. The committee has to evaluate the ethics of conducting the trial (§ 13<sup>4</sup> Subs. 2 MPA).

Furthermore, the consent of the competent state authority<sup>55</sup> must be obtained. The Agency of Medicines may refuse to grant its consent on grounds of non-compliance with the provisions of the MPA, one of them being the lack of approval by an ethics committee. All information concerning the trial must be submitted to the Agency of Medicines at least two months before the proposed trial’s beginning.

In conformance with § 13<sup>4</sup> Subs. 3 MPA the Ministry of Social Affairs issued a Regulation (RTL 2001, 90, 1258) on July 9<sup>th</sup> 2001 concerning the *Requirements for Membership of Medical Ethics Committees for Clinical Trials, Rules of Procedure for Committee, Rate of Fee for Evaluation of Clinical Trials and List of Information to Be Submitted in Order to Obtain Approval* (abbreviated MECCT hereafter).

The Regulation states the protection of the trial subject’s rights, their safety and well being, to be the committee’s main objective. According to the MECCT, the committee shall be independent (§ 2 Subs. 1) and must comprise of at least seven

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<sup>52</sup> The act has entered into force on 1 April 1996, but the provisions on clinical trial hail from a latter amendment (RT I 2001, 53, 308), having entered into force on 1 July 2001.

<sup>53</sup> The definition of „medicinal product” is given in 2 Subs. 1 MPA. “A medicinal product is any substance intended for the prevention, diagnosis or treatment of a disease or disease symptom, for the relief of a disease condition in a human or animal, or for the correction of vital functions in a human or animal. This definition in conjunction with § 13 Subs. 1 MPA stretches the term clinical trial to encompass trials on animals for veterinarian purposes but excludes psychological research and arguably also certain therapies not involving substances (e.g. radiation and the like).

<sup>54</sup> According to our information, there are currently two independent committees, one in Tallinn and one in Tartu.

<sup>55</sup> The Agency of Medicines is in charge of trials on human beings (§ 13<sup>6</sup> Subs. 1 AMP).

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members. At least one of them must be independent from the research centre and one must not be involved in scientific research.

The committee may charge a fee for its evaluation of the proposals, which may not exceed 400 Estonian kroons (§ 4 Subs. 1). When deciding on a proposal, the committee has the following options: a) it may approve of the proposal, b) it may request the researcher to modify the proposed trial, and c) it may refuse to grant approval.

When refusing to grant the approval, the committee has to give a reasonable explanation of its decision. The committee is also empowered to revoke or suspend a prior positive vote. The decision has to be communicated to the applicant within sixty days after the submission of all required documents to the committee. The decisions of the committee may be contested in court (§ 9 Subs. 2 MPA).

The Convention of Human Rights and Biomedicine was ratified by the Estonian Parliament in December 2001. In 2002 the Estonian Parliament discussed a draft law of Patients Rights. In the chapter on medical research it is foreseen that all biomedical research projects on human beings have to be approved by a competent Research Ethics Committee.

#### b) Historical background

The University of Tartu and Institute of Experimental and Clinical Medicine in the capital of Estonia, Tallinn, are the most important centres for biomedical research in Estonia. The first initiative in the field of bioethics started in Tartu at the beginning of the 1990<sup>th</sup>. The University established an *Ethics Commission of Human Research* in 1990. Besides reviewing biomedical research protocols the commission and their members have been concerned with the bioethical education of medical students and doctors. In 1993 a second committee was founded at the Institute of Experimental and Clinical Medicine in Tallinn. Both committees' work was guided by the principles of the Nuremberg Code, the Declaration of Helsinki and later by Convention on Human Rights and Biomedicine and a number of other relevant documents, especially the papers of the *Committee on Bioethics (CDBI)* of the Council of Europe.

In 1999 the functions of the Ethics Commission of Human Research were divided. The Commission was now called "Human Research Ethics Committee" and is now able to concentrate on the ethical evaluation of research projects. In the University of Tartu the teaching staff of the Medical Faculty obtained the responsibility for teaching bioethics which is mandatory and one of the three basic disciplines of the curriculum.

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c) Current situation

A main task of the *Human Research Ethics Committee* is to evaluate proposals for clinical trials of medicinal products. Moreover, each research project of doctoral students is required to pass the vote of the committee. Following an agreement between relevant research institutions and research funding institutions, the financing of any human research project was made possible only after the approval of the *Human Research Ethics Committee*. This is important since before the law of Patients Rights will be translated into action, only clinical trials are regulated by law in the Medicinal Product Act.

As described by Arvo Tikk in Sigulda, September 2002, the two above-mentioned Human Research Ethics Committees handle about 20 to 40 projects per month.

The majority of projects passed the *Committee* in Tartu.

“The Research Ethics Committee consists of 11 persons in Tartu and of 20 persons (with proxies) in Tallinn. The members of the Tartu University Committee are nominated by the Rector of the University of Tartu and the members of the Committee in Tallinn by the Director of the Institute of Experimental and Clinical Research.”<sup>56</sup> Members of the Committees are specialists in natural and medical sciences as well as clinicians and nurses. There has to be a lawyer in every committee. Besides the lawyer, psychologists, philosophers and theologians are regarded as laypersons. Tikk mentions difficulties in finding laypersons who are able to express the public opinion and are familiar with the problems of biomedical research.

Experts from Estonia indicate the increase of workload for the committees in the last decade.

d) References

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<sup>56</sup> Tikk, Research Ethics Committees in Estonia, Oral presentation, Sigulda, September 6, 2002.

#### 4. Hungary

##### a) Historical background and legal framework

Although the main ethics review body in Hungary, the *Scientific and Research Ethics Council* (Hungarian acronym ETI) is probably one of the oldest such bodies worldwide<sup>57</sup>, Hungarian law did not provide rules for the involvement of ethics committees in research on human beings until recently.

In July 2002 the Ministry of Health issued Decree No. 23/2002 giving a detailed definition of biomedical research, including the field of genetic research. Another decree (Health Ministry Decree 12/2001) sets up the legal framework for the licensing and registration of human pharmaceutical products. Finally, Health Ministry Decree 24/2002 details on clinical trials in products for human use and on Good Clinical Practice.

Under the new legislation, there are three levels of ethics committees involved in the evaluation of biomedical research: the Institutional Ethics Boards (IEB) the Regional Research Ethics Board (RKEB), the *National Scientific and Research Ethics Board* (TUBEK) and, also at the national level, the Clinical Pharmacology Ethics Commission (KFEB).<sup>58</sup> Our sources provide no information on the exact interplay of those institutional levels or the successive stages of appeal, but chances are that they are hierarchical and that there is some means of appeal against the decision of the lower bodies. The law requires the applicants for biomedical research projects to forward a complete description and justification for the proposed project to the relevant body. The responsible committee has to review the projects “in timely fashion” giving special consideration to matters of informed consent, as well as the suitability and feasibility of the proposed project.<sup>59</sup>

Hungary signed the *Convention on Human Rights and Biomedicine* on 7 May 1999. The convention entered into force there on 1 May 2002.

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<sup>57</sup> The history of this body can be traced back to 1864 according to a recent study, q.v. Judit Sándor “Hungary; Kluwer International Law; Medical Law” Suppl. 31 (April 2003), p. 102.

<sup>58</sup> Q.v. Judit Sándor “Hungary; Kluwer International Law; Medical Law” Suppl. 31 (April 2003), p. 109.

<sup>59</sup> As we did not obtain an English translation of those laws, we could not establish the legal force of the ethics committee’s decisions. It is not clear to us for example, if the committees’ opinion must be positive for the research to commence.

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b) Practice of ethical review

With regard to the composition of the committees, we could only uncover some details on the TUKEB. Its members are appointed by the Minister for Health for a fixed term. In the current situation, TUKEB has three members with a legal background, the rest being prominent medical professors. The committee is also responsible for the evaluation of multi-central trials where more than one region is involved. A specific task of the regional committees seems to be the evaluation of epidemiological studies. The Institutional Boards are seen as responsible for the assurance of an adequate qualification of the principle investigator and sufficient facilities to conduct clinical research. One member of the Board is nominated for each trial as special advisor also during the trial.

c) References

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5. Latvia

a) Legal and institutional framework

Biomedical research in Latvia is reviewed by different committees according to the kind of research conducted. Two areas of research are supervised by central committees and therefore of minor importance in this context. One being research involving animals, reviewed by the *Ethics Committee on Laboratory Animal Use in Biomedical Research*, the other being research involving human biological material (blood, organs, tissues, cells, DNA) which is monitored by the *Central Medical Ethics Committee of Latvia* (CMEC). According to the Latvian Human Genes Research Act (having been approved by Latvian parliament on 3 July 2002 and having entered into force on 1 January 2004) the CMEC is empowered to supervise the ethical issues pertaining to the establishment of the Genome Database and the processing of data. Amongst other things the CMEC may grant permission for limited numbers of tissue samples to be brought to other countries if the scientific infrastructure in

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Latvia is not sufficient to conduct certain research projects. Apart from being competent for those research projects, the CMEC shall issue opinions on different topics of bioethics but may also –in stark contrast to central ethics committees in other countries– function as a research ethics committee evaluating concrete research projects.

The legal basis for the evaluation of clinical trials by research ethics committees in Latvia is Cabinet Regulation No. 312 on the *Procedure for clinical trials on medicine and pharmaceutical products and for observational studies* (PCTMP) enacted on 12 September 2000 and grounded on Art. 5 Paragraphs 3 and 6 of the *Law on Pharmacy*.

According to Sect. 30 PCTMP a trial may only commence after obtaining the favourable opinion by an ethics committee and written authorisation of the *State Agency of Medicines*. Sect 31 Subs. 1-10 regulates the documents to be forwarded to the committee for evaluation purposes, implicitly stating the parameters for evaluation (such as informed consent, competence of researchers and adequacy of the institution). The ethics committee has to provide its opinion within 30 days after the submission of the relevant documents (Sect. 33 PCTMP). After the trial has been approved, it is not surveyed by the committee but by the *State Agency of Medicines*. The PCTMP does not provide for rules regarding fees for evaluation by ethics committees but regulates the matter of fees for application to the *State Agency of Medicines* in Sect. 37.

The concerned ethics committee may, under certain circumstances, allow for the participation of unconscious or legal incapacitated persons in a clinical trial pursuant to Sect. 12 PCTMP.

The procedural rules for ethics committees are given in the *Master Statutes of the Ethics Committees for clinical trials of Drugs* (enacted by the Minister of Welfare on August 6<sup>th</sup> 1998). According thereto ethics committees must be independent and include medical persons as well as non-medical lay persons.

Latvia signed the *Convention on Human Rights and Biomedicine* on 4 April 1997, but the Parliament has not yet ratified it.

## b) Historical background

The first initiative to create an ethics committee for the ethical review of research projects was taken by the Association of Doctors of Latvia in 1996. The established *Central Medical Ethics Committee of Latvia* (SMEC) had to review projects of the Medical Academy of Latvia. An Ethics Committee was established in the same year for the review of protocols for the clinical trials of drugs. In 1998 the CMEC started to assess projects involving humans as research subjects. Later, an independent ethics

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committee for the investigation of drugs and pharmaceutical products was founded, as well as another committee at the Institute of Cardiology.

c) Current situation

According to Aberga Augškalne and L. Rudze, the majority of protocols are reviewed by the CMEC and the committee of the medical Academy of Latvia (now Riga Stradiņš University). They indicate that insufficient explanations in the protocols have negative consequences for the workload of the committees. For the CMEC the financial equipment seems to be inadequate. The CMEC tries to provide training and teaching material for bioethics as well as specifically for research ethics.

d) Reference

Rudze, Laima (2000). „Ethics committees in Latvia.“ In: Glasa, Jozef (Ed.). *Ethics Committees in Central & Eastern Europe. Proceedings of the International Bioethics Conference Ethics Committees in Central & Eastern Europe: Present State & Perspectives for the 21st Century.* Bratislava, Slovak Republic, October 26–27, 2000. Bratislava: 197–204.

## 6. Lithuania

a) Legal framework and institutions

Lithuanian *Law on Ethics of Biomedical Research* from 11 May 2000 (further abbreviated as LEBR) deals with the matter of biomedical research. The law has a very broad approach not only referring to clinical trials with medication, but also covering various other issues. Biomedical research is defined as any “...verification of hypotheses by methods of scientific investigation and development of knowledge about characteristics of human health” (Art. 1 Subs. 1 LEBR) probably encompassing psychological research as well as clinical trials of medicine. Furthermore, it is made clear that not only individuals, but also foeti, organs, cell and genetic material, cadavers and even medical documents may be considered subjects of biomedical research. Special consideration is given to individuals (and groups of individuals) and foeti. These can only be subjected to biomedical research, where data about appropriate non-clinical research is available (Art. 3 Subs. 1 LEBR). Human embryos may only be subject to non-invasive investigation and their creation for purposes of biomedical research is forbidden.

According to Art. 4 Subs. 5 LEBR biomedical research may only be conducted if, among other conditions, the *Lithuanian Bioethics Committee* (LBEC) or one of the *Regional Biomedical Research Ethics Committees* (RBREC) gives approval. Any conduct of biomedical research, without prior approval, is unlawful (Art. 12 Subs. 1 LEBR).

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It is up to the LBEC to mandate the RBRECs with evaluating biomedical research projects, this mandate may be suspended if they fail to fulfil these functions appropriately (Art. 12 Subs. 2 LEBR). Where clinical trials of medicinal products are concerned, the approval has to be issued on the recommendation of the *State Medicines Control Agency*.

The LBEC is a body of the Ministry of Health and it receives a state budget. Besides issuing approval for research itself, the LBEC is responsible for monitoring the work of the RBRECs and for informing and educating the biomedical community and general public on moral dilemmas arising in the context of modern health care (e.g. informed consent; privacy and confidentiality; reproductive rights; ethical issues of genetics; abortion; death and dying, palliative care etc.). Should biomedical research be carried out in more than one region, the Lithuanian Bioethics Committee shall issue the approval.<sup>60</sup>

The RBRECs grant approvals as mandated by the LBEC, they must be composed proportionally of representatives from the academic community, health care specialists and the general public. The decision has to be submitted to the inquiring institution within 45 days after the registration of the query. If the committee disapproves of the research project, it has to substantiate its reasons. The committees may charge a fee, whether the approval is granted or not. Certain institutions are exempt from this fee (Art. 15 Subs. 2 LEBR). The committees are responsible for monitoring research projects for which approval has been granted by them (Art. 14 Subs. 2 No. 2 LEBR). The LBEC and RBRECs may revoke their approval on grounds of non-compliance with requirements of ethics or at the request of the principal investigator. When the approval is thus invalidated, the research project is to be promptly terminated.

Lithuania has signed the *Convention on Human Rights and Biomedicine*. The Convention entered into force on 1 February 2003.

#### b) Historical background and current situation

The Lithuanian National Committee on Biomedical Ethics (LBEC) was established in 1995, long before its status and functions were mandated by the specific laws. Then a group of medical professionals and non-medical specialists were appointed by the Ministry of Health. LBEC's main functions were and are to develop

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<sup>60</sup> As noted in Sec. II. Subs. 9 of the *Procedure to issue approvals to conduct biomedical research* attainable at <http://www.sam.lt/bioetika/btyr/eng/index.htm> . This Procedure also contains provisions regarding the composition of LBEC and RBRECs as well as rules of decision making.

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education in bioethics, as well as the ethical review of research protocols. The LNCBE started to build up a network of regional and local research ethics committees, and is still responsible for monitoring procedures and for the education of committee members. Currently, there is only one regional (institutional) Ethics Committee at the Kaunas University of Medicine; on some occasions, LBEC acts as a regional committee for Vilnius city and district.

c) Reference

Gefenas, E. (2000). „A Short Information on Lithuanian National Committee on Biomedical Ethics.“ *Journal International de Bioethique* 11/1: 63.

7. Malta

a) Legal regulations

In Malta there seems to be no specific legal material concerning the function of research ethics committees. The *Data Protection Act* (DPA having been set into force on March 22<sup>nd</sup> 2002 to comply with the EU Directive 95/46/EC) makes reference to research ethics committees in Art. 16 Sect. 2 b. The provision stipulates that personal data may be processed for research purposes only by approval of the Data Protection Commissioner. The Commissioner has to be advised by a research ethics committee being recognised for purposes of this article, but the act does not further elaborate on the matter of research ethics committees. The only other instance of legal text mentioning some form of ethical standards in research is the *Animal Welfare Act* (AWA having entered into force on February 8<sup>th</sup> 2002). But that act does not even deal with ethics committees, only hinting at ethical rules and standards in Art. 33 Sect. 1.

b) Current situation

We were able to locate information about three ethics committees in Malta, one of them having no regard to biomedical issues but dealing with psychological and social research<sup>61</sup>. The second committee is the *Bioethics Consultative Committee*<sup>62</sup> functioning as a national bioethics advisory body. The only true local research ethics committee is the committee of the Medical School University of Malta. It evaluates those research projects submitted to it. Researchers are under no obligation to submit their projects to that committee.

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<sup>61</sup> The research ethics committee set up by the Senate of the University of Malta.

<sup>62</sup> For a summary of functions and procedures q.v. <http://www.synapse.net.mt/bioethics/>.

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Malta has not signed the Convention on Human Rights and Biomedicine.

c) Reference

Malta (2001). Data Protection Act, 2001 (Act NO. XXVI OF 2001). <<http://www.dataprotection.gov.mt/filebank/documents/DataProtectionAct.pdf>> 3 December 2003.

8. Poland

a) Legal framework

Polish law contains provisions on medical experiments in the *Law on the Profession of a Physician and a Dentist* (of December 1996, further abbreviated as LPPD). The law stipulates, that medical experiments mean therapeutic experiments as well as medical research. Therapeutic experiments “consist of introduction by the physician of new or only partly tested methods of diagnostics, treatment or prophylaxis for the purpose of direct benefit to the health of the patient.” (Art. 21 Sect.2 LPPD) They may only be carried out if the currently applied methods are ineffective or insufficient for the patients’ treatment.

However, medical research “is carried out mainly for the purpose of medical knowledge. It may be carried out both with the participation of sick and healthy people.” (Art. 21 Sect. 3 LPPD) The law contains a provision prohibiting the conduct of medical research unless it does not entail any risk for the subject or unless that risk is very minor in comparison to the proposed benefit.<sup>63</sup> The law further elaborates in Art. 22 LPPG, that “A medical experiment is allowed if the expected benefit to treatment or to medicine in general is essential and the anticipated attainment of such benefit and the usefulness and the manner in which such an experiment is carried out are justified by the current level of medicine and do not violate medical ethics.” The reference to medical ethics bears consequences as any form of medical experiment, be it a therapeutic experiment or medical research, must be approved of by an “independent bioethics commission” pursuant to Art. 29 Sect. 1 LPPG. The commission has to survey whether the medical experiment conforms to the standards of biomedical ethics (some of them, e.g. the rules of informed consent are laid down in Art. 23-27 LPPG) and shall issue its

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<sup>63</sup> Though it is not clear from the provision if the risk may be weighted against the proposed benefit of public instead of the subject itself, the fact that experiments may also be conducted on healthy subjects (who do consequently not stand to gain much from the experiment) hints in exactly that direction.

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opinion concerning the purpose and feasibility of the project (Art. 29 Sect. 2 LPPG).

The law provides just one criterion for the composition of the committee, stating that each of its members must be of “high moral authority and high professional qualifications” (Art. 29 Sect. 1 2<sup>nd</sup> Sentence LPPG). Depending on the scope of activity of the respective committee it is appointed by: the director of a medical research and development unit (Art. 29 Sect. 3 No. 3 LPPG), the rector of a medical academy or a university with a faculty of medicine (Art. 29 Sect.3 No. 2 LPPG) or for all other projects by the regional medical council within the area of its activities (Art. 29 Sect. 3 No. 1 LPPG).

The Minister competent for health matters shall, after consultation with *the Supreme Medical Council* appoint the *Bioethics Commission of Appeal* competent for appeals against the decisions of the bioethics commissions (Art. 29 Sect. 5 LPPG). The law contains no further rules for the work of the bioethics commissions, but empowers the Minister to pass regulations on the appointment of and compensation for the bioethics commissions as well as on their procedures.<sup>64</sup>

Poland signed the *Convention on Human Rights and Biomedicine* on 7 May 1999. The convention has not yet been ratified by Polish Parliament.

#### b) Current situation

As a second instance the Appeal Committee is only engaged by researchers if a protocol is not approved by a local committee. In multi-centre trials every local bioethics committee, relevant for the certain area or institution (where the research will be conducted), shall give the approval. There is actually no procedure how a single opinion in multi-centre research can be assured. Since the Appeal Committee is a public body that is not dependant on fees and money from sponsors it is seen as an independent instance. Compared to the central commissions in the Netherlands or Lithuania its position in the review system is much weaker. In Poland nurses, clergy-man and lawyers represent the lay people in the committee.

#### c) References

Byk, Christian; Mémeteau, Gérard (1996). *Le droit des comités d'éthique*. Paris (Médecine et droit): 255.

Chlap, Z. (1993). „L'activité des Comités d'éthique en Pologne.“ *Journal international de bioéthique* 4/4: 311–312.

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<sup>64</sup> We have not been able to ascertain if such a regulation has been passed.

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The Minister of Health (1999). *Rozporządzenie Ministra Zdrowia I Opieki Społecznej z dnia 11 maja 1999 r. W Sprawie Szczegółowych Zasad Powoływania I Finansowania Oraz Trybu Działania Komisji Bioetycznych.* (Dz. U. z dnia 27 maja 1999 r.) Dz. U. 99.47.480.

Poland (1992). „Ordre des médecins. Naczelna Izba Lekarska. Code d'éthique médicale.“ *Journal international de bioéthique* 3/3: 181–184.

Safjan, Marek (1991). „Le droit et le débat sur la bioéthique en Pologne (1ère Partie).“ *Journal international de bioéthique* 2/1: 51–55.

Safjan, Marek (1991). „Le droit et le débat sur la bioéthique en Pologne (2ème Partie).“ *Journal international de bioéthique* 2/2: 119–124.

## 9. Slovakia

### a) Historical background and legal framework

Very much like the situation in the Czech Republic, Slovakia looks back on a long history of ethics committees in biomedical research. But, unlike in the Czech Republic, the lack of legal backing for ethics committees has not yet been addressed by Slovakian parliament. Nevertheless, there has been some development with regard to ethics committees and their role in the evaluation of biomedical research. When the *Central Ethics Committee* (CEC) was founded in 1990 (at that time Slovakia was still part of Czechoslovakia, so the CEC functioned as a provincial institution) the then Minister of health recommended the appointment of local ethics committees in health care and research facilities. In 1992 the CEC issued “*Guidelines on Establishment and Work of Ethics Committees in Health Care Facilities and Biomedical Research Institutions*”. Although these guidelines had some practical impact, their status is not very strong legally speaking. They were published as ministerial recommendations and have not been strengthened by attaining a more binding status afterwards. Despite the unsatisfactory legal framework many ethics committees have been established in Slovakia since 1990. In 1993 (after the Slovak Republic attained independence) a survey undertaken by the *Institute of Medical Ethics and Biomedicine* (IMEB) numbered about 70 local ethics committees<sup>65</sup> (albeit of different function, not all of them concerned with the review of biomedical research). Since then this number seems to have dwindled significantly, as they receive no public funding and are wholly dependent on the private commitment of the participating scientists.

The Slovak Republic signed the *Convention on Human Rights and Biomedicine* on 4 April 1997. It entered into force on 1 December 1999.

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<sup>65</sup> Q.v. Jozef Glasa et. al. “Ethics Committees in the Slovak Republic” in J. Glasa *Ethics Committees in Central & Eastern Europe*, p. 233.

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## b) References

- Byk, Christian; Mémeteau, Gérard (1996). *Le droit des comités d'éthique*. Paris (Médecine et droit): 256
- Glasa, Jozef (2000) [Bielik, Ján; Dacok, Ján; Glasová, Mária; Porubský, Ján]. „Ethics Committees [HECs/IRBs] and Healthcare Reform in the Slovak Republik: 1990–2000.“ *HEC (HealthCare Ethics Committee) Forum* 12/4: 358–366.

## 10. Slovenia

### a) Legal framework

The legal system in Slovenia does not offer much in the way of providing for matters of biomedical research. There are provisions in the *Infertility Treatment and Procedures of Biomedically-Assisted Procreation Act* (Ur.l.RS, no. 70/2000), the *Law on Medical Practice* and the *Slovenian Penal Code*, dealing with issues as informed consent, medical malpractice or the requirements for research on human embryos. But none of these provisions detail the role of ethics committees in biomedical research.

Slovenia signed the *Convention on Human Rights and Biomedicine* on 4 April 1997. The treaty entered into force there on 1 December 1999.

### b) System of ethical review

In spite of the lack of a specific national legislation, there is a system of review in place. There are two local ethics committees associated with regional medical centres (Maribor and Celje) but they may not give authorisation of research projects in their own right. Instead, they may give their opinion and provide information to the National Medical Ethics Committee (NMEC).

Currently the NMEC reviews most research projects in Slovenia. Without having an explicit legal mandate (other than internal regulations) the NMEC reviews all research projects aiming at M. Sc. and D. Sc. Degrees, as well as any form of biomedical research funded by state agencies. The NMEC has originally been established at the Ljubljana Medical School and has later on been given the status of a national ethics committee (1977, being the first national ethics committee in the EU candidate countries). Originally founded to co-ordinate and conduct the ethical review of biomedical research in Slovenia, the mandate was expanded to act as an advisory body to the government concerning biomedical issues. They may issue opinions on their own initiative and are expected to comment upon drafts on different matters as, for example, transplantation, assisted reproduction etc. But they retain their original mandate for the research of clinical trials and research projects aiming at certain academic degrees.

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By rights of a Ministerial Order (published in the Official Gazette of the Republic of Slovenia No. 30, 2 June 1995) the composition and procedure, terms of appointment and duties have been laid down. The committee is composed of thirteen members, nominated by the Slovenian *National Health Council*, the university and the medical association and appointed by the Minister of Health. The committee contains members from the fields of medicine, law, psychology, social sciences, humanities and ethics. Although the NMCE is authorised to review all forms of novel treatment procedures, only a modicum of such procedures are reviewed in practice due to the fact that the majority of techniques are transferred from other countries rather than developed in Slovenia. This has led to some public discussion in the past. Besides the NMCE, there are two committees specialized in oncological research and assisted procreation.

c) Reference

Trontelj, Joze (2000). „Ethics committees in Slovenia.“ In: Glasa, Jozef (Ed.). *Ethics Committees in Central & Eastern Europe. Proceedings of the International Bioethics Conference Ethics Committees in Central & Eastern Europe: Present State & Perspectives for the 21st Century*. Bratislava, Slovak Republic, October 26–27, 2000. Bratislava: : 239–249.

C. Candidate countries

1. *Bulgaria*

a) Legal and governmental regulations

In Bulgaria clinical investigations of drugs are regulated by the *Law on Drugs, Pharmacies and Humanitarian Medicine*.<sup>66</sup> Chapter 4 of this Law provides the entire administrative procedure for such examination. Further details are given through Ordinance No. 14 of the Minister of Health concerning the conditions and order of implementation of clinical experimentation on human beings.

In Bulgaria clinical examinations on human beings are considered if one of the following conditions is fulfilled:<sup>67</sup> 1) if such examinations are required for the

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<sup>66</sup> *Polya Goleva-Panova*, “Bulgaria; Kluwer International Law; Medical Law” Suppl. 26 (May 2002).

<sup>67</sup> Since the official translations of this laws was not accessible, it cannot be guaranteed that author has a clear and throughout understanding of the legal situation in Bulgaria. The source (*Polya Goleva-Panova*, “Bulgaria; Kluwer International Law; Medical Law” Suppl.

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registration of medication, 2) if they are necessary to prove the clinical efficiency and safety of new medication, or 3) if they are necessary to prove the efficiency and safety of medication, which are already registered in the country or that have to be registered due to the altered situation. For the first two cases, the administrative procedures are as follows: the proposal for examination, which should include all necessary information about the examination, qualifications of researchers, capacities of the institution, etc., should be submitted to the Ministry of Health. The proposal is then submitted to the Central Commission of Ethics<sup>68</sup> at the Ministry of Health, and the decision should be provided within two months. Then the Minister of Health would make a final verdict referring to the commission's *motivated decision*<sup>69</sup>. The Central Commission is appointed by the Minister of Health which has to consist of at least nine members representing medical and non-medical specialists, as well as representatives of both genders; their mandate is authorized for two years. None of the members shall be involved in the respective project on which it has to issue a decision.

At the local level, local Commissions of Ethics monitor the research. These committees have to periodically supervise each of the ongoing research project (in adequate periods) and report to the central authority. The local Commissions of Ethics are appointed by the chief institution and they prepare their own standard working procedures. These have to be approved by the director of the Executive Agency of Medicines. The commission has to consist of at least seven members and include at least one person without a medical background and one person financially independent of the health care institutions. Again, special consideration is given to the non-involvement of the committee members in the respective research projects. The meetings of the Commissions of Ethics are public and the documentation may be reviewed by anyone.

In the last case mentioned above, the responsibility to evaluate the research is delegated to a specialised commission with expertise in the respective field of medicine. As interpreting the meaning of the law, these occasions arise if there is a reason to doubt the safety or clinical efficiency of a medication already registered in Bulgaria or if a medication is widely applied, although it has not yet been registered<sup>70</sup>.

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26 (May 2002) contains certain ambiguities of wording that necessitate a caveat on the validity of our understanding.

<sup>68</sup> In other sources – the *Ethics Commission for Drug Trials*

<sup>69</sup> This term is common in the used sources and seems to notify a legal concept in Bulgarian law, meaning simply that the decision has to be accompanied by a (probably written) justification of the decision.

<sup>70</sup> Alas, the meaning of the source text is somewhat ambiguous

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The specialised commission, which is also appointed by the Ministry of Health, determines in which institution the necessary examination shall take place and monitors that research. By deciding on a project it has to give special consideration to the constitution of Bulgaria, the *Law on Drugs, Pharmacies and Humanitarian Medicine* and the applicable international regulations.

It lays out a plan for the research and has to decide on proposed modifications of that plan. We have no information on the composition and working procedures of those specialised commissions.

Bulgaria signed the *Convention on Human Rights and Biomedicine* on 31 May 2001. It entered into force on 1 August 2003.

## b) Reference

Goleva-Panova, Polya (2002). *Bulgaria*. The Hague; London; New York (International Encyclopaedia of Laws: Medical Law, Suppl. 26).

## 2. Romania

### a) Legal regulations and current situation

As far as we could ascertain, there is not yet a legal basis for the review of biomedical research by research ethics committees. Although there are some domestic regulations dealing with matters of biomedical research, none of them assigns a function to ethics committees in biomedical research just for the more narrow field of clinical trials. There are local research ethics committees at the major research institutes in Romania<sup>71</sup> and even an *National Research Ethics Committee* working within the framework of the *Academy of Medical Sciences*. The *National Research Ethics Committee* supervises biomedical research, both in humans and animals. But, as mentioned above, there seems to be no legal requirement to ask for their opinion before a research project may commence.

As far as clinical trials are concerned, one must distinguish between phase I-III trials and phase IV trial. Phase I-III trials must be approved by the *Drug's National Agency* review by the *National Ethics Commission* is facultative. In the case of phase IV trials, the procedure is pretty much the same but the review by the *National Ethics Commission* is obligatory<sup>72</sup>. This conforms to Art.85 of *Emergency Ordinance 152/1999* (on Medicinal Products for Human Use) which itself refers to *Law 336/2002*.

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<sup>71</sup> Q.v. Florentina Negrutiu „Ethics Committees in Romania” in J. Glasa “Ethics Committees in Central & Eastern Europe”, p. 222.

<sup>72</sup> Josef Reisunger „Klinische Studien in Rumänien“ in DZKF 5/6 – 2001, p. 48.

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Romania signed the *Convention on Human Rights and Biomedicine* on April 4<sup>th</sup> 1997. The treaty entered into force there on 1<sup>st</sup> of August 2001.

b) References

Byk, Christian; Mémeteau, Gérard (1996). *Le droit des comités d'éthique*. Paris (Médecine et droit): 255

Constaninescu, D.; Filisianu, C. (1991). „Quelques préoccupations ‚bioéthiques‘ dans la législation roumaine.“ *Journal international de bioéthique* 2/4: 251–253.

Maximilian, Constantin (1994). „La bioéthique en Roumanie.“ *Journal international de bioéthique* 5/4: 331–333.

Reisinger, Josef (2001). „Länderprofil Rumänien (2). Klinische Studien in Rumänien.“ *Deutsche Zeitschrift für Klinische Forschung* 5/6: 46–48. <[http://www.dzmf.de/heft/2001\\_5-6/pdf/DZKF-5-6-2001-S.46-48.pdf](http://www.dzmf.de/heft/2001_5-6/pdf/DZKF-5-6-2001-S.46-48.pdf)> 18. November 2003.

3. Turkey

a) Legal framework

The amendment to the Turkish law regarding drug research (*İlaç Araştırmaları Hakkında Yönetmelik*) was issued in 1993. Prior to this there was no special law regulating research on human beings. As far as the protection of human subjects in medical research is concerned, there are other provisions on the ethical guidelines for members of the medical profession (*Hekimlik Meslek Etiği Kuralları*) and the decree on patients' rights (*Hasta Hakları Yönetmeliği*).

b) Historical background and current committees' system

Discussion on ethics in medical research started already in the second part of the 1980s. The first medical ethics committees, which dealt with biomedical research, were established at the Faculty of Medicine of Hacettepe University and at the Gülhane Military Medical Faculty. At the end of the 1980s, stimulated by the debate on new drugs in oncology, the Turkish Ministry of Health established an Ethics Committee. The 1993 amendment for the drug research covers materials used for diagnostic, therapeutic and/or preventive purposes. The law is in accord with the Helsinki Declaration and the Turkish Medical Deontology Regulation, and contains provisions for the role of the local and the central ethics committee and the procedures for working on new drugs.

Concerning membership, the law “does not require a medical ethics specialist to be on the Central Ethics Committee”. This committee consists of the following members: the undersecretary of the Ministry of Health, who is the chairperson of

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the committee, three officials and three clinicians from the ministry, university teachers (three pharmacologists and three clinicians from medical faculties, three academics from pharmacy faculties and one from a faculty of law) and representatives from medical, dental and pharmacy associations.

Local ethics committees are composed of three clinicians, one medical pharmacologist, one pharmacist, one biochemistry specialist, one pathologist, one specialist relevant to the investigation and, if possible, a medical ethics specialist (deontologist). The reason why the expression ‘if possible’ is used might be that for the time being there is not a medical ethics specialist in each faculty.” (Aydin 1999)

Some of the local committees are not only responsible for research issues, but also for ethical questions in clinical and academic contexts (Aydin 1999).

A survey on research ethics committees, which was performed by the Ethics Committee of the Turkish Medical Association in 1998, showed that “[a]lmost 70 % of the ECs’ major responsibilities are the research activities. 67 % of the university hospitals and 15 % of the other hospitals do mention responsibilities other than research, such as daily practices (40 %), ethics education (20 %), interpersonal relations between the physicians, reports and educational activities. 75 % of the respondents indicated that the REC was the only committee in their hospital. The remaining 25 % stated the presence of a second committee, and it was indicated that their major responsibility was animal studies. Other topics on which these second committees commented were listed as sexual identification and the problems faced during daily practices. More than 90 % of the hospitals did not have a committee for multicentered studies.” (Arda 2000, 496-497)

Berna Arda, who was also involved in the survey, remarks that “[o]nly 33.3 % of the ECs had a medical deontologist as a member. Only one of the ethics committees located in Ankara had a lawyer member.” (Arda 497) She adds that she could not find a “concept as ‘patient representative’ was considered by the ECs” (Arda 2000, 497).

After being considered by the local ethics committees, research protocols are sent to the central ethics committees at the Turkish Ministry of Health before they are approved by the Ministry of Health. Local ethics committees are only competent to decide on third and fourth stage clinical trial.

There is an ongoing discussion, if the two-staged procedure of ethical review is not too slow and if the criteria are clear enough despite the circular, issued by the Ministry of Health (December 1995), which, amongst others, provides guidelines for responsibilities and working methods of ethics committees. There also seems to exist a disproportion between the increasing number of medical faculties in Turkey and the number of local / institutional ethics committees. “In 1993 there were only

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eight RECs in Turkey, though 24 medical faculties exist. [...] In 1997 there were 41. In most of these new faculties there is no REC.”(Arda 2000, 460)

Medical ethicist, as Berna Arda, emphasizes the need for training in ethics for researchers and sees a possible role of research ethics committees in that field. They also emphasize that firstly education would be necessary for members of ethics committees. Arda as well as Aydin indicate that, at present, Turkish research ethics committees only focus on consent in a written form and do not question that this consent should be an informed one. They also stress the deficient awareness of moral problems in the practice of medicine and medical research in the public.

### c) References

- Arda, Berna (2000). „The Experience of the Research Ethics Committees in Turkey.“ *Medicine and Law* 19/3: 493–500.
- Arda, Berna (2000). „Evaluation of Research Ethics Committees in Turkey.“ *Journal of Medical Ethics* 26/6: 459–461.
- Arda, Berna (1996). „The Activities of the Ethics Committee of the Turkish Medical Association.“ *Journal international de bioéthique* 7/3: 235.
- Arda, Berna (1995). „Ethics and the Commercial Use of Genetics.“ *Bulletin of Medical Ethics* 111: 19–22.
- Aydin, Erdem (1999). „Medical Ethics around the World. Bioethics Regulation in Turkey.“ *Journal of Medical Ethics* 25/5: 404–407.
- Oğuz, Yasemin; Arda, Berna (1991). „Medical Ethics Interest Grows in Turkey.“ *Bulletin of Medical Ethics* 73: 13–17.
- Pelin, Serap Sahinoğlu; Arda, Berna; (2000). „Physician’s Attitudes towards Medical Ethics Issues in Turkey.“ *International Journal of Bioethics* 11/2: 57–67.
- Sari, Nil (1995). „History of Medical Ethics. Near East and Middle East. Turkey.“ Vol. 3. Ed. Warren Thomas Reich. 5 vols. New York: 1449–1452.

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D. Associate countries to the 5<sup>th</sup> and 6<sup>th</sup> Framework Programmes

1. Iceland

a) Legal framework and relevant institutions

Iceland has issued a number of laws applying to scientific research within the Health Sector. Three of them regulate the activities of the ethics committees: Act no. 74/1997 on the *Rights of Patients* (ARP), Regulation no. 552/1999 on *Scientific Research in the Health Sector* (RSRHS) and Regulation no. 32/2000 on *Health Sector Database* (RHSD).

ARP entitles the Minister of Health and Social Security (Chapter VIII, Art. 29 ARP) to issue regulations on scientific ethics committees and other ethics committees. In Chapter I Art. 2 it states that “...an evaluation of the research [meaning scientific research aimed at the improvement of health and curing of diseases] made by the scientific ethics committee or an ethics committee must have revealed, that scientific and ethical views do not oppose its implementation”.

Relying on the delegated competence by the Art. 29 ARP, the Minister has issued RSRHS (29 July 1999), establishing the National Bioethics Committee (Art. 1 RSRHS) and ethics committees at the National University Hospital, the Reykjavik Hospital and the Akureyi Central Hospital (Art. 2 RSRHS), as well as in the health care service.

According to the Art 4 RSRHS, no scientific research on human beings may be conducted without prior approval of the aforementioned committees. Furthermore, any scientific studies may only be implemented if it was evaluated and approved by one of those committees and that their report yielded no scientific or ethical objections.

The ethics committees, referred in the Art. 2 RSR, have to evaluate plans for scientific studies to be conducted by the relevant parties. The National Bioethics Committee has to evaluate collaborative projects, multinational studies and other projects, which do not fall under the aegis of the local ethics committees (Art. 3 RSRHS). It is also responsible for reviewing the decisions reached by the local ethics committees (Art. 8 RSRHS).

The National Bioethics Committee shall also monitor the progress of studies it has approved of as specified in Art. 6 RSRHS and may revoke its prior consent. The withdrawal of previous consent has immediate effect for the study concerned. The same rules apply for the ethics committees as described in the Art. 2 RSRHS.

The National Bioethics Committee consists of five persons, who are appointed by the Minister of Education and Culture, Minister of Justice and Minister of Health

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and Social Security (the latter appoints two members) respectively for the period of four years. The fifth member is nominated by the Director-General of Health. Art. 1 RSRHS spells out that the committee has to include specialists from the fields of health sciences, scientific ethics and human rights.

The committees referred in the Art. 2 (except the committee within the health care service) are appointed by the boards of the respective hospitals. Each of the committees should include at least one member with no connection to the relevant hospital, and thus is appointed by the Director-General of Health. The committee within the health care service has three members, appointed for a term of four years.

As specified in Art. 21 RHSD the National Bioethics Committee must also be notified on a three-monthly basis about the queries submitted to the Health Sector Database. According to the Art. 25 RHSD an Interdisciplinary Ethics Committee is established, whose role is to ensure that the processing of the data at the Health Sector Database is compliant with the rules of science ethics. Research, queries or classes of queries referring to the Health Sector Database may not be processed without the consent of the aforementioned committee (Art 26 RHSD).

The decisions of the Interdisciplinary Ethics Committee may be appealed to the Minister for Health and Social Security, who must consult with the National Bioethics Committee before deciding on the appeal.

#### b) Current activities

As indicated in the description of the existing regulations, medical research in Iceland was strongly stimulated by the creation of Icelandic genetic, epidemiological and health care databases. The ethics committees at the national level are confronted with questions of informed consent in a new way.<sup>73</sup>

#### c) References

Ministry of Health and Social Security (2000). *Government Regulation on a Health Sector Database* No. 32/2000. <<http://ministryofhealth.is/interpro/htr/htr.nsf/pages/Govreg32-2000>> 25 June 2003.

Ministry of Health and Social Security (1999). *Regulation on Scientific Research in the Health Sector* No. 552/1999.

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<sup>73</sup> Vihjamur Arnason, coding or consent? Consent issues in Iceland, Lecture August 22, 2003, Vilnius.

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<<http://ministryofhealth.is/interpro/htr/htr.nsf/pages/Regulation-552-1999>> 25 June 2003.

Ministry of Health and Social Security (1997). ACT on the Rights of Patients No. 74/1997. <<http://ministryofhealth.is/interpro/htr/htr.nsf/pages/act-rightspatients>> 25 June 2003.

## 2. *Israel*

### a) Legal framework and ethical review system

The *Public Health Ordinance* (5741-1980 *Medical Experimentation on Human Beings*), passed in 1980, is the main legal document to regulate the conduct of research with human beings in Israel. The Ordinance was issued following the principles of the Helsinki Declaration and is intended to establish a valid legal basis for the ethical considerations, described therein.<sup>74</sup>

In the above-mentioned Ordinance, the definition of medical experimentation is very broad: “employment of medication, radiation or chemical, biological, radiological or pharmaceutical components...intended to affect the health, body, mind or genetic system of a person wholly or partly...as long as the use of these materials is not statutory, not acceptable in Israel for their present objectives or applied to objectives not previously tested in Israel”.<sup>75</sup> Furthermore, any unconventional process or action performed on human beings as well as any unconventional examination also fall under the scope of this definition, making it indeed very comprehensive.

The experimentation<sup>76</sup> may only commence if it has the approval of the Director-General (DG) of the Ministry of Health or authorized by a DG official. The approval is only to be expected if the Director-General (or his proxy person) is convinced of the experimentation’s compliance with the Helsinki Declaration’s principles and the Ordinance. In certain cases (which are detailed by the Ordinance)

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<sup>74</sup> Q.v. *A. Carni* „Israel“ in *Kluwe Law International; Medical Law.*“ Suppl. 20 (May 2000), p.127.

<sup>75</sup> A somewhat altered wording of the translation provided by *A. Carni* in „Israel; *Kluwe Law International; Medical Law.*“ Suppl. 20 (May 2000), p.127. We did not have access to the genuine English translation of the Ordinance and therefore had to rely on the aforementioned text, confirmed by the information at the website of the Hadassah Medical Organisation (<http://www.hadassah.org.il/English/>)

<sup>76</sup> The term „experimentation“ indicates clinical research as well as well as purely professional research. The Ordinance provides even stricter standard for the conduct of experimentation that is not primarily aimed to improve a given patient’s health. Most importantly, it states that under no condition public or societal interests may outweigh the subject’s interest or overrule his wellbeing.

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also the advice from the Medication and Food Directorate of the Ministry of Health must be obtained. Most important in this context is the establishment of the Helsinki Committee at the concerned hospital. Prior to the Director-General or his proxy may authorize the experimentation, a written evaluation and approval of the Helsinki Committee at the relevant hospital (where the experimentation is planned) has to be presented.

The Helsinki Committee is responsible for the evaluation of any experiments on human beings, which are conducted at the respective hospital. The Committee is appointed by the hospital's director and has to be acknowledged by the Ministry of Health's Director-General. It must include at least seven members, three of whom should be senior hospital physicians (heads of the hospital or at least associate professors), a physician, representing hospital's governing board, and a public representative (either a lawyer or a religious minister).

According to the Israel regulations, all the local ethic committees operate in hospitals. These committees have the mandate to evaluate and approve/disapprove experiments with humans and the duty report to the Ministry of Health.

Other research, as multi-centre studies, genetic experimentation, all phase I studies, etc. should be approved by the local committees and then submitted to the central committees of the Ministry of Health. There are four local committees including the National Helsinki Committee.

The National Helsinki Committee<sup>77</sup> appointed by the Director-General of the Ministry of Health, who is also a member of the committee<sup>78</sup>. The Committee has nine other members: a lawyer, religious minister, the chairman of the IMA and six professors of recognised academic institutions. At least three of these must be physicians and full-time professors.

Israel is not a Member state of the Council of Europe and has not signed the *Convention on Human Rights and Biomedicine*.

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<sup>77</sup> We were not able to allocate the exact statutory framework for this committee and its responsibilities. . . *A. Carni* „Israel“ in *Kluwe Law International; Medical Law.*“ Suppl. 20 (May 2000), p.72 and p. 128. seem to imply, that it is either located at the Israeli Medical Association (IMA) or Medication and Food Directorate of the Ministry of Health. We suspect that the Committee could serve as an appeal institution against the decisions of the hospitals' committees or those cases of research that do not take place at hospitals or constitute multi-centre studies.

<sup>78</sup> Only in case that he is a licensed physician. If the Director-General is no licensed physician he has to appoint a representative who is a licensed physician.

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## b) References

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## 3. Liechtenstein

### a) Legal situation and ethical review

The Principality of Liechtenstein does not have its own regulations on biomedical research. According to a dispatch of 1 January 2001, the principality of Liechtenstein acknowledges the Swiss *Federal Law on Medicinal Products and Medical Devices (Heilmittelgesetz – HMG)* and some related decrees within its territory. Liechtenstein has joined the customs and monetary union with Switzerland and adopts a number of regulatory acts from Switzerland especially those dealing with the matters of trade.

Liechtenstein has no research ethics committee of its own, but recognises decisions on clinical trials, formulated by the Cantonal Ethics Committee of Zürich.

(For more information see legal report on Switzerland).

### b) Reference

- Eidgenössisches Departement für auswärtige Angelegenheiten (2001). *Notenaustausch vom 11. Dezember 2001 zwischen der Schweiz und Liechtenstein betreffend die Geltung der schweizerischen Heilmittelgesetzgebung in Liechtenstein. In Kraft getreten am 1. Januar 2002*. [Adressat: Botschaft des Fürstentums Liechtenstein <Bern>] Bern.

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#### 4. Norway

##### a) Legal framework of ethics committees' system

The situation for scientific research in Norway is both somewhat informal and comprehensive. In contrast to the other Scandinavian countries, especially Denmark, Norway's legal framework concerning the work of ethics committees is distinguished by a certain absence of binding regulations. At the same time, Norway features a wide range of institutions, concerned with the ethics of science.

On the national level there are three independent, but assisted by the same Secretariat, committees, dealing with Medicine, Science/Technology and Social Sciences/ Humanities, respectively. However, these committees do not monitor research projects *per se* and are involved in the issues of a broader concern, like coordinating with the relevant national research activities, issuing opinions on relevant matters and the like. In significant contrast with the Danish model, the Norwegian *National Committee for Medical Research Ethics* (NEM) does not act as a body of appeal for the regional research ethics committees either. In this sense, the Norwegian system of ethical review in research can be described as a one-staged.

Most laws on the biomedical matters in Norway (e.g. the *Act Relating to the Application of Biotechnology in Medicine*) make no reference to the ethics committees. There are two legal texts, relevant for the subject. One of them is the *Regulation Concerning Clinical Trials on Human Drugs* (RCTHD). This regulation (approved by the Minister of Health and Social Affairs on 18 June 1999 under the provision of the Medicines Act, § 3) sets standards for the conduct of clinical trials in Norway.

The other text is the *Terms of Reference for the Regional Committees for Medical Research Ethics* (TRCMRE),<sup>79</sup> which was issued by the Norwegian Ministry of Education and Research on 19 January 1989 and amended on 1 July 2003.<sup>80</sup>

According to § 2-1 RCTHD all clinical trials must be reported to the *Norwegian Medicines Control Authority*, which, according to § 3-1 RCTHD, has to give its approval before the trial may commence. This consent may be withdrawn at a later date according to § 4-4 RCDHT.

The role of ethics committees in clinical trials is described in § 1-6 RCDHT. According to this provision, the Regional Research Ethics Committee must evaluate

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<sup>79</sup> Q. v. <http://www.ethikkom.no/REK/english/reference>

<sup>80</sup> The *Terms of Reference* does not refer to a formal law as a legal basis. Since they are "laid down by the Ministry" and not issued by the Minister they do not seem to have the same legal status as a regulation

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all clinical trials before any of the trial is initiated. But, neither the positive vote is required to conduct the trial nor does the regulation provide further details on the working procedures or composition of the committees. Although not a strict requirement for the beginning of the trial, the ethics committee's vote has to be submitted to the *Norwegian Medicines Control Authority* and may, if negative, well constitute grounds for denial.

The TRCMRE specifies that each of Norway's five health regions has to have a medical research ethics committee. According to the TRCMRE biomedical research projects on humans include those projects involving identifiable or anonymous human material and even data. The provisions apply analogously to research on cadavers, aborted fetuses and foetal tissue. No project shall start before the regional committee according to the TRCMRE has reviewed it. The TRCMRE also contains a provision on fees for the review, ruling that the research ethics committees shall be paid according to the government committees' rates.

Norway signed the *Convention on Human Rights and Biomedicine* on 4 April 1999, but the Parliament has not yet ratified it.

#### b) Current situation

The regional committees<sup>81</sup> are part of the university hospitals and bear the responsibility for regions of between 600.000 to 1.2 million inhabitants each. They are associated with the administrative apparatus of the respective university and funded (budgeted) by the medical faculties. Although not part of the public administration, the members of committees are appointed by the Minister of Research and Education. The committees consist of a medical professional (chairperson), recommended by the regional medical faculty, another medical professional, recommended by the health service authorities of the region, a member with nursing qualifications, a member from the regional hospital owner, a person with competence in ethics, a lawyer, a psychologist and one layperson. Decisions are reached by consensus and, as mentioned above, there is no body of appeal. The *National Committee for Medical Research Ethics* (NEM) is in the process of producing a checklist, which should assess and ensure the quality of the regional committees' evaluation procedures.<sup>82</sup> Once a year members of all (national and regional) committees meet for a two-day seminar to discuss particular topics or current issues. There are intentions by July 2004 to establish a national database, where all research projects will be registered and publicly accessible to anyone.

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<sup>81</sup> The following information is available at the web page of the *National Committees for Research Ethics* <http://www.etikkom.no/REK/english/RREC>

<sup>82</sup> According to Knut W. Ruyter, Director of NEM, November 2003

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The significant specific feature of the Norwegian system is the issue of Sami people: the Sami Parliament has the right to veto any project regardless of the opinion of research committee.

c) References

National Committee for Medical Research Ethics (1993). „Rules of Norwegian National Committee.“ *Journal international de bioéthique* 4/4: 309–310.

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5. *Switzerland*

a) Historical background

Before the *Federal Law on Medicinal Products and Medical Devices* (*Heilmittelgesetz* – HMG) entered into force on 1 January 2001, Switzerland had few federal regulations on clinical trials and biomedical research. *The Medicinal Products Decree* (*Medizinprodukte-Verordnung* MepV) from 24 January (year?) predetermines that all clinical trials with medicinal products shall be registered with the Federal Health Authority (*Bundesamt für Gesundheit, BAG*). Another decree from 1 August 1996, regulating clinical trials on immune-biological products, states an obligation to notify the BAG about such trials and gain prior approval from an ethics committee. Apart from these regulations, clinical trials fall under the competence and supervision of the Swiss cantons. To accomplish some degree of legal coherence the Inter-cantonal Control Authority (*Interkantonale Kontrollstelle IKS*) issued regulations, which states that clinical trials had to be conducted in accordance with the standards of good clinical practice. The regulation prescribes that before trials on medicinal products can be launched, an approved consent of a medical ethics committee has to be obtained. It also imposes the conditions for participation in clinical trials, questions of insurance, responsibilities of the researcher, the sponsor and the authorities, the rules of conduct for which the committees are specified.

The exact design of the rules on clinical trials and ethics committees' role was left for the cantons to decide. Some of them referred to the guidelines<sup>83</sup> of the *Swiss Academy of Medical Sciences* (SAMS), some created their own regulations.

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<sup>83</sup> Schweizerische Akademie der Medizinischen Wissenschaften „Medizinisch-ethische Richtlinien für Forschungsuntersuchungen am Menschen“, 1997. Available only in German and French.

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b) Legal framework

Since the HMG entered into force, the federal rules on clinical trials are quite explicit and all embracing. According to the Art. 54 Sect. 3 HMG clinical trials have to be notified to the *Swiss Agency for Therapeutic Products (Swissmedic)* before they commence. The Agency may forbid the trial if the requirements of the HMG are not fulfilled. One of those requirements (besides adequate insurance, written consent, etc.) is the approval of the competent ethics committee (Art. 54 Sect. 1 c).

According to the Art. 57 Sect. 1 HMG the ethics committee has to safeguard that clinical trials are conducted in accordance with the acknowledged standards of good clinical practice. Special consideration has to be given to ethical aspects and the scientific quality of the research taking local conditions into account. The committees are appointed and supervised by the cantonal authorities according to Art. 57 Sect. 4 HMG.

In a recent case the Cantonal Court of Basel decided on the complaint of the *Freiburger Ethik Kommission International (FEKI)*, which claimed the decision of the half-cantons Basel not to affirm the FEKI as an ethics committee (pursuant to the HMG) for Basel to infringe on its right of free economic development. The court decided to reject the claim, citing that the tasks of an ethics committee according to Art. 54 Sect. 1 c and Art. 57 Sect. 1 HMG constitute a genuine public function. According to the reasoning of the court, there can be no *claim* of a private body to be endowed with public tasks.

Based on the authorisation of Art. 53- 57 and 82 HMG, the *Swiss Federal Council* has issued a decree which contains further rules on clinical trial, the *Decree on Therapeutic Products (DTP)* from 17 October 2001. DTP contains procedural rules on the authorisation of clinical trials by *Swissmedic* (Art. 13-18 DTP), as well as rules for the approval by the competent ethics committees (Art. 9-11 DTP). It grants the ethics committee the power to revoke a prior positive decision under certain circumstances and establishes a time limit (30 days) for the approval of the committee and the decision of the *Swissmedic*.

The DTP contains a legal definition of clinical trials (in Art. 2 und Art. 5) defining clinical trials as “Research which is conducted on human beings with the intent to analyse security, effectiveness and other features of therapeutic products”. The DTP explicitly includes somatic genetherapy but excludes research on organs, tissue or cells of human or animal source and ex-vivo genetherapy.

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Art. 4 DTP also refers to the international standards of good clinical practice, especially citing ICH-GCP and Directives 93/42/EWG and 90/385/EWG. Switzerland signed the *Convention on Human Rights and Biomedicine* on May 7<sup>th</sup> 1999 but it has not been ratified.

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#### c) Ethical review procedures of biomedical research on human beings

Whereas clinical trials cover a good part of scientific research on human beings, they do not encompass all of it. Those parts of scientific research that do not come under the HGM's scope of application continue to be ruled by cantonal law. In the first place this means certain kinds of research (e.g. psychological research which doesn't involve the application of pharmaceuticals). But there are also other areas left out by the HMG. Neither the HMG nor the DTP contain regulations on composition and procedural rules for the ethics committees. As Art. 57 Sect. 4 authorizes the cantons to appoint the committees, rules for their procedures and compositions are also under the responsibility of cantonal law. Although there are

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some procedural rules in cantonal law (e.g. Art. 21 of the Decree on Patients Rights in Cantonal Health Service of Thurgovie<sup>84</sup>) most cantons refer to the SAMW guidelines mentioned above. This guideline contains a section that offers some suggestions for make up and procedures of ethics committees. Another issue of relevance in this context is the problem of multi-centre-studies.

Before the HMG entered into force, a subgroup of the SAMW the *Überregionale Ethische Kommission für Klinische Forschung* (UREK) was available, who also counselled other ethics committees without compromising their autonomy. With the HMG, the UREK's mandate expired and another solution has to be put forward. Article 10 Sect. 3 of the DTP allows for a simplified procedure in case of multi-centre-studies. It shall be allowed to use such a simplified procedure as soon as one of the concerned committees has given its approval. The *Working Group on Standardisation and Registration*<sup>85</sup> (StAR) issued a proposal for the exact design of such a procedure. This proposition has, to our knowledge, not yet been put into practice.

Another practical issue is the interplay between the different ethics committees and *Swissmedic*. For all the concerned parties there seem to remain questions on the exact distribution of competence between the committees and *Swissmedic*. For this reason the yearly conference of the ethics committee's presidents decided to commission StAR to draw up a check list for the cooperation of *Swissmedic* and the committees.

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<sup>84</sup> Q.v. Dominique Sprumont „La protection des sujets de recherche”, Bern 1993, S.291.

<sup>85</sup> An informal body consisting of members of the SAMW, of different ethics committees, of the BAG (Federal authority for Health Care and the cantons. Representatives from Swissmedic have the status of permanent visitors.

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Deutsches, Europäisches und Internationales Medizinrecht, Gesundheitsrecht und Bioethik der Universitäten Heidelberg und Mannheim, 2): 185–208.

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## IV. General Findings

### *A. Establishment, affiliation and independence*

In each of the study's target countries there exist committees for the ethical evaluation of research on human beings. The establishment of such committees is either required by law, governmental decrees, professional codes of conduct and guidelines, or were institutionalised based on the private initiatives. In each target country of the study we could identify at least relevant legal regulations or practising central or local committees. Most of the countries have a functioning committee system.

Historically, in some countries such system of the committees was first established following the requirements of the Second Declaration of Helsinki. Besides, the Institutional Review Boards of the United States of America has been setting a good example as well. Nevertheless, the American model and the idea the authors of the Declaration of Tokyo had differ concerning questions of affiliation and independence: *“The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed.”* (Declaration of Helsinki/Tokyo, Edinburgh Version, § 13)

On the other hand, in 1978 the National Commission for the Protection of Biomedical and Behavioural Research in the USA recommended that research ethics committees should be *“located in institutions where research ... is conducted. Compared to the possible alternatives of regional or national review ... local committees have the advantage of greater familiarity with the actual conditions ...”* Therefore American relevant committees were called Institutional Review Boards. The historic analysis of the development of Institutional Review Boards in the United States would reveal the continuity between the traditional of in-house systems of scientific peer review and the establishment of research ethics committees.

In Europe those hospitals, where research on human beings is conducted, also established their own committees, or the committees are housed by those hospitals as the CCPRBs in France. Even if there is no direct contradiction between the notion of independence and the local, i.e. institutional, principles, there may still remain conflicts of interest, which could endanger independent vote. Since the end of the seventies, the American scholar John Robertson alerted that research institutions could use their ethics committees to protect themselves and their researchers rather than subjects.

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This special kind of expert dilemma in Europe is resolved differently. Some trust in the conscience of the members of research ethics committees, which are located in the same institution where the research is planned, as it is for the majority of CCPPRB in France, the majority of local committees in the UK or the committees at the German medical faculties. Others, like Denmark, established a regional system of ethics committees, hoping to guarantee the independence thereby. *“The regions are large enough to represent a balance between local insight and necessary distance from personal bias.”* (Riis 1998) Other countries, like Spain, require that some of the members of the local research ethics committee must be institutionally independent.

Independence can also be endangered by political influence or industrial influence. Our survey was not designed to find out if and how such influence could manipulate the certain decision of the committees. None of the answers, received to our questionnaire from members of ethics committees did indicate that such pressure is real. In some cases members from central committees indicated the possibility that local committees could be influenced. The overall estimation was that at present political and industrial influence is not a central issue in the everyday activities of the committees.

In the countries, where state authority does not regulate the establishment of research ethics committees, there is an ongoing discussion about their accreditation. Since even where the vote of the committees has no legally binding force, their authority with regard to the national and international drug administration bodies and with regard to the funding organisations and the professional journals requires some transparency of the criteria for decision-making (Indo-German workshop on Bioethics, Mumbai 2002) (Nuffield Council, *“Ethics of Research Related to Healthcare in Developing Countries”*). Our survey did not indicate that in Europe there would be an actual debate on committees’ accreditation. At least the status of the committees inside particular countries seems to be more or less clear.

### *B. Local competence*

Some members of research ethics committees, for instance in Belgium, are critical about the ‘go shopping’ possibility, when there is a flexibility to approach another ethics committee if the research project was not approved at the first one. The research sponsor has the possibility to choose a committee by opting the research institution or a hospital for a drug test. However, sometimes also the researcher, who is professionally affiliated to a specific research institute, is provided with several options, to which ethics committee the research protocol could be submitted. Such options are possible, where the competence of a registered committee is not fixed to a special area; for instance, in Germany with regard to research that has to be approved according to the Medical Products Act, or, to give another example, in the Paris area (Île de France) were several competent

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committees are registered, which have adequate rights with regard to research on human beings.

### *C. Competence for different kind of research on human beings*

Considering the research on human beings, the term “research” as well as the term “human beings” are open for interpretation. It is not always easy to distinguish therapeutic measures from research activities. Concerning the term of “human being”, some countries consider the research on human tissues (Norway) or human embryonic cells to be also reviewed by local research ethics committees. Others have established or want to establish national authorities for research on embryos or for the research on embryonic cells (UK, draft legislation France).

The frames of research local research ethics committees’ competence is mainly determined by the national legal systems. While in France the law covers research on human beings including biomedical research and research in behavioural sciences, other committee systems, like in Lithuania, are legally bound to biomedical research. In other countries medical law deals only with the approval of drug research by competent ethics committees. Even if research on drugs is relevant to all European regions as the most important part of research with human subjects (at least from a quantitative point of view), the different legal perception of research is remarkable and may even have an impact on the general level of protection of human beings in research.

### *D. Competence for ethical review and scientific assessment*

The major task of research ethics committees is the protection of human subjects. Thus, the issues of consent, risk and burden are important for every committee in Europe. Answers to our questionnaire indicated that the principles of the Declaration of Helsinki are considered in the daily work of LEC all over Europe, while others also noted compliance with the Oviedo Convention. According to the wording of some regional and national laws and guidelines, the balancing between benefit and risk sometimes links the ethical review with a scientific evaluation. In the opinion of some members of ethics committees research on human subjects cannot be ethically justified underneath a minimal scientific standard. Whereas sometimes this evaluation seems to be more implicate some answers indicated that it has a central role in the review process. One expert from the Netherlands emphasized that research of high quality would be one of the main goals of the ethical evaluation.

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### *E. Membership*

An adequate judgement, concerning the risks and burdens of the research subjects, on the one hand and the expected benefits for the individual, group of patients or society on the other hand, requires expertise from many scientific and medical disciplines. In addition competence in moral assessment as well as knowledge of law and ethics is also important. Our findings indicate that the characteristics of membership qualification did not change a lot as compared to the findings of Susan Venables in her survey, prepared for the Council of Europe in 1998 (Table 2, p. 8). The membership of hospital doctors is mandatory for all European ethics committees and in many systems together with specialist from medical research they represent a majority. Lawyers and nurses tend to be regarded as a second and third group of mandated representatives. The differences among committees systems appear on the bases of requirements for the specific medical scientific disciplines (paediatricians, biostatisticians, pharmacologists, etc.). Despite the formal requirements those disciplines are represented in fact quite often. In most countries either representatives of religions, theologians, philosophers or ethical experts are often members of the committees. Thus one of the biggest differences among the target countries and even within the countries themselves is the representation number of those experts. The same is true for the participation of lay people. In the Scandinavian countries they present a significantly large group, while in Denmark lay persons even form the majority of all committees' members and are elected by the county councils or the provincial councils. In other countries lay representation is perceived as a representation of patients or patients groups and not as a democratic requirement. In most of the answers "lay person" was interpreted as anyone but a medical doctor or a scientist. Thus laypersons in Estonian ethics committees are psychologists, philosophers and theologians. The same is true for some regional or institutional committees in Germany.

Despite the legal and institutional requirements it is not always easy to find those experts who are willing to work on the committee. In different European regions members of ethics committees indicated the difficulties to find trained lawyers. In some Central and Eastern European countries committee members pointed out, that there are not enough philosophers, who are interested in research ethics and are familiar with the field of biomedicine and the ethical issues of research. The absence of members is also a problem.

### *F. Staff*

In its recommendations on "Ethics of Research Related to Healthcare in Developing Countries" the Nuffield Council indicated that Committees might "be ineffective for a variety of reasons, including a lack of financial and human resources, and a lack of training in, and experience of, ethical review." This general statement is also true for the many target countries of this study. As the answers to

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our questions showed not all of the committees in Europe can afford to employ supporting staff respectively secretariat. Ethics committees can only cope with the increasing workload if they have a qualified staff. In most cases one person seems to be sufficient. According to our findings the establishment of a small supporting office is also possible for poorer countries, like Portugal or Poland, if the fees from the research sponsors are distributed in an adequate way.

### *G. Education*

The question, if there is a need for formal training for LECs members, was not answered unanimously. Some experts and members of local ethics committees expressed their opinion that training would cause the increase in workload and over and above that is not necessary since the expertise, which was initially required for nomination to the committee could be regarded as sufficient. Some indicated that experts as well as lay people would show good results in learning by doing. Based on these findings, one could assume that this scepticism with regards to the need of LECs members' training might be one of the reasons that there are no requirements for compulsory training in most of the target countries, except an internal training in Poland. On the other hand many experts did emphasize the need for such training. Representatives from Central and Eastern Europe explained that there is a lack of education in bioethics and research ethics. Some argued that training for ethics committee members should be part of an entire culture of medical ethics and bioethics. Where lawyers are missing in the committee the need for training committee's members in medical law was indicated.

In spite of this discourse over the need of formal training, the interviewed ethics committee members agreed that more exchange of know-how on the national and especially international level could be helpful. Learning from the so called case studies and samples of other LECs' decision making process can also be facilitated by establishing a database, which would compile the most significant cases from various LECs practise on particular vote or issues. The need for such database or at least some system of know-how sharing and exchange was often emphasised by most of our interviewees. Norway has worked for several years on such project. A national data base, which will register all research projects, shall be implemented by July 2004. The data base will be publicly accessible.

### *H. Public awareness*

The Norwegian open publicly database will not only meet the needs for training of LECs' members, but also will ensure required transparency of ethics committees activities. A lot of committee members see the necessity to convince the public that research on human beings corresponds to ethical principles. On the other hand they

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acknowledge that ethics committees' work is not very well known to the public and that it is not in the focus of general interest.

*I. Interaction between Local Ethics Committees and national institutions*

In his report to the Council of Europe on Ethical Review of Biomedical Research in Europe (1998) Povl Riis emphasized that the decision making of ethical review procedures differ significantly between a single- or a double-stringed committee system. Our findings do support such assumption but indicate that a double-stringed system may take very different shapes. The central institution can be limited to the function of a consultant on behalf of the regional committees, like the Central Committee at the German Federal Chamber of Physicians. But also it can be an instance of appeal, a provider for general education and public awareness, a coordinating authority or an office of accreditation. Where those competences are combined, as it is in the Netherlands, the central position is very strong. On the other hand the establishment of a double-stringed system is not necessarily a solution for the problem of multi-centre trials.

*J. Procedure for Multi-Centre Trials*

The requirement of one national vote in multi-centre-studies is perhaps the most important innovation of the European Clinical Trials Directive and its implementation into national law (cf. Baeyens 2002). A central committee does not guarantee one national vote if its function is only of an appeal court. To delegate the final vote in multi-centre-studies to a central committee is one way to meet the European Directive's expectations. Another possible way of answering to the European requirement could be the election of a head committee as in Sweden or in France or as proposed by the German Working Group of Medical Ethics Committees. Finally there is the possibility to follow the Scottish and English example by creating special regional bodies, which cooperate (interact) with the local committees. Probably the plurality of procedures will continue to exist after the implementation of the Directive.

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## V. Conclusions and Recommendations

As it could be predicted from the earlier national and international surveys, there are immense variations on the base of membership, workloads and working practices of local ethics committees. These differences are grounded in the diversity of the health care and research sector at the particular country of interest as well as in economical and cultural distinctions. The results of our survey also indicated the immense diversities regarding LECs tasks and the legal base of their work, requirements for members' training and structure (if at all existence) of the supporting staff, availability of funds and their distribution. From an ethical point of view, nevertheless, it may be emphasized that all members of all research ethics committees are committed to the same ethical principles. There was no strong indication that any of the countries' or regions' individual philosophical or ethical traditions would be important or even binding for the work of the LEC, although such possibility is mentioned in the Norwegian Terms of Reference for the Regional Committees for Medical Research Ethics.

It could be rather problematic to allocate certain cases of excellence in general LECs' practise. Thus we are limiting ourselves to indicate some patterns of excellence regarding special criteria. Concerning the division of labour and tasks there seems to be a consensus that the task of research ethics committees reviewing research on human beings and the tasks of clinical ethics committees should be clearly distinguished. The situation is somewhat different at the regional *vs.* national layer, i.e. relationship among the research ethics committees and national advisory committee on ethics. In smaller countries, where there is a significant shortage of experts in medical research ethics, it may be plausible to leave an important role of the review system to a national committee, as the models of Lithuania or Slovenia show in different ways.

Concerning the local competence it should be mentioned that the possibility of "forum-shopping" is still the source of permanent frustration for ethics committees and their members. Setting an end to such practices would be possible when every research institution is specifically assigned to one ethics committee. We have to admit that an absolutely uniformed standard of LEC is not realistic in particular when the local principle regarding safety of the tests persons are intended to be preserved. On the other hand, it is important to ensure that existing differences are not used selectively to undermine ethical review standards. The Danish system seems to be an example of excellence in that sense, but it is not the only one.

The efficiency and transparency of a review system depend on a clear regulatory framework. The French system is an example of excellence regarding the broad and comprehensive legal framework. Nevertheless the notion of self-esteem is sometimes also positive in countries, where the committees work in part on the

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basis of national and regional laws and in part on the basis of professional laws and the scientific community's notion of self-control.

The feasibility of each system depends on the existing institutions, their conception and reliability. Our study once again revealed how diverse and complex LECs system is throughout all European states (EU Member states, EU-candidate states or Associated states to the 5<sup>th</sup> and 6<sup>th</sup> Framework Programme); this diversity mainly is an outcome of historical traditions and the structure of national and regional institutions. These differences will not be eliminated even after the implementation of the European Directive on Good Clinical Practice since the directive tolerate a plurality of ethics committees system, their other area of activity, beside the ethical review of drug research, and the training of committees members. Instead of trying to harmonize all institutional settings it could be wise to use these differences in preserving high standards in protection of human subjects in research by acknowledging possibilities of different approach. Nevertheless it is necessary to understand the pros and cons of the individual national system to eliminate or to cope with its drawbacks.

As it is mentioned in the chapter 4 of this study, education of ethics committees members remains a controversial issue. Although there are training programmes in the Netherlands, the UK, Austria, Finland, Switzerland, France, Estonia and some other countries, it is not evidently clear what methodology and which curriculum should be used. Training programmes should be sensitive to the cultural and traditional differences of European countries and the expertise of local experts and members of LEC should not be overwritten. Therefore a modulated curriculum would be feasible.

The results of our study cannot be claimed to present a thorough picture of the LECs effectiveness and work specifics. Neither the workload nor the funding, nor the training, nor the time spent on reviewing research proposals are sufficient indicators. The same applies to the general self-esteem, which was indicated by our questionnaires and interviews. Results of our survey, moreover do not answer the question if monitoring of the Ethics committee system would be desirable. The existing reports on committee system in France<sup>86</sup>, Germany<sup>87</sup>, Switzerland (before the legal reform)<sup>88</sup> and others<sup>89</sup> are good examples for further studies to evaluate the national specifics. We have detected a clear indication of interest and importance of the like studies and examinations and the continuation of such projects were emphasised not only from the current target countries, but also some Council of

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<sup>86</sup> Huriet 2001.

<sup>87</sup> Wilkening 2000, Just 2003.

<sup>88</sup> Sprumont 1993.

<sup>89</sup> Nicholson 2000.

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Europe's Member states, not belonging to the target countries of this study as Croatia and Ukraine.

The European Union in co-operation with the Council of Europe should encourage the continuation of similar studies in the future. It is expected that implementation of the Council of Europe Convention on Human Rights and Biomedicine as well as its Protocol on Medical Research and implementation of the European Directive on Good Clinical Practice will cause changes in the practice of at least some national ethics committee systems. A network of experts and members of research ethics committees could be set up to exchange information and to provide continuous survey.

Such a network should consider at least the following topics:

1. The development of ethical review between the call for harmonisation and streamlining and the need for thorough review and internal discussion especially regarding innovative and complicated questions of research and consent (tissue research, genetic research, stem cell research, research with children as human subjects etc.).
2. The development of the national systems with regard to the tension between ethics and law respectively between ethical advice and legally binding vote.
3. The development of training programmes and the possibilities to create modules for national and international use.
4. The impact of the research ethics committees' work on the general trust in research and the general public awareness of the work the committees.
5. Since the lay representation at the committee differs not only in quantity, but also in definition and understanding, there should be an international discussion on the function of lay people in the committees. The question should be addressed what kind of training is appropriate and if lay members have to be prevented from becoming experts.
6. The debate about adequate means of monitoring research on human beings (Robertson – Levine) could be translated into European context.
7. Finally the network could be a place to exchange the experiences and know-how regarding the different systems of review in multi-centre-trials.

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This report was written by Michael Fuchs, IWE, Bonn, and collaborators.

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