ARBEITSKREIS MEDIZINISCHER ETHIK-KOMMISSIONEN

IN DER BUNDESREPUBLIK DEUTSCHLAND

- DER VORSTAND -

Statement of the Permanent Working Party of Research Ethics Committees in Germany concerning the 'Draft Guide for Research Ethics Committee Members' of the Council of Europe CDBI/INF (2009)6

The Permanent Working Party of Research Ethics Committees in Germany (PWPREC) has been asked to comment on the 'Draft Guide for Research Ethics Committee Members' of the Council of Europe (DG). The PWPREC which represents more than 85% of all RECs in Germany has circulated the DG to all its members and asked for comments and consented the following statement. To avoid any appearance of lack of impartiality (the president of the PWPREC is coauthor of the DG) the vice president of the PWPREC was asked to coordinate and finalize this statement.

The PWPREC appreciates the chance to contribute to the final version of the DG. We consider the DG an effort to harmonize the organisation, tasks, procedures and actions of RECs wherein it being understood that the independence of RECs remains respected. The DG is certainly a considerable achievement in its attempt to provide an administrative and organisational guidance as well as a manual for the ethical assessment of biomedical research proposals. Since 2000 there are the Operational Guidelines for Ethics Committees that Review Biomedical Research of the WHO, however, and thus we are not convinced that there is a need for another guidance document. The growing multiplicity of guidance documents in the various fields of biomedical research add to a, meanwhile, considerable complexity. Thus it might have been advisable to update the WHO document instead of drafting a new one.

With regard to research with medicinal products (drugs) there are already three partly different terminologies in use: the CTD's, the ICH-GCP's and the national laws' and regulations'. Thus we ask that no new terminology is used unless there is a definite need to do so.

The ICH-GCP, which is in many countries part of the drug law, discusses at length responsibilities; composition, functions and operations; and procedures of RECs but the current DG adopts only some of the specifications and standards of the ICH-GCP. As this may negatively impact the acceptance of the DG and increases complexity we ask to crosscheck carefully for avoidable differences in the respective documents.

Relevant references are missing in the DG.

1. Introduction

We missed reference that there is (at least in many countries) a constitutional right of freedom of research. In the field of biomedical research this right of freedom of research has to be balanced with the constitutional right of research subjects to be protected. It is the major task of RECs to protect the rights of research subjects.

Page 3, 3rd paragraph

The sentence:' Research must be carried out freely but only subject to specific provisions for the protection of human beings.' can be misunderstood in the sense that biomedical research is not permitted unless there is a *specific* provision or law for the protection of human beings. Please clarify.

Page 4, top

With reference to 1.27 of the ICH Topic E 6 Guideline for Good Clinical Practice (ICH-GCP) one should mention as a task of the RECs : to provide public assurance that the protection of the rights, safety and well-being of human subjects involved in clinical trials is ensured.

2. Ethical Principles

Page 4

It may be questioned whether the ethical principles: autonomy, beneficence, non-maleficence and justice, which prevail in the individual therapeutic situation, can be used in the same way as a fundament for the ethics of research. To give an example: Placebo-controlled trials and research without direct benefit for the research subject (e.g. most pharmacokinetic studies) are common, but it is difficult to define the benefit received by the participating research subject. Therefore additional principles have to be considered, for example the prohibition of instrumentalisation of human beings or The Golden Rule.

We accept that there are legitimate situations, e.g. when the research aims for results that may confer subsequent benefit to other individuals with the same or similar disease, but we think there is a need for further deliberations to develop ethical principles which allow for such research.

The ethical principles-based approach mentioned here has been outlined (among others) by T.L. Beauchamp and J.F. Childress in The Principles of Biomedical Ethics but there are other legitimate approaches too, e.g. the Belmont Report or the CIOMS Biomedical Research Ethics. We missed a discussion or at least a proper representation of the different ethical rationales. The Belmont Report e.g. uses the term 'respect for persons' which encompasses more than 'autonomy'. One wonders why 'respect for persons' is not mentioned at all.

Furthermore the DG does not clarify sufficiently which competence RECs should have and what to do in case of conflicting rules or decisions (e.g. ethics vs. law, or, more often, vs. requirements of drug authorities).

2nd paragraph, 7th line

Correct spelling error: …of which go form physical…….

Page 6, Beneficence and non-maleficence 3rd paragraph

The statement:' Research on human beings may therefore only be undertaken when there is no alternative method which could provide similar results.' restricts too far the constitutional freedom of research. This statement refers to all types of research and does not differentiate between research subjects who are able respectively unable to give informed consent.
One has to keep in mind too that there are people who think that research with animals is only acceptable in case that similar results cannot reasonably be obtained by other means.
These comments equally apply to 'Justification for involving human beings in the research' page 23.

Page 6, bottom

In some European countries biomedical research involving individuals unable to consent is unlawful, if the research has no potential for direct benefit. We suggest mentioning explicitly this legal situation in the text to avoid misunderstandings. This comment applies to chapter 6, too. Active controlled trials usually provide the potential for direct benefit. But a discussion of the ethical issues involved in placebo-controlled trials with patients who are unable to give consent is missing.

We appreciate that the DG tries to provide examples of research with minimal risk and minimal burden. We are afraid, however, that the examples provided may be misunderstood as a carte blanche. Thus we recommend adding examples of the required *individual* assessment: One x-ray exposure in an elderly person (>50 years) may be considered acceptable, whereas one research-driven x-ray exposure in a child or a pregnant woman is not acceptable (In Germany, actually any research-driven x-ray exposure needs a permit by the competent Federal Office for Radiation Protection). With regard to computed tomographic exposure one has to take into account the considerable higher x-ray exposure. One should mention too that a procedure which, if applied only once, does not cause more than minimal risk and burden, may well do so if applied repeatedly. We think that taking a blood sample from a peripheral vein (when a venous access is not already present) in individuals unable to consent to a research project with no potential for direct benefit is beyond the limits of minimal risks and burden. Likewise further examples given in footnote 2 are in our opinion not per se within the limits of minimal risks and minimal burden: removal of additional tissue during surgical operation may lead to extra risks like bleeding, local tissue dysfunction etc, and are thus not to

be performed in vulnerable persons not able to consent. Also imaging by MRT may represent a stressful procedure for some patients.

3. B.2 Legally binding instruments

The Commission Directive 2005/28/EC has to be mentioned here too, as it asks for Ethics Committees in section 2, and the UN Convention on the Rights of Persons with Disabilities.

4. A REC – Description

Page 9, 1st paragraph

One may consider to add 'privacy' to the agenda that the REC has to help ensure.

4. A.1 Roles and activities of RECs in the research process

2nd paragraph

Better: - *roles* aim to fulfil RECs' main objective – to ensure that biomedical research is conducted ethically correct and in agreement with applicable national laws and regulations.
Furthermore it should be explained what is meant with 'is conducted ethically.' If this means that the study has to be done in conformity with the ethical principles outlined in chapter 2 the DG should mention it.
The subchapter ' REC review and implications for publication of research results' from page 12 could be added here just before Figure 4.1 .

Figure 4.1 Roles of RECs in the research process

The figure provides a role (consultation with researchers) for RECs even in the planning and preparation phase of a research project. Details about this role are missing in the text however. If a REC collaborates with an investigator already in the planning phase, one may question the independence of this REC's assessment of the ethical acceptability of the final research proposal. We suggest to avoid such a potential conflict of interest situation and to drop that point. The provision of information, e.g. about the legal situation or about the procedures of a REC is not considered by us as 'consultation with researchers'.

A.1.1 RECs' roles before research begins

Page 10, last but one paragraph, last line

Better: …ethically sound research is ensured.

Page 11, top

The order of two bullet points 'main standpoints' should be reversed, as there is no doubt that the interests of the research participant (rights, dignity, safety and well-being) should be the dominant standpoint (see Declaration of Helsinki, too).

Page 11, Clinical audit

It is certainly useful to try to differentiate between research and clinical audit projects. One has to keep in mind however that clinical audit projects can generate data privacy issues. Furthermore a clinical audit project may be a disguised 'marketing project' pretending to aim for better quality of care only, but with an implicit impact, e.g. on prescribing a particular drug. Finally we assume that most projects assessing outcome quality are at least in part patient-oriented research.

Page 11, last paragraph

One should mention here that although the CTD 2001/20/EC asks for one single opinion by the competent REC, in multicenter trials local RECs are quite often involved too. In Germany the legal task of these participating local RECs is to review the quality of the investigators and the suitability of the trial sites in their circuit. Of course these local RECs can provide comments about the research plan etc. to the REC in charge of the single opinion. This is current and well accepted practice in Germany .

Page 11 and 12 RECs' independence

We were surprised to learn that RECs' independence is needed only before research begins as this subchapter is part of A.1.1 only. Isn't it better to add this subchapter to 4.A.1 and to confirm that the RECs' independence is essential whenever it acts ?

4. A.1.2 RECs' roles during research

Although we sympathize in principle with the present statement we think that it generates considerable problems.

Most RECs and its members in Europe work on a honorary basis with limited funds and support. Thus, the means to monitor proactively ongoing research projects are just not available. Further on, such tasks require different expertises, e.g. to evaluate the benefit/harm balance of an ongoing clinical trial particular expertise in the disease and its current state of the art treatment, in clinical trial methodology and statistics, and in the causality assessment of alleged adverse drug reactions is needed. This know-how is most often not readily available. Given the empiric data that clinical testing of new treatments, e.g. in phase I is usually quite safe, one may doubt whether a uniform approach towards overseeing ongoing research projects by RECs makes sense and is efficient.
There might be even a 'conflict of interest' for a REC when it has to ask to stop a trial or to modify a research protocol which it had approved initially.
Thus self-restraint is definitely recommended. Notwithstanding the fact that RECs usually cannot provide a comprehensive supervision and monitoring of a research project RECs should have the right to intervene once they learn about non-negligible risks in a project, but there should be no obligation for routinely monitoring ongoing research projects.
Data Safety and Monitoring Boards are most probably more suited for such tasks.
This comment equally applies to 'Information to the ethics committee during the conduct of research', page 28.

4. A.2.1 Expertise

The statement about the professional members of RECs is rather vague. With regard to the medical profession clinicians and/or practitioners, a clinical pharmacologist, a paediatrician (when there are paediatric studies), and a biostatistician should be considered as absolutely essential. For diagnostic studies, medical devices and epidemiological studies additional professional expertise is needed.

4. A.2.2 Specific posts – Chair, Vice-Chair, Administrator

Page 14

There is too much detail and recommendations which are not evidence-based, e.g. 'who command the respect of REC members'. This part should be deleted as it sounds very outdated. 'Anyone appointed to chair a REC should have gained the necessary experience by being a REC member for some time'. Is such kind of trivial advice really needed?
Interestingly, nothing is said about the way chair and vice chair are supposed to be appointed, although this may be an essential indicator for the independence of the REC.

Page 15, Figure 4.2.

The chair comprehends too many duties, the administrator too few, e.g. bullet points 3, 4, 6 and 7 should be primarily tasks of the administrator. That the administrator prepares the minutes is mentioned twice. Close cooperation between chair and administrator is needed.
We missed a statement who is responsible that all procedures of the REC are carried out in strict compliance with the law and the state-of-the art.

Page 16, top

We missed a statement that a member of a REC who is personally involved in the research project under review or when concerns about his/her impartiality exist, should be excluded from the review and discussion of this research project.

4. B.1 Statutes

We recommend to reverse the order of the bullet points: Duties and responsibilities …. and Procedure for membership renewal in Figure 4.3 .

4. B.2 Rules of Procedure

We recommend avoiding too much detail, in particular there is often very little evidence about what best practice is, e.g. appointment of adhoc rapporteurs (p. 18). One may doubt that this guidance makes sense as it may be difficult to find of a rapporteur who is equally qualified in the subject matter of the project itself, biostatistics, insurance issues, informed consent requirements and clinical pharmacology just to mention the typical expertises needed. Thus RECs may prefer with good reason a different, more focused approach, i.e. the clinical pharmacologist reviews the clinical and preclinical data, the biostatistician the sample size estimation and the plan for the statistical analysis and the lawyer the legal issues and so on.

We missed a statement
- that discussion and decision making of RECs should be done in personal meetings to allow for an unhindered interactive discussion among the members
- that the chair of a REC has a special obligation to find a consent among the members of the REC and to formulate it. The individual members of a REC contribute their special expertise, e.g. clinical pharmacology, law, biostatistics, which should not be overruled by a majority vote
- that the applicant has the right to be heard, at least prior to an imminent negative vote.

4.C Independent audit of REC functioning

Although we do not object to the idea of auditing the REC's functioning, great care has to be taken to safeguard the independence of the REC.

5. Application process

Is there really a need to specify that electronic submissions should be accepted by the REC? There are still some technical and legal problems even in highly developed countries, e.g. the validity of electronic signatures; also the issue of insufficient data protection in public areas, like offices, trains, lounges, internet cafés has to be considered.

5. Information to be provided to and examined by the REC

Page 22, 1st paragraph

The CTD does not use the term 'principal investigator' nor does it assign such tasks as mentioned here to him/her. Please use the CTD terminology, here 'sponsor', to avoid further confusion. In addition it is among the tasks of a REC too to review the suitability of the trial centers, thus respective information has to be provided to the REC.

Page 23, Healthy volunteers

In studies with healthy volunteers special care has to be taken that dependent individuals, e.g. employees of the sponsor, the CRO or prison inmates are not eligible for participation. We suggest to refer here to the definition of Vulnerable Subjects in the ICH Topic E 6 Guideline for Good Clinical Practice 1.61.

Page 24, Use of placebo, figure 5.2

It should be mentioned that the use of placebo in patients unable to give informed consent is unlawful in some countries. Furthermore the statements on the use of placebo in the most recent version of the Declaration of Helsinki (Soeul 2008) should be cited here.

Page 25, Benefit and risks

We missed a note that in case that there are no direct or indirect benefits for the research participants (but only advancements for scientific knowledge and society in general) that such research must not entail more than minimal risk and minimal burden if research subjects unable to provide informed consent are involved. (By the way, such research is not permitted in Germany).

See our comments under **2. Ethical principles** too.

Page 25, Recruitment arrangements

The subchapters ‘recruitment arrangements’, ‘information for potential participants’ and ‘potential undue influence’ should be merged.

Figure 5.3 and the respective text do not clearly specify the purpose. Is it meant as a checklist for the written participant information to obtain ‘Informed Consent’ or to raise awareness that there is a clinical study that looks for participants?
In any case we missed

- Do I have to pay for participating in that study?
- Do I get active treatment or is there the cchance/risk to receive placebo?
- Will I get insurance for any harms I may suffer from?
- How is my data protected?

We suggest to move bullet points 8-11 further down, as the potential participant should receive information about treatment alternatives and possible side effects etc. first.
We missed a statement that the REC has to critically review the qualification of the responsible investigators and the appropriateness of the study center(s).

Page 27, Informed Consent

We are rather surprised how little space is devoted to the most important prerequisite of ethical research which signifies that the participants’ autonomy is respected – Informed Consent. Absolutely essential is the requirement that only experienced investigators are permitted to explain and discuss the essence, the consequences, the meaning and the risks of the research project with the potential participant.
Furthermore the potential participant should have sufficient time (if medically acceptable) to deliberate and to discuss his/her potential participation with relatives and/or peers.

Page 28, Information to the ethics committee during the conduct of research

The last sentence of this subchapter should be deleted in toto or use at least a different wording, e.g. …by RECs may be useful. RECs are no enforcement agencies. See comments under 4.A.1.2 too.

Page 28, Data protection

This subchapter should start with a statement concerning the participants’ rights of data privacy and the right of informational self-determination.

6. Persons unable to consent

Page 34, Figure 6.2

We missed in the checklist: Is the written Informed Consent material adequate for the age of the potential paediatric participants? If there is a wider age range, more than one Informed Consent material has to be provided.
We missed the note that at least in some countries pediatric drug research involving more than minimal risk and minimal burden is not permitted.

7. Research in specific situations

We missed any deliberations about research involving human fetuses.

8. Biological Materials of Human Origin

The text of this chapter is with few exceptions rather general and is thus not considered very helpful. In particular we reject such general recommendations like the one on page 42 last paragraph:' When RECs are asked to review proposals concerning the establishment or use of collections and population bio banks they should be satisfied that the proposal includes a satisfactory oversight mechanism and that the conditions governing access for research use of the samples are appropriate and transparent'. We think that the principle of autonomy of the donor of the material has to be respected here too.

We missed references to

- the right to ask for destruction of the biological material as long as it is not anomysed
- the right to be informed in an understable manner about the relevant aspects of collecting, storing and using biological material with particular reference to the purpose of the investigation. A blank consent without an explanation of the objectives is hardly acceptable
- the ethical issues involved in the information of the donor about research findings (e.g. genotyping) and its implications, in particular about incidental findings and the right to not learn about the results
- the potential for genetic discrimination at the work place, for life insurance etc
- the potential risks when biological materials are sent to countries (e.g. for analysis) with a lower level of data privacy
- adequate methods used to pseudonymise the samples.

Munich 21.3.2010

Prof.Dr.Joerg Hasford
- Vice President of PWPREC -