



Comments of the German Medical Association

On the Council of Europe draft guideline entitled
“Draft Guide for Research Ethics Committee Members”, CDBI/INF (2009)6

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Elaborated by the
Group of Specialists on Biomedical Research (CDBI-CO-GT2)
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Preliminary comments

The *Group of Specialists on Biomedical Research*, working under the authority of the *Steering Committee on Bioethics (CDBI)* of the Council of Europe, elaborated a "Draft Guide for Research Ethics Committee Members" (hereinafter referred to as the "Draft Guide"), which is intended to be used as a tool for research ethics committee members.

First it should be stated that, in the view of the German Medical Association, ensuring the protection of medical research participants is the primary objective of a research ethics committee (REC). Pursuant to German law, the function of a research ethics committee is to act as a patient protection institution with the character of an official authority. The REC decides whether a scientific research project is ethically acceptable and personally acceptable to the patient. Therefore, in the view of the German Medical Association, it is essential that the principle of respecting and protecting the "*primacy of the human being*" (p. 5, line 2) be implemented throughout the entire Draft Guide. When in doubt, the protection of the individual human being must prevail over the interests of society, including any general research interests. This weighting of the central standpoints of ethics committees is clearly represented in Section 2 (p. 5, line 2f.) of the Draft Guide, but not in Section 4.A.1.1 (p. 11). It should also be clearly stated in that part of the text that the interests of the study participants take precedence over the potential consequences of research results for society.

In the commentary that follows, core theses are presented together with additional remarks on individual recommendations of the Draft Guide for specific research situations.

1) The principles presented in the Draft Guide represent a far-from-complete account of the ethical and legal foundations relevant to the work of ethics committees.

This must be clearly stated in the body of the text in order to emphasize the non-binding nature of the Draft Guide.

The work of ethics committees is woven into a dense network of European and nationally binding legal norms and non-mandatory standards. In view of the diversity of these framework conditions, a guideline summarizing the core ethical principles of these tasks would be much appreciated. However, as this inevitably results in a generalized account of ethical principles, such a guideline cannot claim to be either complete or binding.

In many places, the text clearly lays claim to validity and is therefore misleading to the reader. For example, the portrayal of questions relating to ethical issues is insufficiently differentiated (cf. Section 5) and insufficiently commentated checklists are used. At any rate, the principles outlined in the Draft Guide do not represent the generally accepted consensus beyond national peculiarities (cf. page 7, lines 41-43), as is shown in numerous examples in the following sections.

The fact that the Draft Guide cannot claim to be either complete or binding in any respect should be mentioned more frequently in the text.

The Draft Guide is not a suitable basis for future European standard-setting for the above-mentioned reasons.

- 2) **The ethical standards depicted in the Draft Guide are mainly based on those set out in the European Convention on Human Rights and Biomedicine and its Additional Protocol. However, certain Member States consciously provide for more stringent standards or higher levels of protection of research participants. These States have not signed or ratified the European Convention on Human Rights and Biomedicine for this reason. For this reason, ethics committees in these States are obligated to ensure a higher level of protection.**

In order to avoid misunderstandings, differences in applicable national legislation must be clearly stated in the corresponding passages of the text. Failure to do so would limit the prospects for practical implementation of the Draft Guide.

The Draft Guide makes evaluative statements on the acceptability of several ethically challenging positions using references to the aforementioned convention and its protocol. For example, long passages of the Draft Guide are taken from the European Convention on Human Rights and Biomedicine (Oviedo, 4 April 1997) and its Additional Protocol concerning Biomedical Research (Strasbourg, 25 January 2005). The evaluative decisions of some Member States concerning the level of protection afforded research participants deviate significantly from these norms because their national law provides for a higher standard of safety for research participants. This applies, in particular, to measures for the protection of persons unable to consent and to the applicable prohibition of research for third-party benefit in such individuals in these Member States. Consequently, the European Convention on Human Rights and Biomedicine and its Additional Protocol were neither signed nor ratified by several Member States, including the Federal Republic of Germany.

In order to give the readers a correct overview of the regulations and conditions applicable to them, the Draft Guide should explicitly highlight these important national regulatory differences. In this respect, the information provided in the Draft Guide so far does not appear to provide sufficient clarity for the user. In this case, application of the principle of "*minimal risk*" and "*minimal burden*" is a particular challenge (cf. item 5). It would be feasible to insert, for example, a table and/or footnote indicating the ratification status of the relevant documents in individual Member States in the appropriate parts of the Draft Guide.

- 3) **The ethics committee operating procedures and organizational structures recommended in the Draft Guide do not necessarily derive from the cited ethical principles. Therefore, the Draft Guide should differentiate more clearly between descriptions of ethical principles on the one hand and recommendations concerning ethics committee operating procedures and organizational structures on the other.**

The question of whether and to which extent procedural and organizational issues can and should be covered in the Draft Guide at all should be subjected to critical review.

Detailed regulations (e.g. the Declaration of Helsinki or Directive 2001/20/EC and the national legal documents based on it), the ethical implications of which have been thoroughly explored, exist for many aspects of ethics committee work. The Draft Guide does an admirable job of summarizing the basic ethical principles of medical research involving human subjects and, in particular, it addresses some ethical issues that are not expressed very clearly in existing legal documents.

However, the generalization mentioned in item 1 becomes rather problematic when applied to ethical principles. Considering the diversity of existing regulations, it is legitimate to ask which additional benefit a guideline that is limited to summarizing existing documents might provide. However, the Draft Guide also covers—in great detail in some cases—issues that go beyond the scope of a guideline for members of research ethics committees.

Consequently, the Draft Guide should distinguish more clearly between descriptions of ethical principles on the one hand and recommendations concerning ethics committee operating procedures and organizational structures on the other. One could, for example, take the European Convention on Human Rights and Biomedicine and its Additional Protocol as an example of how to distinguish between the description of ethical principles and procedural issues.

The authority of an ethics committee is based on its rootedness in the prevailing regional cultural traditions and values (p. 14, line 33f). Important regulatory disparities exist between EU Member States regarding issues such as the handling of biomedical research involving minors or persons unable to consent, data protection and professional codes. Furthermore, the fact that there are considerable differences between healthcare systems in the individual Member States must be taken into account.

Regarding the treatment of procedural and organizational issues in the scope of the Draft Guide:

In addition to delineating ethical principles, the Draft Guide also provides detailed procedural and organizational recommendations for ethics committees on subjects such as the duties and responsibilities of REC members and administrative officers as well as the composition, statutes and rules of procedure, evaluation, cooperation and external auditing of research ethics committees. In these areas, research ethics committees and their supporting institutions are bound by the national and regional structures of their healthcare systems and, within this framework, they are entitled to regulate their internal organizational affairs themselves. The Draft Guide's recommendations concerning the procedural and organizational affairs of ethics committees encroach upon the organizational sovereignty of ethics committees and their supporting institutions.

It is questionable whether some of the procedural recommendations in the Draft Guide can be practically implemented. From the point of view of the researcher, the list of information to be submitted for ethics committee review (Section 5.B, p. 21f.) in particular could pose an unreasonably high obstacle to ethics committee access for applicants from the academic sector. While this information is indubitably useful in painting a complete picture of a proposed study, it must not be regarded as a checklist of mandatory documents such as that provided in the Appendix to the Additional Protocol of the European Convention on Human Rights and Biomedicine. A main characteristic of ethics review processes outside the scope of clinical trials for drugs and medical devices is that the ethics committee procedures should be adapted to regional conditions and handled flexibly. In particular, the dialogue with researchers has proved effective, not the "one-stop mailbox" approach.

Summary:

Member States differ with respect to their legal frameworks for research ethics committee work. That being said, the fundamental question of whether procedural and organization issues can and should be covered in the scope of the Draft Guide should be subjected to critical evaluation.

4) Recommendations regarding the tasks and responsibilities of research ethics committees during the course of research and after completion of a study are problematic. Ethics committees are not monitoring agencies—at least not according to German law.

The self-conceptions, infrastructures and legal freedoms of action of ethics committees in different Member States differ so greatly that it is impossible to make explicit recommendations regarding their tasks and responsibilities during and after a study. Instead, we recommend an open formulation such as that in Section 4.A.2.1, which does not specify whether this should be the task of an ethics committee or not. Vigilance and safety monitoring during the course of clinical research and after completion of a study are not the task of an ethics committee but rather, the responsibility of the national competent authority—at least in Germany, where the BfArM (*Bundesinstitut für Arzneimittel und Medizinprodukte*) and the Paul Ehrlich Institute are the competent authorities.

We also refer to the corresponding explanatory memoranda to the German law on the amendment of regulations governing medicinal products of 17 July 2009 (BT-Drs. 16/12256, p. 50, no. 44/§ 42 and p. 51, no. 45/§42a) and the law on the amendment of medical device procedures of 29 July 2009 (BT-Drs. 16/12258, p. 30, preliminary note to nos. 16 to 19 and p. 32, no. 19/§22b). The German Ordinance on Medical Devices Vigilance assigns responsibility for vigilance to the sponsor and the (national) competent authority. At the European level, the current version of the "Guidelines on a Medical Devices Vigilance System" (MEDDEV 2.12-1 rev 6, December 2009) states that responsibility for vigilance lies with the manufacturer or operator of a medical device and the competent authority, not the ethics committee. Insofar as a codified reporting system exists (particularly for pharmaceuticals and medical devices), ethics committees lack the necessary authority to ensure control to the extent specified in the Draft Guide. Furthermore, national competent authorities have jurisdiction over the tasks outlined in Section 4.A.1.

Against the background of these considerations, the recommendations concerning the roles and responsibilities of research ethics committees during and after conduct of a reviewed study, as specified in Sections 4.A.1.2, 4.A.1.3 and 4.A.2.2 and on page 28f. of the Draft Guide, are problematic.

5) The opinions represented in the Draft Guide as undisputedly presupposed ethical positions give one the impression that a consensus already exists at the European level. However, this cannot be assumed offhand.

As is accurately stated in the Draft Guide, the authority of an ethics committee is based on its rootedness in the prevailing regional cultural traditions and values (p. 14, lines 33-34).

Thus, any recommendations regarding a harmonization of standards must be compatible with the different national legal frameworks and values.

In view of the regulatory disparities between EU Member States regarding issues such as research involving minors and persons unable to consent, data protection and codes of medical ethics, the representation of ethical principles in the Draft Guide must be challenged and clearly expanded where necessary.

In the Draft Guide, ethical principles are portrayed only in an exemplary and summary manner that fails to take a number of existing sets of regulations and recommendations into account.

The following comments on the Draft Guide's individual recommendations for specific research situations are provided for this purpose.

a) The fundamental remarks concerning the weighing of risks against benefits (Section 2, p. 6) do not reflect the current state of discussion sufficiently and without contradiction.

Regarding risk/benefit assessment, Article 21 of the Declaration of Helsinki and Article 3, para. 2a of Directive 2001/20/EC require the positive assessment that the expected benefits of medical research involving human subjects "*outweigh*" the inherent risks associated with them.

The Draft Guide, on the other hand, states that "*A research project should proceed only if its foreseeable risks and burdens are not disproportionate to its potential benefits.*" This wording is unacceptable. The negative requirement that risks and burdens be "*not disproportionate*" deviates from the positive formulation

of existing norms and does not ensure adequate protection of the participants in clinical trials. The wording of the corresponding passages of the Declaration of Helsinki and Directive 2001/20/EC should be given precedence over the wording in Article 16ii of the Oviedo Convention.

In particular, the Draft Guide states: "*Research on human beings may therefore only be undertaken when there is no alternative method which could provide comparable results*" (p. 6, line 23). This statement can pose problems in the case of (principally acceptable) non-inferiority studies in which only marginal advantages are achieved for secondary target variables and a disadvantage within the margin of non-inferiority is accepted for the primary variable.

b) Minimal risk / minimal burden

Special significance is rightfully placed on the ethical postulate of minimal risk and minimal burden only. Although frequently attempted, no universally accepted definitions of the terms "*minimal risk*" and "*minimal burden*" have been established.

In cases where this principle is applicable¹, ethics committees have the challenging task of deciding case-by-case whether a specific procedure means that the risks and burdens associated with a given study are still minimal or not. Including examples of minimal risk and minimal burden conditions in a guideline could be helpful in decision-making. This challenging subject and the special need for protection of research participants are issues that cannot be adequately dealt with in a footnote. This is particularly true considering the fact that extensive documents on this subject that deviate in part from the examples used in the Draft Guide already exist (for example, the statement of the Central Ethics Committee of the German Medical Association on research involving minors, 2004). Proper interpretation of the terms "*minimal risk*" and "*minimal burden*" requires a broad ethical discussion, and this process is not yet completed.

c) Research involving persons unable to consent

Deciding which conditions are acceptable for research involving persons unable to consent is one of the most challenging tasks of ethics committees. This question centres on the core principle of autonomy and therefore requires particularly thorough consideration. However, the discussion process is not yet complete.

¹ See also items b) through e)

Therefore, any simple recommendations issued on this subject at present are problematic.

Research in persons unable to consent that does not provide any potential direct benefit to the affected individuals (but to third parties) is prohibited in Germany. The Oviedo Convention takes the more liberal stance that research performed in the interest of third parties is permissible under conditions of minimal risk and minimal burden. Many Member States reject this position.

In order to avoid misunderstandings, an appropriate note should at least be inserted in places where the recommendations in the Draft Guide deviate from national laws (for example, "*The Protocol allows for research without the potential for direct benefit under the additional protective condition that the research must entail no more than minimal risk and burden*", p. 35, lines 32-34).

d) Research involving minors

The information provided in Figure 6.2 (page 34) is intended as a checklist of questions to help REC members decide whether children may ethically be involved in a proposed research project. In addition to its questionable wording, the checklist is incomplete in terms of content. At any rate, it does not take the applicable laws and recommendations of the European Medicines Agency regarding clinical drug trials adequately into consideration. (cf. item 1 for more on the problem of incompleteness). Apart from clinical drug trials, the minimum requirements of the European Convention on Human Rights and Biomedicine (e.g. Article 17, para. 1) or Directive 2001/20/EC (Article 4 e) are not completely implemented in all parts of the Draft Guide, for example, in the checklist in Figure 6.2 (page 34).

e) Research involving persons deprived of liberty

Research involving persons deprived of liberty is expressly forbidden in Germany, not least for historical reasons (cf. Section 40, para. 1, sent. 3, no. 4 of German Drug Law and Section 20, para. 1, no. 3 of the German Medical Devices Act). Contrary to this, Section 7.B of the Draft Guide states that research involving persons deprived of liberty can be permissible if their autonomy in deciding whether to participate in the research is adequately ensured. Research involving persons deprived of liberty is not possible in Germany, at least not according to currently valid law. The arguments cited in the Draft Guide in support of such research are not very convincing.

f) Research in clinical emergencies

The Draft Guide takes the position that the conduct of clinical research not providing any potential direct benefit to the patient can be permitted in emergency situations provided there is minimal risk and minimal burden. This appears unacceptable from a medical point of view and is incompatible with German law.

The statements in the Draft Guide concerning the ethical acceptability of research in emergency patients are based solely on the Additional Protocol and, thus, have a very narrow basis. It is therefore imperative to consider these statements against the background of national law. This should be mentioned in the Draft Guide in a suitably clear form.

g) Use of placebo

Regarding the use of placebo in clinical studies, the Declaration of Helsinki states:

"32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or*
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option."*

Even in situations where patients are not subject to any risks, the use of placebo is only acceptable if necessary for compelling and scientifically sound methodological reasons. Special justification of the methodological necessity for placebo comparison is therefore needed. Suitable indication of this is lacking in the Draft Guide.

The remarks in the Draft Guide concerning the acceptability of placebo comparisons (p. 24, line 18 ff.) lack sufficient differentiation and do not consider methodological justifications such as the fact that approval authorities recognize that placebos are needed in order to demonstrate assay sensitivity for external validation and/or proof of the group benefits of a study and, thus, for justification of an approval decision.

h) Research involving biological materials

For information regarding the position of the Central Ethics Committee of the German Medical Association on the use or reuse of human materials for medical research purposes (2003), please refer to the website (<http://www.zentrale-ethikkommission.de/downloads/Koerpermat.pdf>).

i) Declaration of Helsinki

Some recommendations in the Draft Guide are not in sufficiently precise agreement with the Declaration of Helsinki (e.g. Article 17, no. 27). The Declaration of Helsinki has been the authoritative document on the ethical principles for medical research involving human subjects for years and is widely recognized around the world,. Therefore, the positions held in the Draft Guide, at least, should not contradict the principles of the Declaration of Helsinki.