

ARBEITSKREIS MEDIZINISCHER ETHIK-KOMMISSIONEN

IN DER BUNDESREPUBLIK DEUTSCHLAND e. V.

- DER VORSTAND -

AK Med. Ethik-Kommissionen ◦ Scharnitzer Str. 7 ◦ 82166 Gräfelfing

ICH Secretariat
Route de Pré-Bois, 20
P.O Box 1894
1215 Geneva
Switzerland

27/9/2019

Public Consultation: General Considerations For Clinical Studies E8(R1)

The Association of Medical Ethics Committees in Germany represents all Ethics Committees in Germany that are involved in the assessment of clinical trials with medicinal products and medical devices. We appreciate that the ICH has initiated a public consultation on the draft **General Considerations For Clinical Studies E8(R1)**. This offers the chance to contribute to the further improvement of this document.

In general, we think that this is a useful guidance which updates appropriately the current version of the ICH E8-Guideline. However, we would like to comment on several issues.

General comments

We appreciate that issues regarding data monitoring committees are considered. Given that a blinded and standardized assessment of endpoints is highly important for the robustness and validity of the results of many trials we suggest to add relevant points to consider regarding Endpoint Adjudication Committees.

Given that Contract Research Organisations and other types of vendors play an ever increasing role in the planning and conduct of clinical trials a short section on „Selection and qualifications of CROs and vendors“ could be helpful too.

Since many years physicians are expected to comply with the principles of Evidence-based Medicine. Thus it is time to use this concept for the regulation of clinical trials too. Therefore ICH should encourage and promote the independent scientific evaluation of its guidelines and their respective revisions. In particular it is important to identify and subsequently abandon requirements which failed to provide added value for the protection of research subjects and the quality of the data and subsequently the results of the trial.

VORSITZENDER:

Prof. Dr. med. Joerg Hasford
Ethik-Kommission der
Bayerischen Landesärztekammer
Tel.: +49(0)89 / 89866971
Fax: +49(0)89 / 89892174
E-Mail: has-ethik@ibe.med.uni-muenchen.de

STELLV. VORSITZENDER:

Prof. Dr. med. Georg Schmidt
Ethik-Kommission der Technischen
Universität München
Tel.: +49(0)89 / 41404371
Fax: +49(0)89 / 41404199
E-Mail: gschmidt@tum.de

SCHRIFTFÜHRER:

Prof. Dr. jur. Sebastian Graf von Kielmansegg

SCHATZMEISTER:

Dr. med. Guido Grass

BEISITZER:

Dr. phil. Angelika Hüppe
Prof. Dr. med. Kurt Racké
RAin Julia Rümmler
Prof. Dr. jur. Jochen Taupitz
Prof. Dr. med. Ignaz Wessler

POSTANSCHRIFT:

Scharnitzer Straße 7
82166 Gräfelfing

E-MAIL:

med.ethik.komm@netcologne.de

Homepage:

www.akek.de

BANKKONTO:

Postbank Frankfurt am Main
IBAN DE73 5001 0060 0499 5316 01
BIC PBNKDEFF

Eingetragen in das Vereinsregister beim
Amtsgericht Berlin-Charlottenburg
unter VR 31275B

We appreciate that the role of patients and patient representatives is emphasized (see section 2.3 and 3.3.3).

Comments on methodological and statistical issues

Lines 491 – 533 (Section 5.1.3 Control Group)

The description of the use of an external control group is in our opinion too positive and encouraging. Although disadvantages of an external over an internal control group are addressed, the description in the present guideline might be interpreted as if both types of control groups are valid options, with the external control being only slightly inferior. The usually unknown or unquantifiable problems in bias, confounding, data quality, consistency, comparability, etc. arising from the use of an external control group should be emphasized in more detail. Although the ICH E10 guidance document is referred to, some of its caveats could also be included into the ICH E8(R1). Otherwise, sponsors and investigators might believe that the high standards of an internal control group is a design feature that can be refrained from, resulting in only minor decrease in trial quality and validity. A clarification is essential that external control groups are only acceptable under very special circumstances (e.g. very rare diseases) and that the internal (randomly allocated) control group remains the state of the art.

Lines 595 ff (Section 5.1.6 Statistical Analysis)

We prefer to have the SAP ready before the first trial patient level follow-up data are collected. In particular, the analysis even of so-called blinded data which is currently permitted can allow relevant insights for the specifications of the SAP and introduce bias, e.g. the analysis of attrition-/dropout/follow-up-rates, adverse event/adverse drug reactions may often even allow the identification of treatment groups. Thus the text should be modified accordingly: see in particular line 601; analyses of so-called blinded study data needs either a very strict definition (e.g. no analyses for different groups even when formally still blinded), but we prefer to delete this option completely.

Lines 604 – 606

The ‘Statistical analyses of primary and secondary endpoints to achieve study objectives with respect to both efficacy and safety should be described, as well as interim analyses and/or planned design adaptations’ in the trial protocol (not only in the Statistical Analysis Plan). The trial protocol should cover the exact definitions of the different patient analysis sets used, the statistical tests and procedures, whether statistical adjustments are used, as well as the procedures to handle missing values. If this information is missing, neither the assessors of the NCAs nor the members of ethics committees can decide about the quality and correctness of the planned statistical analyses, as typically the SAP is not part of the dossier for approval.

Lines 606 – 611 (Section 5.1.6 Statistical Analysis)

The basics of the listed aspects of analysis (estimation/ tests of hypotheses, analysis populations, handling of intercurrent (e.g. competing) events, rescue medication, missed visits, protocol violations) should be described in the trial protocol, too.

Further specific comments:

Line 43: "The investigator and sponsor share responsibility for the protection of study subjects ~~together~~ ~~with~~ supported by the Institutional Review Board/Independent Ethics Committee".

Comment: From a legal point of view, the sponsor and the investigator are responsible for the wellbeing of study subjects, not the IRB/IEC.

Line 57: "primary objectives,"

Comment: Many studies have more than one objective, and more than one primary endpoint (e.g. as one endpoint does not appropriately represent the relevant treatment effects, e.g. in Alzheimer's disease).

Line 57: "{...} and explicitly stated. Results of a terminated study should to be publicly made available within reasonable time, e.g. 12 months after the last study related patient visit."

Comment: Clarification of the requirement for transparency.

Lines 107/108: "{...} selection of appropriate subjects that have the disease {...}, and ethical means of recruitment with adequate recruiting procedures;

Comment: An extra emphasis is needed in particular for the recruitment of vulnerable patients.

Lines 202-204: "...e.g. defining patient populations, procedures, endpoints or logistical issues like the use of 'flying nurses or remote trial visits by TC or WebConferences (Skype) {...} regulatory authorities and the competent IRBs/IECs should also be considered."

Comment: As the IRBs/IECs play a major role in the authorization procedure they should be explicitly mentioned here too. We would like to emphasize that the involvement of investigators located in different locations (even in different EU Member States) for one trial subject in the setting of very rare diseases, the involvement of so called-flying study nurses, remote trial visits by TC or WebConferences e.g. via Skype, performed by staff, which is not directly connected with an investigator site etc. can generate relevant ethical issues too.

Line 228: "{...} are captured and transparently as well as meaningfully incorporated into the development programme."

Comment: Transparency is essential for obvious reasons.

Line 364: "{...} use of the drug, e.g. in reality/real life setting".

Comment: This type of study gets more important.

Line 420: "{...} and patient assent for paediatric studies; and regional standards of care, as well as adequate recruitment methods."

Comment: see comment for line 107/108.

Lines 539/540: "endpoints and variables" .

Comment: see line 57.

Line 647: "With secondary data use, the appropriateness of the available data as well as the adequate legal basis for using this kind of data for the purpose of scientific research should be considered."

Comment: In many countries, the legal basis is an important issue.

Line 665: "Local regulations related to privacy of participants' data ~~should~~ ~~be~~ need to be followed."

Comment: Clarification.

Line 677: "{...} a clear description of the rationale for the modification and the impact on each part of the study as well as on each document (duration of insurance, patient information, informed consent form, CRF, SAP etc.) should be provided in a protocol amendment (ICH E6) where the modifications are compared to the original documents, for transparency and traceability."

Comment: Clarification needed to facilitate the work of NCAs and of the members of IRBs/IECs.

Line 682: "{...} should receive thorough training prior to enrolment of the first subject and implement safety measures where needed (especially safety SOPs for sites conducting FIH or Phase I-studies)."

Comment: For obvious reasons to protect the wellbeing of trial participants.

Line 714: "...the use of an independent data monitoring committee..."

Comment: The members of the DMC should be external and independent with regard to the sponsor.

Line 717: 'external safety monitoring committee'. Please use terms that are properly defined, e.g. use established terms like 'data monitoring committee' or 'independent data monitoring committee' to avoid confusion.

Line 720: "{...} procedures governing its operation, selecting its members and the required scientific backgrounds {...} should be established (Charter)."

Comment: Clarification.

