The Position of German Ethics Committees on the proposed Draft Regulation on Clinical Trials

Joerg Hasford
Permanent Working Party of Research Ethics Committees in Germany
Email: med.ethik.komm@netcologne.de
Col – Statement and Caveat

• I am an active researcher, member of the European LeukemiaNet, which has been funded by the EU, and of the EU-IMI-Project PROTECT.
• The views expressed here do not necessarily represent exactly those of the PWPREC.
Appreciation

• evaluation of the directive 2001/20/EU after 10 years
• harmonisation and standardisation of the clinical trial requirements in the EU
• introduction of the risk-proportionate approach (→ minimal interventional trial)
• option for co-sponsors
• single submission
• IMPs free of charge for the subject
Achievements of the Clinical Trials Directive 2001/20/EU

- There is a very high level of safety for clinical trial participants in the EU.
- Since 2001 we know just one major accident in premarketing clinical testing (Phase I: Tegenero, UK).
- In Germany (≈ 1200-1500 trial applications/year) less than 3% of all trial applications pass the Ethics Committees’ reviews without modifications and less than 5% of all applications get definitely rejected.
Achievements of the Clinical Trials Directive 2001/20/EU

• Thus independent Ethics Committees are successful in protecting the rights, the safety and the well-being of patients and healthy volunteers in clinical research and freedom of research.
• The timelines set by the directive were and are met.

WHY ENDANGER THIS SUCCESS STORY?
Major Flaws of the Proposal

• Ethics Committees (RECs) are neither mentioned nor involved in the assessment of clinical trial applications.
• Drift to social ethics, wordings like “individual therapeutic benefit”, “well-being” etc. are largely missing, instead: “public health benefit” and “relevance” are frequently used.
• Ethics mainly limited to informed consent issues.
Major Flaws of the Proposal

• Co-determination rights of the member states concerned are extremely limited → decisive role of the reporting MS.

• Extremely short time-lines, e.g. 5 calendar days, which do not allow for a sound assessment.

• Vulnerable people like minors, incapacitated and persons deprived of their liberty were not properly protected.
The proposal displays an outdated concept of research ethics by limiting its wording in this context to

- informed consent and
- the safety and the rights of subjects
However, for many years it has been widely accepted that research ethics have to take at least the following into account

- autonomy, respect, dignity and privacy
- beneficence
- non-maleficence and
- justice

**Necessary modifications:**

To complement the full spectrum of ethical review in the text of the proposal wherever indicated
Major Critical Points

The proposal negates internationally accepted, substantial ethical standards in that it does not even mention ‘Ethics’ or ‘Ethics Committees’.

The Declaration of Helsinki states explicitly:

“The study protocol must be submitted prior to the study for consideration, comment, guidance and approval of a research ethics committee” (B.15).
Major Critical Points

The Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research* states explicitly:

“Every research project shall be submitted for independent examination of its ethical acceptability to an ethics committee. Such projects shall be submitted to independent examination in each state in which any research activity is to take place. ” (Article 9, 1.)

*Entry into force: 1/9/2007
Major Criticisms re Vulnerable Persons

Minors:

- Art. 31 does not differentiate between studies which may provide individual benefit for a minor patient and those who do not. It is not specified who provides the Informed Consent information.

Necessary Modifications:

- Direct benefit expected: proportionate risks are acceptable.
- No direct benefit expectable (group benefit): risks and burden (distress) have to be minimal! (Current wording: the clinical trial has been designed to minimise pain, discomfort, etc. …)
- Informed Consent communication should be provided by a paediatrician.
Major Criticisms re Vulnerable Persons

Prisoners and other institutionalized persons:

• not mentioned at all in the Commission’s proposal

Necessary modifications:

- These persons should not be eligible for clinical trials, as the voluntariness of Informed Consent cannot be safeguarded in this situation.

Art. 30 and 32 need modifications similar to Art. 31.
Major Criticisms - Timelines

• The proposal is aiming to establish a centralised approval process with extremely shortened timelines, as a European location advantage.

• For certain processes laid down in the proposal, requiring national and often international coordination, deadlines of 3, 4, 6, or 10 calendar days are set.

• Time limits like these do not allow for an appropriate assessment. In addition, often neither international nor academic sponsors will be able to respond within the time limit set.
Ethics Committee - Timelines: Suggested Modifications

Part I and II: 40 days  Low risk trials: 33 days
Part I only: 30 days  Low risk trials: 25 days

Current status

60 days for multicenter trials per Member State
→ Considerable faster assessment
Major Criticisms – European Voices

Our assessment of the ethical aspects of the commission proposal is in line with the statements of the European Network of Research Ethics Committees (EUREC) and the European Group of Ethics in Science and New Technologies of the European Commission (EGE).
Results of the 1st Reading of the EP: Achievements (29 May 2013)

- REC: again an essential part of the regulation (definition, tasks, etc.) and participate in the assessment of the clinical trial applications.
- The level of protection for minors, incapacitated persons, persons deprived of their liberty and people with special needs were noticeably and rather satisfactorily raised.
- The wording is now much more in agreement with the Declaration of Helsinki and emphasizes individual ethics.
Result of the 1st Reading of the EP: Achievements (29 May 2013)

• Co-determination rights of the MS have been strengthened. Disregarded comments have to be notified, the rationale for disregarding explained.

• Transparency of trials’ results is addressed.
Critical Points

• Clarification of the role of the RECs of the MS concerned regarding the assessment of part I of the application (trial protocol, risk-benefit assessment).

• Clarification of the impact of the assessment of the competent REC. → Approval, Opt out reasons

• Clarification that the deliberations and voting of the REC should remain separate and independent of the decision-making of the NCAs (→Article 9).
Critical Points

• Article 29, 3a (new) considers trials were subjects are informed only, no Informed Consent is asked for. Subjects are expected to proactively reject participation if they want. → should be deleted.

• Clinical Trials with pregnant or lactating women shall be widely permitted even if not providing the potential for direct benefit (Art. 31a (a))

• Clinical trials in emergency situations allow proportionate risks and burdens even if there is no potential for direct benefit (Art. 32 (e) and (ea)).
Critical Points

• Still much too short time-lines linked with the concept of tacit approval → lack of responsible decision-making and responsibility.

• Definition of 'low risk trial' too wide, covering treatments recommended by standard guidelines or supported by sufficient published evidence.

• It needs to be stressed that the Informed Consent interview should be done by physicians only.
Further proceedings

• The EP and the European Council start now negotiations to prepare a final und mutually acceptable text.
• The second reading in the EP is currently planned for early March 2014.
Summary and Conclusions

• The Commission’s proposal tried to meet regulatory challenges of therapeutic research.
• From an ethics point of view the proposal was seriously flawed: it showed a too limited understanding of research ethics, and Ethics Committees were not even mentioned. Thus the proposal did not comply with accepted international conventions and guidance documents.
• Consequently the rights, the safety and the beneficence of the patients were not adequately protected.
Summary and Conclusions

• The European Parliament has already considerably improved the proposal. There are, however, still many important issues that need to be addressed for further improvement.

• As a *regulation* is planned extraordinary care is needed for preparing the final version.

• As Ethics Committees we respect freedom of research and patients’ interests in better medicines.
References

• EGE:

• EUREC: