How Will Ethics Committees be Impacted by the EU Clinical Trials Regulation?

EUCROF-Conference 26 February 2018, Vienna

Prof. Dr. Joerg Hasford
Association of Research Ethics Committees in Germany
E-Mail: has-ethik@ibe.med.uni-muenchen.de

CoI – Statement and Caveat

- There are no conflict of interests to declare.
- The views expressed here do not necessarily represent exactly those of AKEK Germany.

Structure

- Introduction: Aims and provisions of the CTR 536/2014
- Challenges for the ECs
- Implementation of the CTR in Germany
- Registration requirements for ECs
- Responsibilities NCAs / ECs
- Résumée

Present state of trial approval

- **The drug laws and the GCP-ordinance implemented the CTD 2001/20/EU in the EU MS**
- **Assessment of the application dossier independently by REC and NCA**
- **Approval by REC needed to start a drug trial**
- **Only national laws and regulations applicable**
- **Option for oral discussions with sponsor**
- **Truely independent and autonomous RECs, regulated by state law**

Revisions of the CTR 536/2014

- Harmonisation of the clinical trial requirements
- Single submission via EU Portal
- Coordinated multistate assessment
- Scope of the ethical assessment not specified, and varies MS-wise.
- Extremely short timelines and many options for tacit approval
- Single decision by MS
- One fee per MS
- Communication with sponsor in writing only

Tasks of Ethics Committees

- **To ensure the protection of the rights, safety and well-being of human subjects involved in a trial *and***
- **To provide public assurance of the protection *by***
- **Reviewing and approving the trial protocol, the suitability of the investigators, facilities, and the methods and material to be used in obtaining informed consent.**

ICH-GCP (E6) and CTD 2001/20/EU Art.2 (k)

Role of Ethics Committees

- **The ethical review shall be performed by an ethics committee (EC) in accordance with the MS's national legislation. The review by the EC may encompass Part I and Part II as appropriate for each MSc.**
  → Contradiction to DoH and ICH-GCP
- MS shall ensure that the timelines and procedures for the review by the EC are compatible with the Regulation.

CTR Art. 4

Ethics Committee - Definition

‘an independent body in a Member State established in accordance with national law and empowered to give opinions for the purposes of this Regulation, **taking into account the views of lay-persons, in particular patients or patients organisations’.**

CTR Art.2 2. (11)

Application Dossier for Initial Application

- **Part I:** **Trial protocol**, scientific background, risk (harm) – benefit assessment, IB, details specified in Article 6 and Annex I
- **Part II:** **Informed Consent material**, qualification of investigators and suitability of study sites (centres), insurance etc., details specified in Article 7 and Annex I

Part I: Evaluated by all MS concerned, reporting MS coordinates the assessment and provides ‘single decision’.

Part II: Evaluated by all MS concerned, each MS provides **its** decision.

Assessment Report: Part I

Multinational studies:

- rMS provides initial assessment report within **26 days** from the validation date.
- rMS and MSc jointly perform a coordinated review phase within subsequent **12 days**.
- rMS provides final consolidated assessment report within **7 days**.

Assessment Report: Part I – Challenges for the EC

Multinational studies:

- → The draft assessment report has to be reviewed immediately (1 – 2 days).
- → Competent (medical, ethical, English) EC-spokesperson needed for the review phase
- → The role and impact of the members of the Ethics Committee get reduced most probably.
- → ECs typically work in an honorary capacity only and do meet once or twice a month.

Decision on the Clinical Trial

- Each MSc shall notify the sponsor as to whether the clinical trials is
  - authorised
  - authorised subject to conditions*
  - refused

within **5** days from the reporting date.

*restricted to conditions which by their nature cannot be fullfilled at the time of that authorisation (Art.8,1.)

Tacit Authorisation

If the MSc does not respond within the respites set, the resulting 'decision' is in favour of the sponsor.

The concept of 'tacit authorisation' pertains to many respites.

What happens if the Ethics Committee does not provide its decision in time ?
→ Nonobservance of the DoH ?

Ethics Committee - Challenges

- **How to learn about the views of patients or patients' organisations about a particular trial given the very short respites ?**

THE IMPLEMENTATION LAW

- In November 2016 the German Parliament passed the implementation law for the CTR 536/2014.
- The law speficies the structure and composition of ECs, tasks and responsiblities of the NCAs and the ECs, and their cooperation.

Implementation Law : Registration of ECs

Requirements (AMG § 41 neu)

1. **State of the art expertise of the members**
2. **Multidisciplinary composition: at least one lawyer, one person with expertise in medical ethics, three practising physicians (one pharmacologist), one biostatistician and one lay person**
3. **Assured equal access for female and male members to the EC**
4. **By-laws covering internal procedures, transparency, decision-making etc.**

Implementation Law : Registration of ECs

Requirements (§ 41 neu)

5. **Business office with adequately qualified staff**

6. **Adequate technical equipment and performance**

7. **Proof of the independence of the members and external experts (= no CoI)**

Responsibilities of EC and NCA

- **PART I will be assessed jointly by NCA and EC, NCA taking the lead → lead coordinator.**

- **Part II will be assessed solely by competent EC.**

- **The final decision (Art.8) by the MS Germany will be provided by the competent German NCA, respecting the opinion of the competent EC.**

Impact of the CTR - Institutionally

- ECs get marginalized
- ECs get dependent to the government
  - registration etc., by-laws
  - loose the right to provide their own statement re Part I and have to col-laborate with the NCA
  - loose their financial autonomy
- The honorary sytem of ECs is at risk, the impact of the individual member weakens.
- The final decision (Art.8) is done by the NCA.

Impact of the CTR - Workwise

- Considerable strain due to very short timelines.
- No more (oral) discussions with the sponsor, communication in writing(foreign language) only.
- Increased affinity to IT-structured workflow needed.
- More communication and compromising with NCAs.
- ECs have to be available 365 days/year.

Traffic lights' - Status October 2017: Results

Major Problems seen in three areas:

- **Resources**
- **National IT System**
- **Safety**

In the majority of the EU MS the restructioning of the REC-System has started or has even been finalised.

AMEK Hasford

Conclusions

- **The coordinated assessment of multinational trials brings major challenges for ECs too.**
- **The role and impact of the individual members of the ECs gets reduced most probably.**
- **The often very short respites ask for pro-fessional Ethics Committees instead of the currently prevailing honorary system.**
- **The request to take the patients' view into consideration remains a soap-box oratory only, given the very short time allowances.**

Conclusions

- **Due to the CTR the ECs will loose a considerable part of their independence from the government: The government defines the registration requirements, the tasks and the fees of ECs.**
- **Many procedures have been standardized but the scope of the tasks of ECs is now completely up to the Member States – a serious step backwards compared to the CTD 2001/20/EU.**

Conclusions

- **The very rigid communication requirements and short respites may result in increasing numbers of relapses/rejections, and subsequent resubmissions, time delays and costs.**
- **The importance of scientific *and ethic advice* prior to submission will thus increase.**

Reference

Hasford J. The impact of the EU Regulation 536/2014 on the tasks and functioning of ethics committees in Germany. Bundesgesundheitsblatt 2017: 60; 830-835.