The Impact of the EU Regulation 536/2014 on the Research Ethics Committees in Germany

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CoI – Statement and Caveat

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

Structure

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- Résumée

Aims of the Regulation 536/2014 (CTR)

- To promote clinical research in the EU
- To effectively harmonize the authorization and conduct of clinical trials in the EU
- To simplify procedures
- To strengthen the position of the EU as an excellent and leading location for clinical research and drug development.

Appreciation of the CTR

- Harmonisation and standardisation of the clinical trial requirements in the EU
- Single submission via EU Portal
- Coordinated multistate assessment
- Introduction of the risk-proportionate approach (→ minimal interventional trial)
- Option for co-sponsors
- Transparency
- IMPs free of charge for the subject

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**
- 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.

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Assessment Report: Part I – Challenges for the EC

Multinational studies:

- → **ECs have to review the application very fast in case rMS needs < 26 days, and to submit requests for additional information.**
- → **The EC of the rMS should provide its own statement already for the initial assessment report.***

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* Provided national law involves EC in the assessment of part I

Assessment Report: Part I – Challenges for the EC

Multinational studies:

→ **For all other MSc the review phase of 12 days is the only chance to get the MSc ECs point of view integrated.**

Mononational studies:

→ **The EC should provide its own statement already for the initial assessment report.**

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.

Request for additional Information Part I

- **Only via/by the rMS**
- Sponsor has to submit/respond within **12** days, otherwise the application shall be considered as withdrawn in all MSc.
- Extension of assessment period for the assessors (NCA/EC) up to 31 days.

Decision on the Clinical Trial

A MSc shall refuse to approve a clinical trial if it disagrees with Part I of the assessment report of the rMS on any of the grounds referred to in the second subparagraph of paragraph 2 of this Article, or finds, on duly justified grounds, that the aspects listed in Article 7, paragraph 1, are not complied with ***or where an ethics committee has issued a negative opinion which in accordance with national law is valid for the entire MS.***

(Article 8, 4.)

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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.)

Decision on the Clinical Trial – Challenges for the Ethics Committee

- ECs have to review the final assessment report part I to decide about acceptance and to provide a conclusive written statement within 3 days.
- ECs typically work in an honorary capacity only and do meet once or twice a month.

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 work-flow needed
- More communication and compromising with NCAs
- ECs have to be available 365 days/year

Actions and Contributions of the Association of RECs in Germany

- ✓ **Since 2012 the CTR is regularly a main topic at the two annual national meetings of ECs in Germany**
- ✓ **The CTR is a regular topic in the continued education curriculum für members of ECs**
- ✓ **There is internal CE für local ECs and its staff too**
- ✓ **NCA and 31 ECs have already started a Pilot Project assessing CTAs according to the procedures and time lines of the CTR 536/2014**

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 full-time professional 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

- With the implementation of 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.
- The Ecs in Germany will try hard to meet these challenges.
- The Pilot Project of the ECs & NCA will provide usefull experience even before CTR 536/2014 enters into force.