The new Clinical Trials Regulation 536/EU – Integration of Ethics Committees into the Process: Challenges

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Col – Statement and Caveat

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

• Single electronic submission through the EU portal, both for national and multinational studies.

• All communication between sponsor and member states concerned (MSc), and some between the stakeholders (NCA, Ethics Committee) via EU portal only.

• One or more national contact point(s) per MS to facilitate the authorisation procedure.
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) 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
Evaluation of the Application Dossier

• rMS validates the completeness of the application within **10 days**.*
  ✓ MSc may communicate their considerations within **7 days**

• If application is considered ‘not complete’, sponsor gets a maximum of **10 days** to complete.

→ **ECs have to be fast, if they want to be involved in the validation.**

* If rMS does not respond in time → tacit approval.
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.
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.
Assessment Report: Part I – Challenges for the EC

Multinational studies:

→ For all other studies 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.
- ECs typically work in an honorary capacity only and do meet once or twice a month.
Assessment Report: Part I

• rMS finalises the assessment report during the consolidation phase (7 days), taking duly into account the considerations of the MSc and records how all has been dealt with.

  (Article 6, 5.)

• Assessment report of Part I has to be submitted to sponsor and MSc within 45 days from the validation date.
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.
Assessment Report: Part II

• MSc shall complete and submit its assessment reports and decisions within 45 days from the validation date.
• MSc may request additional information.
• Same response (12 d) and shorter extension times (19 d) compared to I

→ No particular challenges for EC

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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

MSc may disagree to accept Part I of the assessment report of the rMS on the following grounds:

- Participation in the clinical trial would lead to **inferior treatment than in normal clinical practice in this MS.**

- Infringement of national legislation regarding e.g. animal or human cells, narcotics etc., details see Article 86.

- Disagreement based on safety, data reliability and robustness considerations, already submitted during the coordinated review phase.
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.)
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?
Normal Clinical Practice - Definition -

- the treatment regime typically followed to treat, prevent or diagnose a disease or disorder; (Art. 2 (6))

- MSc could object to almost all placebo-controlled trials.
The ethical review shall be performed by an independent ethics committee (IEC) in accordance with the MS’s national legislation. The review by the IEC may encompass Part I and Part II as appropriate for each MSc.

MS shall ensure that the timelines for the review by the IEC are aligned with the timelines set out in the Regulation.
'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'.
Ethics Committee - Challenges

- How to learn about the views of patients or patients’ organisations about a particular trial given the very short respites?
Informed Consent by simplified means in Cluster Trials

Informed consent shall be deemed to have been obtained if:

• the participant has been informed prior to inclusion about the trial and, in particular, about the right to refuse or withdraw at any time, and
• the potential subject, after being informed, does not object to participating in the trial.

**Important:** No prior interview with a member of the investigating team needed.
Informed Consent by simplified Means - Requirements

- trial in one member state only
- the methodology requires that groups rather than individuals are allocated
- low-intervention clinical trial, and IMP is used in accordance with marketing authorisation
- no interventions other than standard treatment
- the protocol justifies the reasons for obtaining IC with simplified means

Article 29a
Informed Consent by simplified means in Cluster Trials

Issue as seen by the Declaration of Helsinki:

- Articles 25 and 26 do not allow for the inclusion of competent persons in clinical trials without explicit informed consent.
Conclusions

• The coordinated assessment of multinational trials brings major challenges for ECs too.
• The role and impact of the members of the Ethics Committee 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

• The extension period of up to 31 days for the assessors should be carefully used, i.a. for the appropriate integration of the EC members into the decision process.

• The regulation does not clarify how the sponsor learns about the concerns of the MSc in time and how the sponsor can inform the MSc which modifications get accepted to meet the concerns prior to the final decision of the rMS/MSc.
Conclusions

• For mononational trials the time allowances will be longer than the present ones. At least the German ECs will try to not use this option.

✓ The Ethics Committees will try hard to meet these challenges.