II. Clinical Trial Regulation
Challenges for National Competent Authorities
Perspective of BfArM

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Selected Topics

- Definitions
- Communication & Interaction
- Phase I Clinical Trials
- Safety Reporting
- Penalties




Definitions of Clinical Trial and Clinical Study

Current vs future Definitions (Germany, AMG vs CTR)

A **clinical trial** on human beings is any investigation on human subjects intended to investigate or verify

(a) the clinical or pharmacological effects of medicinal products, or

(b) to identify adverse reactions or

(c) to study the absorption, distribution, metabolisation or excretion,

with the aim of ascertaining the safety or efficacy of the medicinal product.

'Clinical study' means any investigation in relation to humans intended:

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;

(b) to identify any adverse reactions to one or more medicinal products; or

(c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products;

with the objective of ascertaining the safety and/or efficacy of those medicinal products;

New Definition of a Clinical Trial

‘Clinical trial’ means a clinical study which fulfils **any** of the following conditions:

(a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the **Member State concerned**;

(b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or

(c) diagnostic or monitoring procedures **in addition to normal clinical practice** are applied to the subjects.

Implications by the new Definitions

- **If a clinical study is not a clinical trial it is considered to be a non-interventional study (NIS)**
- **CT definition refers to Member State specific clinical practise**
  - In some Member States a clinical study could considered to be a clinical trial while in other Member States it would be a NIS
  - What happens in case of disagreement between RMS & MSC?
    - If the RMS considers the clinical study to be a NIS, based on national practise, but other Member States concerned (MSC) disagree?
      - Is it then a NIS in all MSC? [No]
- **Since the (indirect) definition of a NIS does not linked to the marketing authorisation, particular prospective Off-Label Use trials could be NIS according the CTR**

Communication & Interaction in the Assessment of a Clinical Trial Application (CTA)

Initial Decision Process when CTA is submitted to EU portal

@Minute 0

- Determination of the NCA & EC
  - PEI or BfArM: According to Section 77 AMG
    - No input from applicant
  - Competent ethics committee (EC): According to prepared distribution scheme/list?

@Day 3

- Application for RMS or MSC

@Day 6

- Final Decision on RMS

@Day 10

- Decision on validation / request for additional information

Validation

- **Part I**
  - Validation by RMS
  - Comments by MSC up to Day 7 (single opinion)
    - EC comments / requests should be available at the NCA earlier
- **Part II**
  - Validation by each MSC
  - No rules on invalid / incomplete CTAs
    - Missing CVs, insurance documents etc.
  - Current concepts (?)
    - No extra requests for information during validation period but during assessment phase?
    - No validation of Part II in Article 11 procedures?

Note: Elimination of validation shifts issues to assessment phase

RMS Assessment: Interaction between NCA & EC

- **Option A**
  - Draft Assessment Report (dAR) jointly written by NCA and EC
  - Pros: Both opinions fully included and visible, no delay by parallel assessment
  - Cons: Statements could be inconsistent / contradictory

- **Option B**
  - dAR drafted by NCA and is commented/amended by EC
  - Pros: Concise dAR
  - Cons: consecutive process: delay due to compilation of final dAR
    - Problems in shortening assessment period for mono-national CTAs
      - would require flexible EC commission session schedule or national legal requirements
- **Option C**
  - As Option B, but dAR drafted by EC and is commented/amended by NCA

Cooperation Tools

- **EU portal/communication platform currently not designed for joint assessment within a Member State (NCA ↔ EC)**
- **National tools for tracking and information exchange required?**
  - BfArM started discussion on cooperation and tracking tools with PEI and selected ECs
  - National tracking tool requires standardised interface to EU portal / database
    - Not within the scope of the independent audit (therefore not expected in the first version)
  - Currently various positions on “what and how”

Phase I Clinical Trials

Phase I: Current Situation

- **Urgent need for accelerated review times**
  - Both NCA and EC
- **Legal base for accelerated review of phase I CTAs**
  - 14-days review for follow-up Phase I trials with unmodified IMP dossier
    - Section 8 (3) GCP-V for EC review
    - Section 9 (3) GCP-V for NCA review
- **Current situation**
  - Section 8(3)/9(3) hardly used
  - Integrated phase I protocols
    - Several sub-studies incorporated into single trial protocol
      - Complex protocols, difficult to review

Phase I: Future Situation

- **It is anticipated that most phase I trials will remain mono-national trials**
- **Still urgent need for short review times**
  - Both NCA and EC
- **But: integrated protocols are large and complex**
  - Review is even more difficult than with standard phase I protocols
- **Solution?**
  - Simple follow-up phase I protocols should be remunerated by accelerated review times

Safety Reporting

The new freedom?

Article 41 - Reporting of adverse events and serious adverse events by the investigator to the sponsor

1. The investigator shall record and document adverse events (AEs) or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the periods specified in the protocol.

2. The investigator shall record and document all adverse events, unless the protocol provides differently.

   The investigator shall report to the sponsor all **serious** adverse events occurring to subjects treated by him or her in the clinical trial, unless the protocol provides differently.

What could this mean?

The sponsor may specify in the protocol that e.g.

- only treatment related SAEs
- only SAEs that cause a stop of study medication or
- only SAEs of special interests

are reported to him/her

The sponsor may also specify in the protocol that certain AEs are not reported and even not documented [Art. 41 (2)]

What could this imply for non serious AEs?

- **The sponsor may refuse knowledge of already known adverse reactions (ARs)**
  - This would imply that the reporting requirements in clinical trials are less strict than in postmarketing pharmacovigilance (acc. Directive 2001/83/EC)
  - Under certain circumstances the sponsor may refuse knowledge of even new ARs
    - When AE which not has been reported turns out to be related later

Implications for SAEs

Art. 41 (2): The investigator shall report to the sponsor all **serious** adverse events occurring to subjects treated by him or her in the clinical trial, **unless** the protocol provides differently.

- When the trial protocol restricts the reporting of SAEs it could affect the reporting of SARs to the sponsor. If so, there is a chance that
  - the sponsor might not be able to detect an increase in the frequency of known SARs, and
  - the sponsor might not be able to detect unexpected SARs (SUSARs)

If SAE reporting is restricted is a DSUR than still ICH E2F compliant?

Implications for known Adverse Reactions

"We have more than 100 000 patient years recorded in our clinical trial database and observed only 3 cases of a certain AR in all clinical trials"

- Is the number really that low or only because further cases are not reported due to limitations/restrictions on AE/AR recording/reporting in the clinical trial protocols and came therefore not to the sponsor's attention?
- Improper use of Article 41 could affect MAH's pharmacovigilance database

Conclusions for the Assessment

- It should be safeguarded that safety data from clinical trials are not of lower quality than safety data from non-interventional studies
- If AE recording/reporting is limited to certain AEs this could impact the validity of exposure data in DSURs and other reports
- If authorities accepts such limitations the consequences should be clearly commented in the assessment report

Penalties

Penalties

Article 94 (1)

- “Member States shall lay down rules on penalties applicable to infringements of this Regulation and shall take all measures necessary to ensure that they are implemented. The penalties provided for shall be effective, proportionate and dissuasive.”

Current Situation

- **Some infringements of the AMG/GCP-V are currently not in the scope of penalty rules**
  - e.g., Annual Safety Reports, Defraudation

- **Mixed Jurisdiction**
  - Some in the scope of local competent authorities (Länder)
  - Some in the scope of the higher federal competent authorities (BfArM / PEI)
  - Some in the scope of ?

Conclusion

- The new definitions of clinical studies / trials / NIS do not simplify the classification of studies
- Communication and interaction between ECs and NCAs requires new concepts and clear responsibilities
- Mono-national phase I clinical trials should be supported by accelerated review times if the protocols are simple and not overloaded (All-in-one-trials)
- The new flexibility in safety reporting rules should be applied carefully
- Penalty rules should be reviewed for completeness and competence


Thank you for your attention!