
- Major provisions and their assessment -

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Submission of the Application

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

• All communication between sponsor and reporting member state (MS), and some between the stakeholders (sponsor, drug authority, ethics committee) via EU portal only.

• One national contact point 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
The sponsor shall propose one of the MS concerned (MSc) as reporting MS (rMS).

If there is more than one MSc willing to be the rMS, the rMS shall be selected by an agreement between the MSc.
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.
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**.
Assessment Report: Part I

- rMS performs a consolidation phase (7 days) report, taking duly into account the considerations of the MSc and records how all has been dealt with. (Article 6, 5.(c))

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- Sponsor has to submit/respond within 12 days, otherwise the application shall be considered as withdrawn in all MSc.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 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 and extension times as for part I.
Decision on the Clinical Trial

• Each MSc shall notify the sponsor as to whether the clinical trials is
  – authorised
  – authorised subject to conditions
  – refused
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, submitted during the coordinated review phase.
Article 8, 3a

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.
Tacit Authorisation

If the rMS or the MSc does not respond within the time limits set, the resulting ‘decision’ is in favour of the sponsor.

The concept of ‘tacit authorisation’ pertains to basically all timelines.
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 all placebo-controlled trials.
Low-intervention Clinical Trial - Definition -

- the IMP is authorised, and
- the IMP is used in accordance with the terms of the marketing authorisation, or
- the use of the IMP is evidence-based and supported by published evidence on safety and efficacy

in any of the MSc

- the additional diagnostic or monitoring procedures do not provide more than minimal additional risk or burden to the safety compared to normal clinical practice in any MSc.
Role of Ethics Committees

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.
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;’
Sponsor - Definition

‘an individual, company, institution or organisation which takes responsibility for the initiation, management and setting up the financing of the clinical trial’

There may be more than one sponsor → co-sponsor-ship (Art. 69)

• written contract needed, setting out their respective responsibilities.
Protection of Subjects
- General Rules -

Following conditions have to be met:

• The anticipated benefits for the subject or public health justify the foreseeable risks and inconveniences, and the compliance with this condition is permanently monitored.

• The rights of the subject in physical and mental integrity, to privacy and to protection of the data are safeguarded.
Protection of Subjects
- General Rules -

• The clinical trial has been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible, and both the risk threshold and the degree of stress are specifically defined in the protocol and constantly monitored.

• Medical care is provided by an appropriately qualified doctor.

• No undue influence, including that of a financial nature, shall be exerted on subjects.

(Article 28)
Informed Consent

• The information provided shall enable the subject/legally designated representative to understand:
  - the nature, objectives, benefits, risks and inconveniences of the clinical trial;
  - the subject’s rights and guarantees re protection, e.g. right to withdraw at any time;
  - possible treatment alternatives, including follow-up measures in case of discontinuation;
  - the applicable damage compensation regime;
  - the availability of the trial results.
Informed Consent

- the information should be provided in writing, too;
- the information should be provided in an interview with a member of the investigating team, who is appropriately qualified according to national law of the MSc;
- in that interview it shall be verified that the subject has understood the information;
- adequate time shall be given to the subject.

(Article 29)
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
Conclusions

• The final text is in many highly relevant aspects much better than the Commission’s proposal.
• The level of protection of research subjects, in particular of vulnerable patients, has been essentially raised.
• Independent ethics committees are an integral part of the authorisation procedures in the member states.
• A positive vote of the competent IEC is a prerequisite of the authorisation for a clinical trial in the MSc.
Conclusions

- Timelines have been prolonged
- The multinational procedures for the authorisation are now similar to the VHP.
- The transparency of the decision process and the accessibility of the trial results is greatly increased.
- In spite of ‘low-intervention clinical trials’ and co-sponsorships, one may doubt that this will efficiently support ITTs and academic clinical trials.
- The introduction of the ‘tacit approval’ system promotes intransparent decision-making with unidentifiable responsibility.