Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial.

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Main recommendations:

- **To allow more flexibility in the wording about what is included in the protocol.**
- **To remove the requirement to sign the protocol.**
- **To limit the substantial amendments to those that might have affected the original approval (i.e. those affecting the safety of the participant, the scientific integrity of the study or the quality or safety of the IMP).**
- **To designate other amendments 'minor' and not requiring approval**
- **To recommend notification of 'minor' amendments to the relevant authority in a non-urgent manner**
- **To allow flexibility in the definition of the end of a trial**

Specific suggestions

Section 2.2: final paragraph

It is not clear why information about assessment of expectedness should be included in the cover letter. **Suggestion:** delete paragraph

Section 2.5 Protocol

It is not clear why is should be considered mandatory to sign a copy of the Protocol. A signature does not guarantee that the protocol has been read. Clinical trial agreements would generally include reference to agreeing to the content of the Protocol and this should be sufficient. This is an example of a regulation that seems to increase bureaucracy and not add value.
Suggestion: make protocol signature at the discretion of the Sponsor

More flexibility should be allowed in the content of the protocol. **Suggestion:** insert "as appropriate to the study" in the subheading above the bullet points about the contents of the protocol in order to read: 'As appropriate to the study it also should include:…..'

The 2 bullet points under the paragraph about first-in-human clinical trials should apply to all trials rather than just type of trial.

The end of a trial is not always easy to define and again flexibility should be inserted in the wording. **Suggestion:** allow the sponsor to provide a relevant definition of the end of the trial (e.g. one relevant to the agency concerned)

Section 3.3 **The notion of ‘substantial’**

This section aims to describe principle of ‘substantial’. **Suggestion:** in deciding what sort of amendment is to be considered substantial the concept of whether the inclusion of this information might have affected the initial approval should be adopted. By defining ‘substantial’ in this way in Section 3.3 bullet points 1, 2 and 4 would be encompassed but not necessarily changes to the conduct or management of the trial which should be considered substantial or not at the Sponsor’s discretion.

Only substantial amendments meeting this definition should require submission for approval.

Suggestion Other amendments should be designated ‘minor’ and notified to the relevant agency in a non-urgent manner either routinely or when other documents are being updated as described in Section 3.11. Examples of amendments that should be considered minor include the addition of new sites, or changes to a local principal investigator.

Section 3.3.1

For all of the examples listed of types of amendment that are considered substantial, there are circumstances where they would not have any substantial impact on the safety of the participants, the scientific value of the trial or the quality or safety of the IMP. **Suggestion:** Allow appropriate flexibility to give the Sponsor some discretion

Addition of clinical sites in a multicentre study should not be considered a substantial change as it does not meet the definition above. Currently this regulation is causing a huge administrative burden (and cost) which is increased in the UK by the necessity to inform local R&D departments of all substantial amendments.

The examples of which amendments are not considered substantial are helpful.

Section 3.3.2 and Section 3.3.3.

Suggestion: Amendments to other documentation should be guided by the same principles as for Protocol amendments.

Section 4.2

This section suggests that 2 separate end of trial declarations may be required. **Suggestion:** Combine into a single end of trial declaration based on the end of the trial in all member states.