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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Attachment 5: Headings for aspects of a trial that might involve a substantial amendment.

In all cases, an amendment is only to be regarded as “substantial” where they are likely to have a significant impact on:

- The safety or physical or mental integrity of the patients;
- The scientific values of the trial;
- The conduct or management of the trial;
- The quality or safety of any IMP used in the trial.

The headings below are examples of aspects of a trial where amendments may need to be made, of which only some need to be notified as substantial. There may be other aspects of the trial where amendments meet the criteria for substantial in section 4.2.3.1.

Amendments related to the protocol

Purpose of trial
Design of trial
Informed consent
Recruitment procedure
Measures of efficacy
Schedule of samples
Addition or deletion of tests or measures
Number of participants
Age range of participants
Inclusion criteria
Exclusion criteria
Safety monitoring
Duration of exposure to the investigational medicinal product(s)
Change of posology of the investigational medicinal product(s)
Change of comparator
Statistical analysis

Amendments related to the trial arrangements

Change of the principal investigator or addition of new ones
Change of the co-ordinating investigator
Change of the trial site or addition of new sites (See section 4.2.4 on how to notify changes)
Change of the sponsor or legal representative
Change of the CRO assigned significant tasks
Change of the definition of the end of the trial

Amendments related to the IMP

Changes to investigational medicinal product quality data concerning:
Change of name or code of IMPs
Immediate packaging material
Manufacturer(s) of active substance
Manufacturing process of the active substance
Specifications of active substance
Manufacture of the medicinal product
Specification of the medicinal product
Specification of excipients where these may affect product performance
Shelf-life including after first opening and reconstitution
Major change to the formulation
Storage conditions
Test procedures of active substance
Test procedures of the medicinal product
Test procedures of non-pharmacopoeial excipients

Changes to non-clinical pharmacology and toxicology data where this is relevant to the ongoing trials (i.e. altered risk:benefit assessment).

For example concerning:
Results of new pharmacology tests
New interpretation of existing pharmacology tests
Result of new toxicity tests
New interpretation of existing toxicity tests
Results of new interaction studies

Changes to clinical trial and human experience data where this is relevant to the ongoing trials (i.e. altered risk:benefit assessment).

For example concerning:
Safety related to a clinical trial or human experience with the investigational medicinal product
Results of new clinical pharmacology tests
New interpretation of existing clinical pharmacology tests
Results of new clinical trials
New interpretation of existing clinical trial data
New data from human experience with the investigational medicinal product
New interpretation of existing data from human experience with the investigational medicinal product