

Substantial Protocol Amendments

1. Protocol amendments

If the protocol is substantially amended after initiation, then there are certain procedures to follow. These are detailed in the Sub map [Protocol Amendments](#).

Substantial amendments for MHRA approval

There must be arrangements for taking appropriate urgent safety measures to protect participants against any immediate hazard where new events relating to the conduct of the trial or the development of the IMP are likely to affect the safety of the subjects. In many trials, the individual best able to take these measures will be the Chief Investigator or another identified person or organisation – rather than the Sponsor¹ directly. The protocol should identify the specific individual(s) who accept(s) this responsibility. Otherwise, the Sponsor¹ remains directly responsible.

These safety measures, such as temporarily halting the trial, may be taken without prior authorisation from the MHRA but must be reported to the MHRA and Ethics Committee. For all other substantial amendments, MHRA authorisation must be sought before the amendment is implemented.

Substantial amendments to the conduct of the clinical trial may arise from changes to the protocol or from new information relating to the scientific documents in support of the trial. Amendments to the trial are regarded as “substantial” where they are likely to have a significant impact on:

- the safety or physical or mental integrity of the subjects, or
- the scientific value of the trial, or
- the conduct or management of the trial, or
- the quality or safety of any IMP used in the trial.

In all cases, an amendment is only to be regarded as “substantial” when any of the above criteria are met. For each amendment, someone has to evaluate on behalf of the Sponsor¹ whether the amendment will have a significant impact on the above issues. This could also involve the advice of the independent Trial Steering Committee, if available.

Also, see the [detailed guidance on the European clinical trials database](#) for further information about notification of amendments:

Guidance on what may be considered a substantial amendment is listed below:

Examples of substantial amendments from the EU Guidance

The headings below are examples of aspects of a trial where amendments may need to be notified as substantial. There may be other aspects of the trial where amendments meet the criteria for substantial.

Amendments related to the protocol

- Purpose of trial
- Design of trial
- Informed consent

¹ The Sponsor is defined in the Directive as an individual, company, institution or organisation which takes responsibility for initiating, financing and /or managing a clinical trial. A group may take on the responsibilities of sponsorship and the UK Regulations are expected to specify how these responsibilities may be allocated/delegated to individuals or organisations responsible for specific aspects of the trial. See 'Quality Partnerships' for latest information on sponsorship.

- 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 (NB this means the lead investigator in each centre)
- Change of the coordinating investigator
- Change of the trial site or addition of new sites*
- Change of 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

For example:

- Addition to stability data/change of expiry date
- Change of formulation
- Additional toxicology data
- Change to route of synthesis

***Addition of a new site should be sent to the MHRA as a substantial amendment but for NOTIFICATION ONLY. This notification does not attract a fee. There is no requirement to wait for a response from the MHRA but your submission will be acknowledged.**

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

Non-substantial amendments

Non-substantial amendments do not have to be reported to the MHRA, but should be recorded and be available upon request for inspection centrally and at the trial site