

Examples of substantial and non-substantial modifications

Regulation (EU) No 536/2014 Questions & Answers – draft, March 2020, Annex III;

(modified and shortened from the EU guideline

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014 ga en.pdf)

Annex III Examples of substantial and non-substantial modifications

The following are non-exhaustive lists of examples of substantial and non-substantial modifications that serve as guidance for a case-by-case decision of the sponsor.

Part I

a. Modifications that are typically considered to be "substantial":

Note: Modifications marked with * may be considered to lead to a completely new clinical trial unless justified.

Protocol

1. Change of secondary endpoint which is likely to have a significant impact on the safety or scientific value of the clinical trial*;

2. Use of a new mode of measurement for the primary endpoint*;

3. New toxicological or pharmacological data or new interpretation of toxicological or pharmacological data which is likely to impact on the risk/benefit assessment;

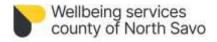
4. A change in the definition of the end of the trial;

5. Removal of a trial arm not foreseen in the approved protocol;

6. Change of inclusion or exclusion criteria if these changes are likely to have a significant impact on the safety or scientific value of the clinical trial*;

7. Changes in the number of scheduled subject study visits;

8. Change of a diagnostic or medical monitoring procedure which is likely to have a significant impact on the safety or scientific value of the clinical trial;



9. Removal of an independent data monitoring board;

10. Change of treatment modalities (mode of administration/duration/frequency/dosing) of IMPs;

11. A change of study design which is likely to have a significant impact on primary or major secondary statistical analysis or the risk/benefit assessment*;

12. Amending the number of subjects to be included, either due to an adaptation of the sample size calculation or to maintain a previously defined sample size calculation due to more withdrawals/drop outs than expected;

13. Addition of an interim/intermediate analysis. No interim analysis was mentioned and specified in the initial protocol but during the study it is decided to do an interim analysis;

14. Deletion of an interim/intermediate analysis;

15. Additional safety monitoring and/or other type of changes in order to minimize a potential safety concern;

16. Change of safety criteria to modify or interrupt IMPs treatment.

IMPD and IB

17. Any change in the quality of the IMP (see also the relevant EMA guidelines);

18. Change in the overall risk and benefit assessment in the IMPD or IB;

19. New toxicological or pharmacological data or new interpretation of the data in the IMPD or IB which might have a significant impact on the risk/benefit ratio;

20. New clinical data e.g. from previous clinical trials and human experience in the IMPD or IB which might have a significant impact on the risk/benefit ratio;

21. Changes to the reference safety information for the annual safety report and SUSAR reporting;

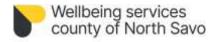
Other modifications

22. A change of sponsor, co-sponsor or the sponsor's legal representative;

23. The revocation or suspension of the IMP's marketing authorization.

If there is a change in one or more of these conditions, it would be considered to be a substantial modification.

A change in the number of clinical trial participants per trial site, if the total number of participants in the Member State concerned is identical or the increase/decrease is insignificant



(i.e. not related to a change in sample size calculation) in view of the absolute number of participants;

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A change in the documentation used by the research team for recording study data (e.g. case report form or data collection form);

Part II

a. Modifications that are typically considered to be "substantial":

1. Addition of a site, change in facilities, change in site suitability or change of principal investigator;

2. New insurance policy;

3. Change in the insurance policy, eg. a new insurance company, changes in insurance coverage, conditions and/or insured amounts;

4. Modifications in any documents for subjects such as the subject information sheet, and informed consent form, which could include change in safety information, study procedures or data handling;

5. Change in access, disclosure, dissemination, alteration or loss of information and personal data processed;

6. Change in collection, storage and future use of biological samples from clinical trial subject;

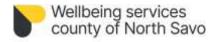
7. Change in financial arrangements;

8. Change in the compensation paid to subjects and/or investigator/site for participating in the trial;

9. Change in recruitment arrangements including procedures for inclusion of subjects and advertising material.

Part I

b. Modifications that are typically considered not to be substantial:



Protocol

The addition/deletion of exploratory/tertiary endpoints;

An increase in duration of the overall time of the trial, provided that the following conditions are met:

- the exposure to treatment with the IMP is not extended;
- the definition of the end of the trial is unchanged; and
- scheduled subject study visits arrangements are unchanged;

General

Correction of typographical errors in any document

Part II

b. Modifications that are typically deemed not to be substantial:

- 1. Extension of validity of insurance certificate;
- 2. Correction of typos in any document.