PSSHP Tutkimuseettinen toimikunta 22.9.2020

# Esimerkkejä merkittävistä ja ei-merkittävistä muutoksista

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

(modifioitu ja lyhennetty EU-ohjeesta
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_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;

A change in the number of clinical trial participants in the Member State concerned, if the total number of participants 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;

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.