# Guidance document on “Substantial modifications to clinical investigations of medical devices”

## Preliminary note:

This guidance document describes the implementation of the Swiss Ordinance on Clinical Trials with Medical Devices ClinO-MD (KlinV-Mep, OClin-Dim, OSRUm-Dmed) regarding substantial modifications. Please also consult the Annex of the European guidance document MDCG 2021-6 *["Regulation (EU) 2017/745 – Questions & Answers regarding clinical investigation”]* released by the Medical Device Coordination Group MDCG. Link here.

All modifications to authorised clinical trials that may have a significant impact on the safety, health, or rights of the participants, as well as on the robustness or reliability of the clinical data to be generated, are considered substantial modifications. Such modifications must be authorised in writing before implementation:

- For category A clinical trials (post-market trials), substantial modifications must be authorised by the competent Ethics Committee (art. 15 ClinO-MD).
- For category C clinical trials (pre-market trials, including off-label use), substantial modifications must be authorised by the competent Ethics Committee and Swissmedic (art. 20 ClinO-MD).
- There is no silent approval of substantial amendments. The competent Ethics Committee and Swissmedic will always provide written decisions; sponsors cannot implement substantial modifications without the required authorisation.
- Measures which have to be taken immediately in order to protect the participants are considered to be safety measures, or protocol deviations on safety grounds. No prior authorisation is required in this situation. Until the corresponding amendment is authorised, the recruitment of subjects and new product use will normally need to be suspended.

Sponsors should also take into consideration the fact that some modifications may seriously impact the design or scientific outcome of the clinical trial, and may require the initiation of a new clinical trial.

## How to submit:

An authorisation request for a substantial modification for a category A clinical trial needs to be submitted to the Ethics Committee through the BASEC web portal. For category C clinical trials the requests must be submitted on the same day to the Ethics Committee (through BASEC) and to Swissmedic (through the ‘eGov Service eMessage’ web portal, see section 7.2 of the Swissmedic information sheet BW600_00_015e_MB).

In general, it is not recommended to submit another substantial modification while assessment of the previous is still ongoing.

For all clinical trials, non-substantial modifications must be submitted to the Ethics Committee with the Annual Safety Report[1] (art. 15 para. 5 ClinO-MD).
For category C clinical trials, non-substantial modifications must be submitted to Swissmedic as soon as possible (art. 20 para. 4 ClinO-MD).

## List of substantial modifications:

**A list with examples of substantial modifications can be found in the Annex of the European guidance document MDCG 2021-6. Link here.**

**In addition** to the examples shown in the Annex of MDGC 2021-6, the following examples are also considered to be substantial modifications requiring written authorisation before implementation in the trial:

Amendments related to the protocol or to the Investigator's Brochure (IB)

1. Any modification affecting the participants' safety and health, or their rights and obligations.
2. Additional use of health-related personal data from medical records not collected within the framework of the investigation (further use of personal data).

Amendments related to the information and recruitment of subjects

3. Additional informed consent form (ICF) for the further use of data/biological material (related to the clinical trial).
4. Approved ICF translated in a Swiss national language.
5. New recruiting material, like flyers (new text, new versions) for the research subjects (i.e., subjects are addressed directly).
6. Modification made to the strategies for the recruitment of the study subjects (e.g., use of social medial instead of distribution of flyers in the hospital).
   Note: A modification of the recruiting method is considered a substantial modification if changes are made to the text of the recruiting material approved by the ethics committee and if the recruitment method is described in the protocol. It is not considered a substantial modification if it is a change of media with an unchanged text (e.g. flyer instead of poster).

Amendments related to the investigational site/research centre

7. Temporary leave of the principal investigator.
   Note: In some circumstances, the temporary leave of the investigator is considered a substantial modification. See guidance document «What if an Investigator of an ongoing clinical trial is absent for an extended period of time? How should this be handled?» published on swissethics.ch under templates/notifications. The document is available in German, French, Italian and English.
8. Change of coordinating investigator in a multicentric clinical trial in Switzerland (e.g. Dr. Dupont CHUV instead of Dr. Mustermann USZ).
9. Modification of the contracts/new contracts (e.g., change in financing, compensation, change in publishing rules, etc.).

[1] Although a change of CRO or the translation of an approved ICF into a non-Swiss national language are non-substantial modifications, the responsible Ethics Committee should be informed in a timely manner, not only with the Annual Safety Report. The Ethics Committee will acknowledge the modifications.

Amendments related to other information

10. Additional questionnaire(s) for the study subjects.
11. Modifications relevant to the Radiation Protection Division of the Federal Office of Public Health (e.g., changes to the device emitting ionizing radiation -> a new FOPH authorization is required).
12. Major changes to the monitoring plan.

    Note: Increased monitoring activities are not per se a substantial modification. However, depending of the reason, the change can be part of a safety measure and must be reported as a safety measure within 2 days.