

## **Q&A. xxx How the different changes to ongoing clinical trials are classified in the Clinical Trials Regulation?**

In compliance with the CTR, a change to a trial data-field or document in the Clinical Trials Portal and Database is either:

- a substantial modification (art 2.2.13)
- a change relevant to the supervision of the trial (art 81.9)
- a non-substantial modification (changes outside the scope of substantial modifications and changes irrelevant to the supervision of the trial)

1. A substantial modification of trial data (incl. protocol, IB or IMPD) is defined in Art 2.2.13. of the Regulation and follows the process of chapter III (for further details see also Q&A 3.2, 3.3).
2. Non-substantial changes relevant to the supervision of the trial (Art 81.9 change) are a new concept under the CTR, which aims to update certain, specified information in the CTIS without the need for an SM application, when this information is necessary for oversight but does not have a substantial impact on patients safety and rights and/or data robustness. Art 81.9 changes can be submitted only if the change does not trigger additional changes, which are expected to be submitted as an SM application. The combination of different art 81.9 changes can cumulate into a change that needs to be submitted as an SM. Specific examples for such changes (e.g. update of sponsor's or CRO contact details) are described in Annex III of this guidance. Importantly, this route can be used to update information to fulfil a condition, depending on the instructions of the RMS (part I conditions) or the MSC (part II conditions). When the route to fulfil a condition is not defined by the relevant MS at the time of setting the condition, it is up to the sponsor to decide on the appropriate route (SM or art 81.9) for document or data submission to fulfil a condition (see additional details also in Q&A 3. 4).
3. A non-substantial modification (NSM, i.e. without substantial impact on the safety or rights of the subjects and/or the reliability and robustness of the data and when the information is not necessary for oversight) should not be notified as such. Correction of typos and other administrative changes with no impact on the content and meaning of the information are always expected to be updated as non-substantial modifications.

There is no legal basis in the CTR to submit changes other than through an SM or art 81.9. Therefore there is no functionality developed in CTIS to support changes to trial data/documents other than via an SM or as an Art 81.9 route with notification—These changes should be implemented during the next substantial modification. NSMs can be introduced in the trial documentation irrespective of the scope of the SM application, but they need to be listed and identified as NSMs in the cover letter of the SM application. NSMs as a rule are not expected to be described in detail in the cover letter, but in case of confidential information in the description of these NSMs, a redacted cover letter can be submitted as necessary. In case the SM application is rejected and the documents with NSM are reverted, the NSMs should be resubmitted with the next SM application. In the meantime, NSMs will have to be recorded in the Trial Master File and made available on request for inspection purposes as appropriate.

In clinical trials with adaptive design (e.g. complex clinical trials), those changes, which are described and specified in the currently authorised protocol can be implemented except in cases where their authorisation through a SM is required (i.e. when indicated in the authorised protocol or as a condition in the decision).

The CTIS will not be able to differentiate between the different types of content changes in a given document. A good example is the IB: a new version of this document can be uploaded as an SM (e.g. with changes impacting benefit/risk in the trial) or as an art.81(9) (e.g. annual update with no significant changes on participants safety and/or benefit/risk in the trial)– it is up to the sponsor to define the correct path depending on the nature of the changes. The guidance will facilitate that task. If a sponsor would disuse this functionality, corrective measures shall be taken by MSC.