Substantial Modifications

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Agenda

- Reminder on CTR pilot substantial modifications
- 3 types of modifications in CTR
- Substantial Modifications in CTR
- Changes relevant to the supervision of the trial
- Non-Substantial modifications
- Some important links

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CTR pilot substantial modifications

- Will still be accepted after 14/10/2021 and after implementation of CTR on 31/01/2022

- Legally CTR pilot dossiers are law of 07/05/2004 dossiers which can continue following the CTR pilot process until the end of the trial or the switch of the trial from Directive to CTR (at the latest by 31/01/2025)

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3 types of modifications in CTR

CTR foresees 3 kinds of changes in a clinical trial:

- substantial modifications
- changes relevant to the supervision of the trial
- non-substantial modification

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Substantial modifications in CTR

Definition

Article 2(2)(13) of The Clinical Trials Regulation defines a substantial modification as " any change to any aspect of the clinical trial **which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data** generated in the clinical trial AND which is made AFTER a decision is issued on a previously submitted application: initial application (article 8), additional member state (article 14), another SM on Part I only or Part II only or both Part I and II (articles 19, 20 and 23)”

Substantial modifications in CTR

Only exceptions

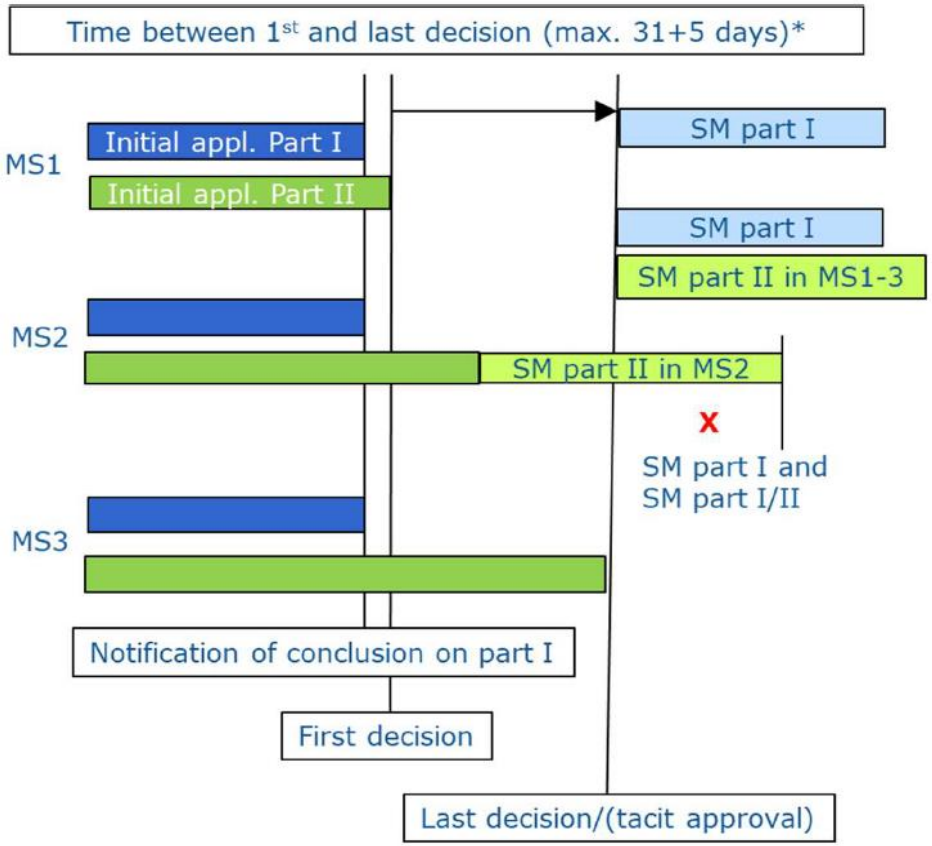
- Parallel assessment of substantial modifications for Part II in different Member States Concerned (MSC) i.e. an application for a SM of Part II in a MSC can be submitted while the assessment of another SM for Part II is ongoing in another MSC

- An application for an additional Member State is possible while there is an ongoing assessment of a substantial modification for Part II in another MSC

This process ensures compliance with the Regulation, the stability of trial documentation for the entire time of the assessment for all assessors and the validity of ongoing assessments and decisions in all Member States concerned

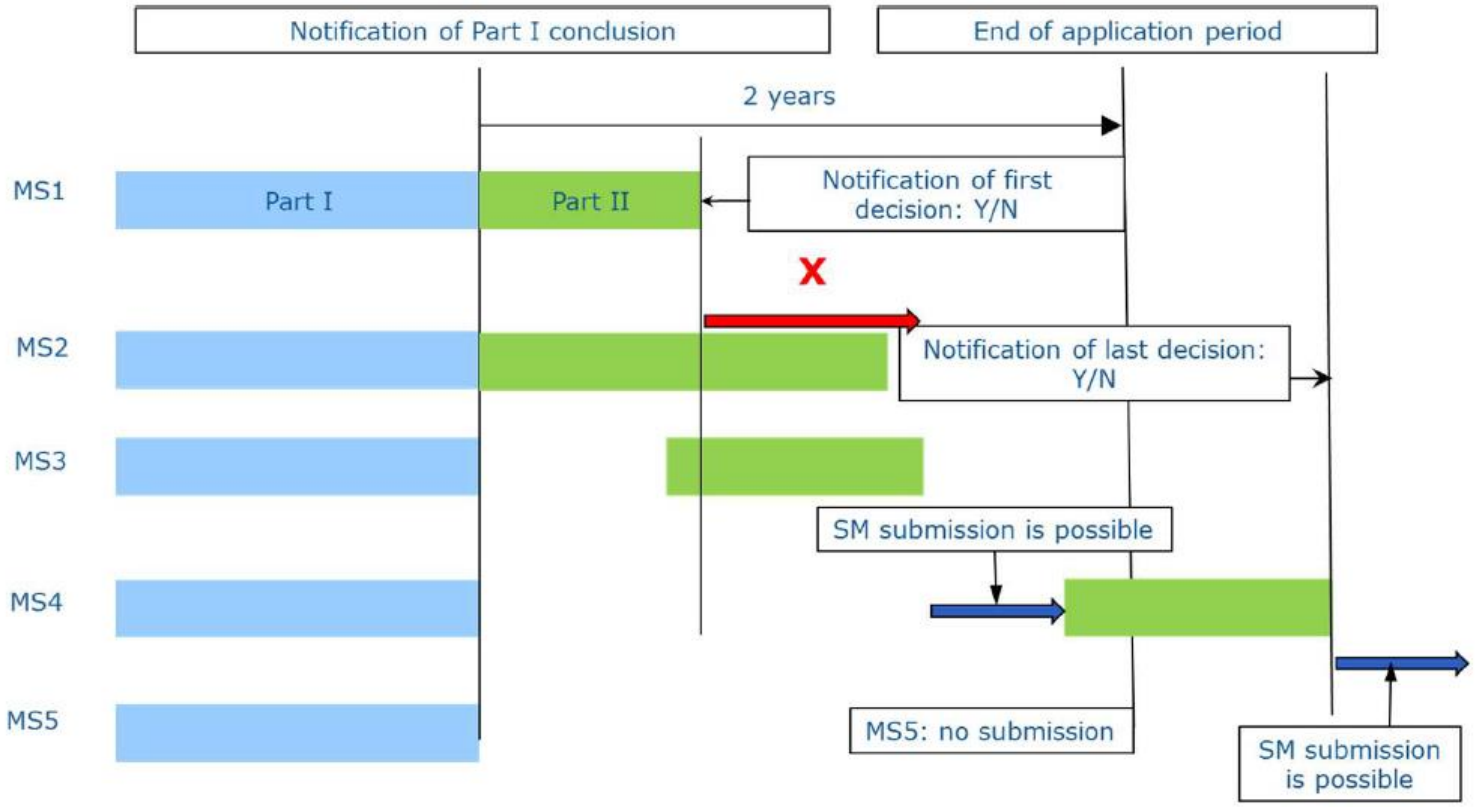
Substantial modifications in CTR

Timing of submission of first SM following an initial full application under Art 5 (Part I & Part II submitted together)



Substantial modifications in CTR

Timing of submission of first SM following an initial full application under Art 11 (Part I and Part II not submitted at the same time)



Substantial modifications in CTR

- It is the responsibility of the sponsor to assess whether a modification is to be regarded as 'substantial'. However, a non-exhaustive list of examples of substantial and non-substantial modifications is available in Annex III of the CTR Q&A document in Eudralex volume 10

- An application for a substantial modification can contain multiple changes concerning Part I, Part II or both and will result in a single decision for that application in each MSC

- Where a substantial modification concerns more than one clinical trial of the same sponsor and with the same investigational medicinal product, the sponsor can submit one single substantial modification application for the concerned trials

Substantial modifications in CTR

The sponsor should assess also, whether a substantial modification (or the combination of several substantial modifications) leads to changes in the clinical trial to an extent that it has to be considered as a completely new clinical trial, which would require an application for a new trial authorisation

Examples:

- change of the investigational medicinal product (IMP)
- significant modifications, such as a change to the main objective or primary end point of the clinical trial
- unplanned and unjustified addition of a trial arm or placebo group

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Changes relevant for the supervision of the trial

- New concept under the CTR (Art. 81.9)

- To update information in the CTIS when necessary for oversight but does not have a substantial impact on patients' safety and rights and/or data robustness

- Can only be submitted if the change does not trigger additional changes, which are expected to be submitted as an SM application

- Combination of different art 81.9 changes can cumulate into a change that needs to be submitted as an SM

Changes relevant for the supervision of the trial

- Specific examples for such changes (e.g. update of sponsor's or CRO contact details) are described in Annex III of the CTR Q&A in Eudralex volume 10

- **Important** : this route could 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)

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Non-substantial modifications (NSM)

- A Non-substantial modification (NSM) in CTR is outside the scope of SMs (without substantial impact on the safety or rights of the subjects and/or the reliability and robustness of the data) and irrelevant to the supervision of the trial

- Should not be submitted as such

- No legal basis in CTR to submit changes other than SMs or Art 81.9 modifications => no functionality developed in CTIS

- Should be submitted with the next SM

- Examples : typos and other administrative changes with no impact on the content and meaning of the information

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Some important links

Link to the CTR in chapter VI of the Eudralex volume 10 :

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN

Link to the CTR Q&A in chapter V of the Eudralex volume 10 :

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/regulation5362014_qa_en.pdf

Conclusion and questions

Thanks a lot for your interest and participation

- Do you have questions ?

- Don’t hesitate to send us your questions to CTRpilot@fagg-afmps.be

Contact

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