Clinical Trial Regulation 536/2014

Changes to clinical trials (classification and submission of non-substantial changes)

Edit Szepessy, DG SANTE

EC-DG SANTE/HMA-CTFG/EMA

joint training - March 9-10, 2021

Contents in this section

- Classification of the different changes to ongoing clinical trials
- Submission of Art 81.9 changes
- Submission of NSM -- **Edit**

- Substantial Modifications:
    - Key principles, Annex II requirements
    - Standard submission, assessment and decision process Chapter III, CTR —**Stefan**

- Submission of SM:
    - first SM in case of an Art 5 or Art 11 application
    - consecutive SMs
    - part I/II SMs in case of ongoing Art 14 assessment
    - part II SM in case of ongoing part II SM in a different MS
    - multiple SMs by the same sponsor to several trials with the same IMP — **Lene**

Background

- CTR: robust and agile system for the assessments with high level of coordination between MSC/RMS and MS/sponsor

- Need for **common understanding on the classification of changes as SM or NSM**

- In compliance with the CTR, there are three types of changes:
  - a substantial modification (art 2.2.13)
  - a change relevant to the supervision of the trial (art 81.9)
  - a non-substantial change which is not relevant for MSC supervision

European Commission

Categorisation of changes

Substantial modification

- Change that has a **substantial impact on the safety, or rights of the subjects and/or the reliability and robustness of the data** generated (Art 2.2.13)

- **Submission and authorisation** required before the change can be implemented – timings and interactions described in the CTR

- **Categorisation of a change as a SM is a responsibility of the sponsor**. In case of doubt, the national contact point of the MSC in question (part II) or the RMS (part I) can be contacted. A SM application should contain at least one substantial change, but can contain multiple (substantial and non-substantial) changes

European Commission

Categorisation of changes (Art 81.9)

Non-substantial modification relevant for supervision (art. 81.9)

9. The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States concerned.

- **New concept** that does not exist under Directive 2001/20

- « Tell and do » - **no autorisation or refusal mechanism, but the change is notified**. Corrective actions remain possible !

- Not possible to submit if a SM ongoing, but no further limitations

-- > aim is to ensure the **integrity of trial documentation at all time***

* non-substantial changes can always be submitted as part of an SM application when the scope (part I or part II) of the non-substantial changes matches with the scope of the application under evaluation

Categorisation of changes (Art 81.9)

Non-substantial modification relevant for supervision (art. 81.9)

- **combination** of different art 81.9 changes can cumulate into a SM

- 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)

- examples for such changes (e.g. update of sponsor's or CRO contact details) are in **Annex III** of the CTR QnA

European Commission

Categorisation of changes

Non-substantial modification

- If a **change is neither a SM nor a change relevant for the supervision** of a trial, it is a non-substantial change
- **notification of non-substantial changes is not required (nor supported**), to be submitted in a ‘real’ substantial modification, irrespective of the scope of the SM.
- **listed and identified as NSMs** in the cover letter of the SM application
- if the SM application is rejected, the NSMs can be resubmitted with the next SM application.

European Commission

Categorisation of changes

Non-substantial modification

- Correction of typos and other administrative changes with no impact on the content and meaning are non-substantial modifications

- Non-substantial modifications should be **recorded in the TMF** and made **available on request for inspection purposes** as appropriate

European Commission

Examples (Annex III, CTR QnA)

	SM	81.9NSM	NSM	Part I/II
Changes to initial documents				
Sponsor	Change of sponsor entity that involves additional changes: e.g. insurance, legal representative, addition of a new sponsor/co-sponsor	Change of the existing sponsor's name, keeping the same legal entity Change of existing sponsor[69] or co-sponsor legal entity if it does not involve additional changes in the trial documentation apart from administrative changes Changes regarding which co-sponsor is responsible for the tasks referred to in article 72(2) of the Clinical Trial Regulation	Minor changes in the contact details e.g. change of mailing address (like PO Box, not physical change) or email address of a site without impact for the supervision of the trial	
		Change in the sponsor/co-sponsor contact details (address, email and phone number)[70] Change of contact point to the Union[71], scientific and public contact point (name and contact details)[2]		
Sponsor's Legal Representative within	Change of legal representative	Change of contact details of legal representative provided that there	Minor changes in the contact details e.g.	

Examples (Annex III, CTR QnA)

		Change of delegated tasks[2]		
Upload data/document to meet a condition	Always when the provision or update of data/document if in the decision the condition requested as a SM or exceptionally when the route is not defined by RMS/MSCs but the change has a substantial impact on safety and right or data robustness in the opinion of the sponsor and was not authorised previously (i.e. in the case of trials with adaptive design)	Any other cases, as defined by the RMS (part I) or MSC (part II)[72] (can trigger a SM as part of a corrective action)	--	Part I and/or II
Full title (English or common language for	Changes that modify the meaning (normally it is expected to be submitted		Administrative changes (typos)	Part I

European Commission

IB/IMPD non-quality	1. new toxicological or pharmacological data or new interpretation of toxicological or pharmacological data of relevance for the investigator or with an impact on risk/benefit; 2. new clinical data with impact on the risk/benefit ratio 3. change in the overall risk and benefit assessment and analysis	Annual IB update without safety, efficacy or benefit/risk update		Part I
RSI (If the IB is not an SmPC, it shall contain a clearly identifiable RSI section[79])	If the RSI is located in the IB, an update to the RSI which has an effect on participants' safety and/or safety reporting and expectedness assessment: i. addition of new expected SAR PTs, ii. change of the frequency of expected SARs, iii. MedDRA updates having an impact on participants' safety and/or on safety reporting and expectedness assessment (e.g. new preferred term (PT)s listed in the RSI)		1. changes to the format of the table that do not affect the expected SARs 2. slight modification of exposure rates that do not result in a change in the category of frequency without the addition of new expected SARs and/or new preferred terms (PTs)	
	If the RSI is contained in the SmPC, any update of section 4.8. of the SmPC with an impact on safety and/or safety reporting and expectedness assessment (e.g. addition of a new term) Change of the location of the RSI information (e.g. change from IB to SmPC) if an impact on safety reporting			

ıropean
ımmission

Responsibility for classification

- It is the **sponsor's responsibility to classify** the changes and **define the correct path to implement** them in CTIS (e.g. a new version of the IB 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).

- If a sponsor would disuse the different functionalities, corrective measures shall be taken by MSC.

European Commission

Thank you

© European Union 2020

Unless otherwise noted the reuse of this presentation is authorised under the CC BY 4.0 license. For any use or reproduction of elements that are not owned by the EU, permission may need to be sought directly from the respective right holders.

Slide xx: element concerned, source: e.g. Fotolia.com; Slide xx: element concerned, source: e.g. iStock.com

European Commission