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Changes to clinical trials

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Disclaimer

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Process for substantial modifications (SM)

Dossier requirements (Annex II)

SM application dossier (Annex II)

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- Cover letter
- Description of modification
- Supporting information
- Modification application form
- Update of EU application form (if applicable)
- Proof of payment per MSC (if applicable)
- Cross-trial submission

Cover letter (section B)

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The cover letter should contain

- in its subject line, the **EU trial number with the title of the clinical trial and the SM code number** (unique identifier, to be used throughout the application dossier)
- **identification of the applicant**
- identification of the substantial modification (**the sponsor's substantial modification code number and date**), whereby the modification may refer to several changes in the protocol or scientific supporting documents;
- a highlighted indication of **any special issues relating to the modification** and an indication as to where the relevant information or text is located in the original application dossier;
- identification of **any information not contained in the modification application form that might impact on the risk to subjects**
- where applicable, a **list of all clinical trials which are substantially modified**, with EU trial numbers and respective modification code numbers

Description of modification (section D)

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The modification shall be presented and described as follows:

- an **extract from the documents to be amended** showing
  - previous and new wording in track changes
  - only the new wording and
  - an explanation of the changes

~~old text~~ new text	new text	explanation

- in case of a new version of entire documents an additional table should list the amendments to the documents, whereby identical changes can be grouped

The **new version** of the document shall be identified by the **date** and an updated **version number**.

This is a clear format that is very helpful for assessment.
Not included by all sponsors.

Supporting information (section E)

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Where applicable, additional supporting information shall at least include:

- summaries of data
- **justification for the changes and updated overall risk/benefit assessment**
- **possible consequences for subjects already included in the clinical trial**
- **possible consequences for the evaluation of the results**
- changes to the information provided to subjects or their legally designated representatives

This will be very useful for assessment within short timelines.

Can be requested already during the validation phase.

Other documents

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- **Modification Application Form (section C)**
  → CTIS SM module

- **Update of the EU Application Form (section F)**
  → done via CTIS
  → changed fields will be highlighted
  → amended documents will be visible via „submission sequence“ in the „documents table“.

- **Proof of payment (section G)**
  → „if applicable“ → not applicable for Austria

SM module in CTIS

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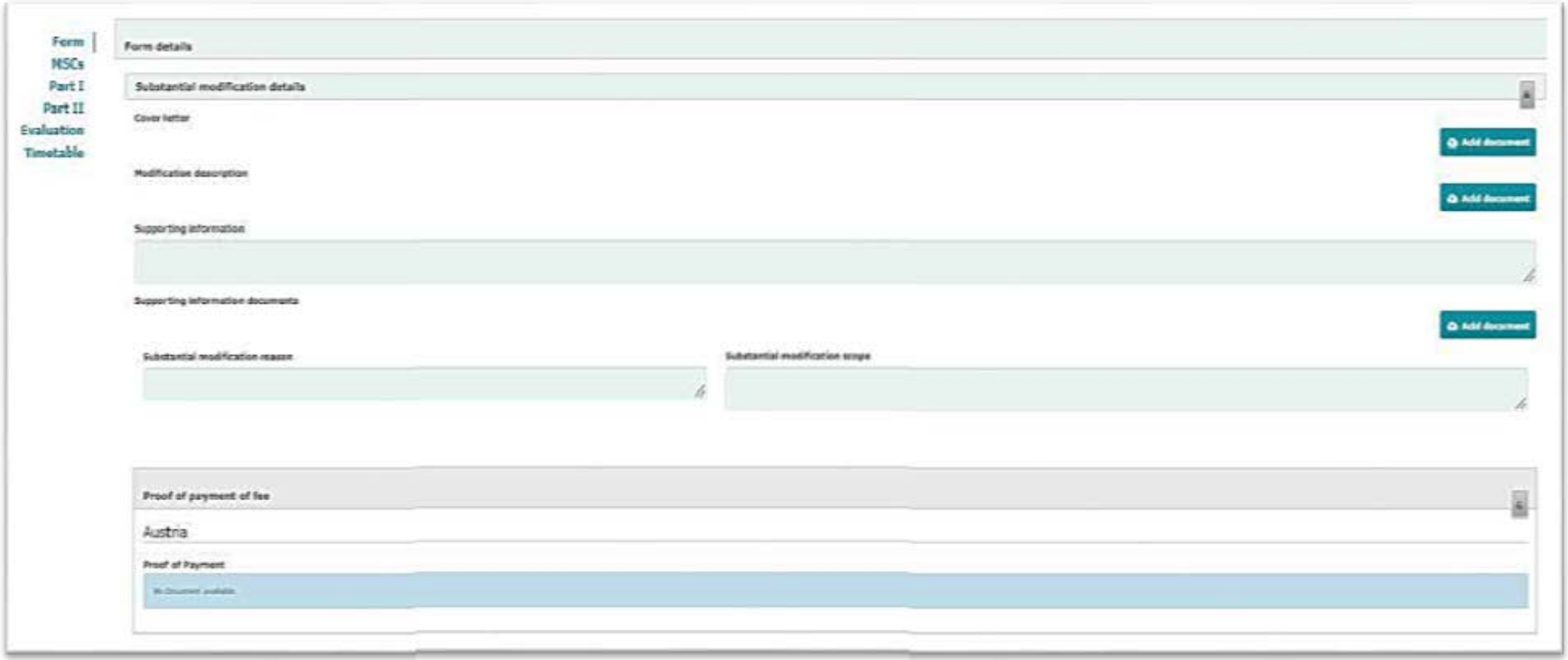

Cross-trial submission of SM (QnA 3.8)

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- **Option 1: synchronised submission (CTIS module)**
  - same sponsor, same IMP and same change
  - all trials have to be authorised and no ongoing parallel (CTA/SM) assessment or pending notification of a decision
  - independent assessment → separate records and decisions in CTIS
  - limited to the IMPD, IB and QP certifications at CTIS go-live
- **Option 2: reference IMPD**
  - "daughter" trials using a reference to the "mother" trial with the approved IMPD
  - MSC in a "daughter" trial has to be a MSC in the "mother" trial as well
  - link to the "mother" trial needs to be established in the section "associated clinical trials"
  - a justification for "no IMPD upload" needs to be filled in
  - changes to the "mother" trial automatically apply to the "daughter"

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Process for substanial modifications (SM)

Validation, Assessment, Decision (Chapter III)

Basic types (scopes) of procedures

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- **Substantial modification for Part I (Art. 17-19)**
  e.g. protocol, IB, IMPD

- **Substantial modification for Part II (Art. 20)**
  e.g. patient information, insurance, trial site, investigator

- **Substantial modification for Part I and II combined (Art. 21-23)**
  e.g. protocol and patient information

When can a SM be submitted?

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- The definition of a SM in the Clinical Trials Regulation (article 2(2)13) implies that a SM request can be considered **only after a decision is taken** on
  - an initial application or
  - an application for substantial modification or
  - an addition of a Member State concern

„You can only change the course when the water is calm."

- This implies that **no SM request can be assessed while any assessment is on-going** (be it an assessment of an initial application, a request to add a Member State concerned (MSC) or a request for another SM).
- Therefore, the **SM can be assessed only after the decision on the previously submitted application is issued or authorized by tacit approval**.

For special cases see presentation from Lene Grejt Petersen.

Step 1: Validation requirements

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- The RMS for the intial authorisation procedure is the RMS for the substantial modification of Part I aspects.

- **Question 1:**
  Is the substantial modification within the scope it is submitted for (Part I, Part II, Part I and II)?

- **Question 2:**
  Is the application dossier complete in accordance with Annex II?

Validation vs. Assessment

Do we all understand it in the same way?

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Validation of e.g. the trial protocol, could mean different things:

Technical approach:

„a file with an accepted format is uploaded and can be opened“

Pragmatic approach:

„a document that looks like a trial protocol (ICH GCP structure)“

Formal approach:

„the document has a valid signature, version and date“

Pre-assessment:

„full requirements of CTR and Annex“

The level of validation for initial application and amendment is not yet harmonised between MSCs and a potential topic for CT Experts Group and CTFG.

Validation process – Part SM I (mononational) or Part II SM or combination

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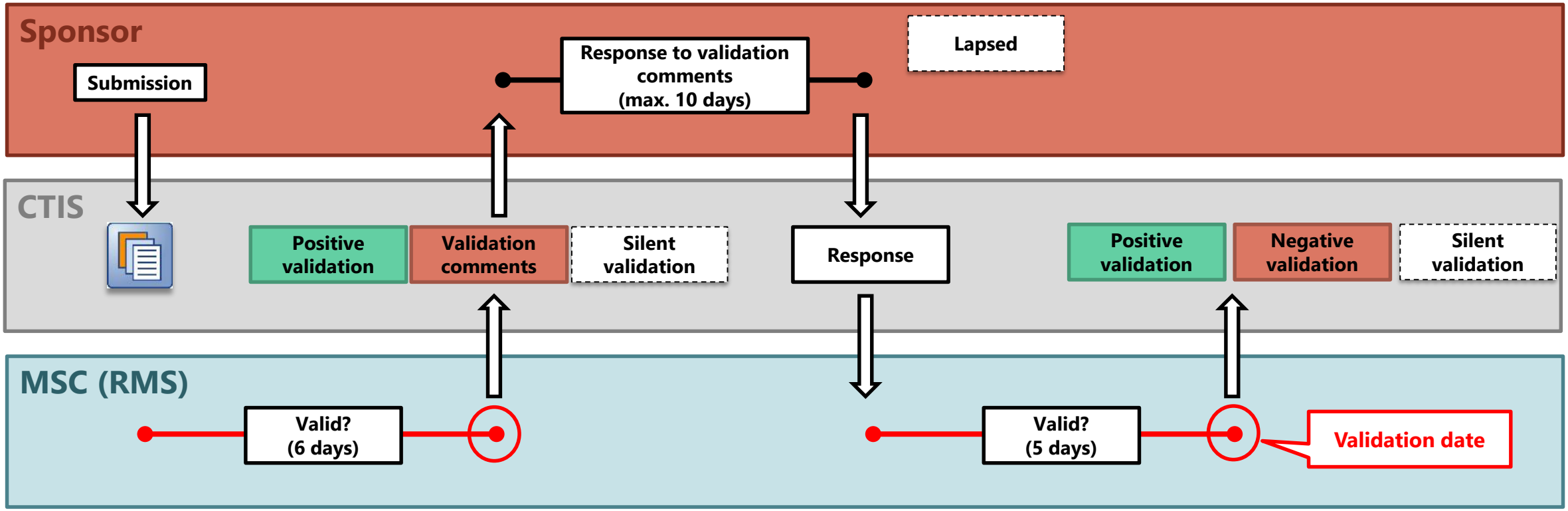

Validation process – Part I SM and Part I/II SM

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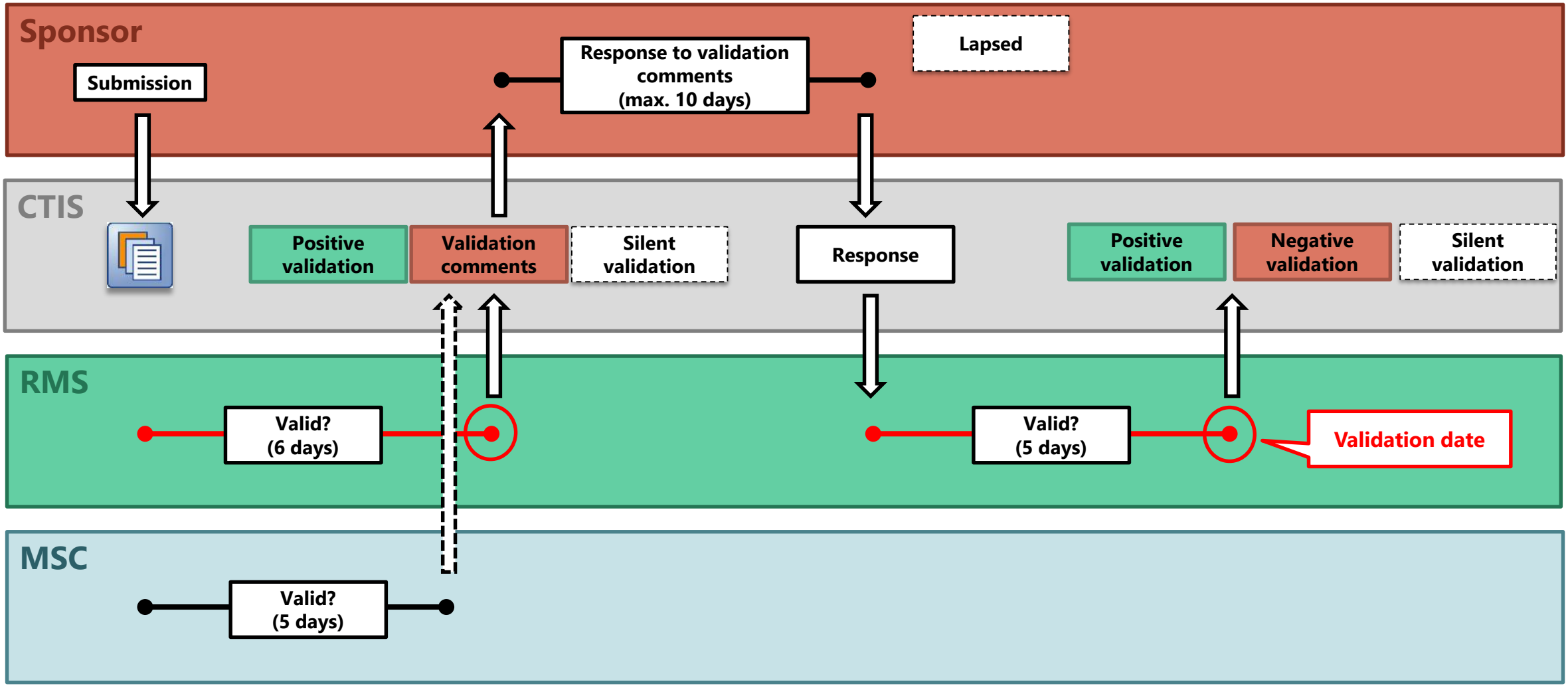

Step 2: Assessment requirements

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- The RMS shall draw up the assessment report for Part I.
- Assessment of Part II is within the remit of each MSC

- **Question 1 (Part I only):**
  Is it still a low-internventional clinical trial (if applicable)?

- **Question 2:**
  Is the substantial modification
  - **acceptable?**
  - **acceptable with conditions to be specifically listed in the conclusion?**
  - **not acceptable?**

Assessment process – Part I SM (mononational) or Part II SM or combination

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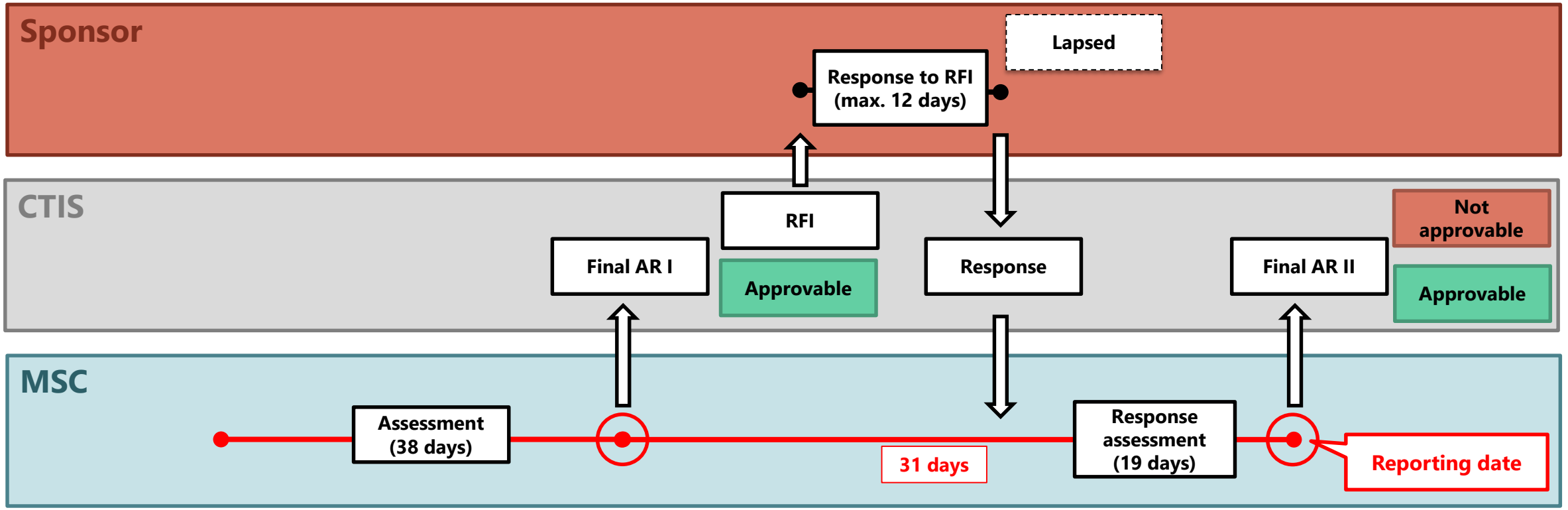

Assessment process – Part I SM (multinational)

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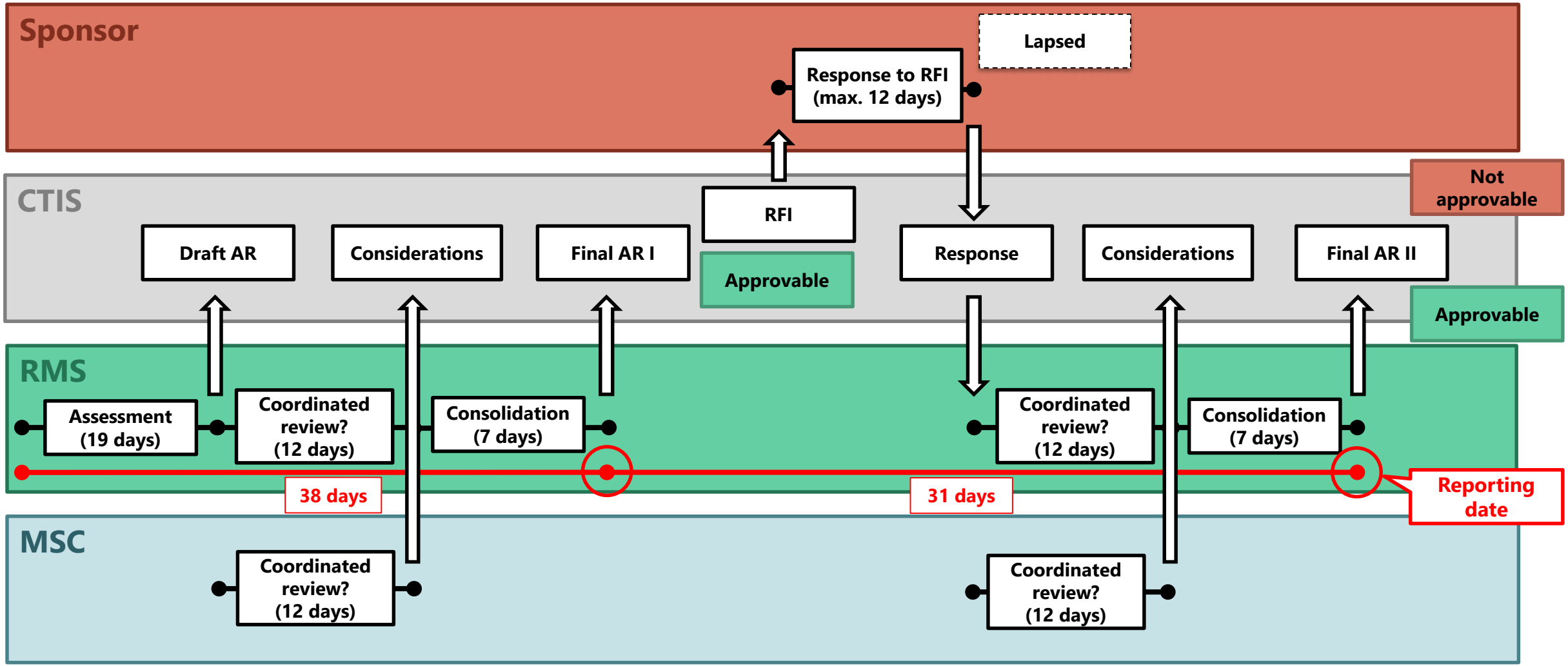

Step 3: Decision

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- Each MSC shall notify the sponsor through CTIS as to whether the SM is authorised, authorised subject to conditions or refused
- Notification by single decision per MSC within **five days** from the reporting date.

- Outcomes Part I:

RMS	**Approvable**	**Approvable**	**Not approvable**
MSC	**Authorised** or **Silent approval**	**Opt-out**	**Not authorised** or **Silent rejection**

- Outcomes Part II:

MSC	**Authorised** or **Silent approval**	**Not authorised**

Attention!

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- Substantial modifications are a critical process in the life-cycle of a trial.
  - Changes for reasons of patient safety
  - Changes for reasons of validity and reproducibility of trial results
- There can only be one SM within the same scope at one time
  → might lead to more combined SM (protocol/IB, protocol/IMPD etc.)
- **There is no partial approval of a combined SM!**
- **RMS and MSC have to make sure that via the RFI either all questions are resolved or not acceptable changes are removed.**
- **Otherwise it will lead to withdrawal or rejection.**

Recommendations for RFI

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- Timelines are short for RMS/MSCs and sponsors
- SMs might become less frequent, but more extensive and complex
- There is minimal time for discussions, and several rounds of questions are unlikely
- Open questions leading to a rejection might have to stand up in an appeal
  → no „nice-to-have“

You have one chance to get it right - nail it!

<u>From our national SOP:</u>

1) **What is the sponsor‘s proposal?**
2) **What is the problem? Why? Reference to legal text or guidance?**
3) **How should it be resolved? Are there more than one option?**

Take-Home Message

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- **Modifications are an essential part for the safe and proper conduct of a trial.**
- **The need for modifications steadily increases.**
- **Modifications might become more complex.**
- **CTR procedure for validation and assessment is strict and ambitious.**
- **Optimal preparation is required during validation**
  - **clear description and justification of changes**
  - **clear way to track old and new versions of structured data and documents**
- **Timelines need to be reliable for MSCs → best practice for RMS/MSC cooperation**
- **RFI needs to be precise, robust and solution-oriented**

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Thank you for the attention!

Questions?

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