EC-DG SANTE/HMA-CTFG/EMA joint training on the Clinical Trials Regulation (EU) 536/2014

Initial application : submission and assessment (II)
Decision , partial applications (Part I only with later Part II) , trial expansion into additional MSCs.

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1: Decision on a clinical trial :

- Each Member State concerned shall notify the sponsor through the EU portal as to :

  - whether the clinical trial is authorised,
  - whether it is authorised subject to conditions,
  - whether the authorisation is refused.

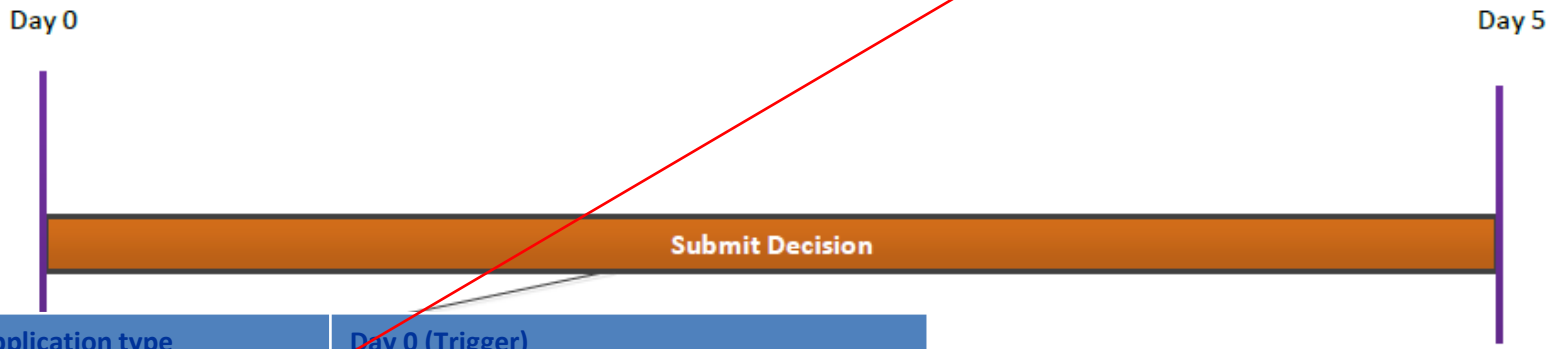
- Single decision within five days from the reporting date or from the last day of the assessment of part II, whichever is later.

- One Single decision per Member State : Part 1 and Part 2

1: Decision on a clinical trial :

Submit Decision

For Part I only - there is only a conclusion (no decision)



Initial Application type	Day 0 (Trigger)
Part I and Part II	Part I and Part II conclusion issued
Part I (only)	Part I conclusion issued
Part II (late submission)	Part II conclusion issued

1: Decision on a clinical trial : what is a condition ?

- An authorisation of a clinical trial subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorisation.

- Setting a condition is only possible in case of an application with a positive benefit/risk balance. This means that if the benefit-risk balance is not positive at the time of the authorisation, the application should be rejected.

1: Decision on a clinical trial : what is a condition ?

- Conditions should be clear and related to an issue already identified in the request for information (RFI) submitted during the assessment.

- When all Member States concerned are in agreement, conditions can be used : i.e. :

✓ To request additional data not available at the time of the authorisation, e.g.data needed for later trial parts, but not preventing the start of the trial.

✓ To indicate aspects that the sponsor need to fulfill after the authorisation, e.g. submission of minutes of the safety data monitoring board meetings.

1: Decision on a clinical trial : Conclusions :

Conclusion of the RMS on Part I: acceptable without / with conditions

- Applies to all Member States concerned (MSc)

- If a MSC disagrees with RMS conclusion on Part I - acceptable with or without conditions = opt-out from decision , based on restricted grounds :

1: Decision on a clinical trial : Conclusions :

✓ Restricted grounds:

(a) it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the Member State concerned ;

(b) infringement of its national law as referred to in Article 90 (e.g. national law prohibiting use of stem cells) ;

(c) considerations raised by MSC on subject safety and/or data reliability and robustness not sufficiently taken into account

✓ Detailed justification, through the EU portal, to the Commission, to all Member States, and to the sponsor

1: Decision on a clinical trial : Conclusions :

- In addition there are other possibilities for a MSC to refuse a trial, even if this MSC agrees with the opinion of the RMS , namely :
  - ✓ Aspects addressed in Part II of the assessment report are not complied with
  - ✓ Negative opinion by ethics committee (if valid according to national law valid for the entire Member State).
- If the RMS Conclusion on Part I is positive , but no Part II submitted
  - ✓ Conclusion of Part 1 is the initial application outcome

1: Decision on a clinical trial : Conclusions :

RMS conclusion on Part I - rejection

- Rejection Part I applies to all MSCs - i.e. application cannot be authorised by any MSC

Notification date is the decision date

- If not issued by a MSC within 5 days = tacit decision

Decision 'expires' after two years

- If no subject has been included in the clinical trial in a Member State concerned within two years from the notification date of the authorisation, the authorisation shall expire in that Member State concerned unless an extension, on request of the sponsor, has been approved

2 : Partial initial applications (Part I only)

- Sponsor can request to apply for an authorization , assessment and conclusions for aspects covered by Part 1 only

- within two years apply for an authorisation limited to aspects covered by Part II

- Lapse if not submitted within two years

- Sponsor needs to declare to be “not aware of any new substantial scientific information that would change the validity of any item submitted in the application on the aspects covered by Part I of the assessment report , which were already assessed by the MSC ” = MSC with Part I only submission must be involved in subsequent Part I substantial modification assessment

3: Sponsor's withdrawal of application

- The sponsor may withdraw the application at any time until the reporting date. In such a case, the application may only be withdrawn with respect to all Member States concerned.

- After the reporting date, but before the decision is taken by a particular Member State concerned

- The reasons for the withdrawal shall be communicated through the EU portal .

4: Resubmission

- Resubmission possible following refusal or withdrawal of an application.
- That application shall be deemed to be a new application for authorisation of another clinical trial.

5: Additional member states concerned (1/4)

- Only after the notification date of the initial authorisation decision
- Notify the sponsor through the EU portal, within 52 days from the date of submission of the application dossier referred to in paragraph 1, by way of one single decision as to whether the clinical trial is authorised, whether it is authorised subject to conditions, or whether the authorisation is refused.
- Note here no separate validation time - thus need for quick exchange (communicated as an RFI) with sponsor if not valid application
- Possible to make considerations for Part I, for the RMS to forward to the sponsor as RFIs. However, only possible to add translation of e.g. labelling (in an additional language) as a new Part I document - dossier already decided upon by the RMS = Part I conclusion

5: Additional member states concerned (2/4)

- All MSCs participate in evaluation of sponsor's response to the RFI = they may choose to apply a corrective measure if e.g. the new Additional MSC points to a valid point on safety/data robustness that was not identified earlier in Part I assessment.

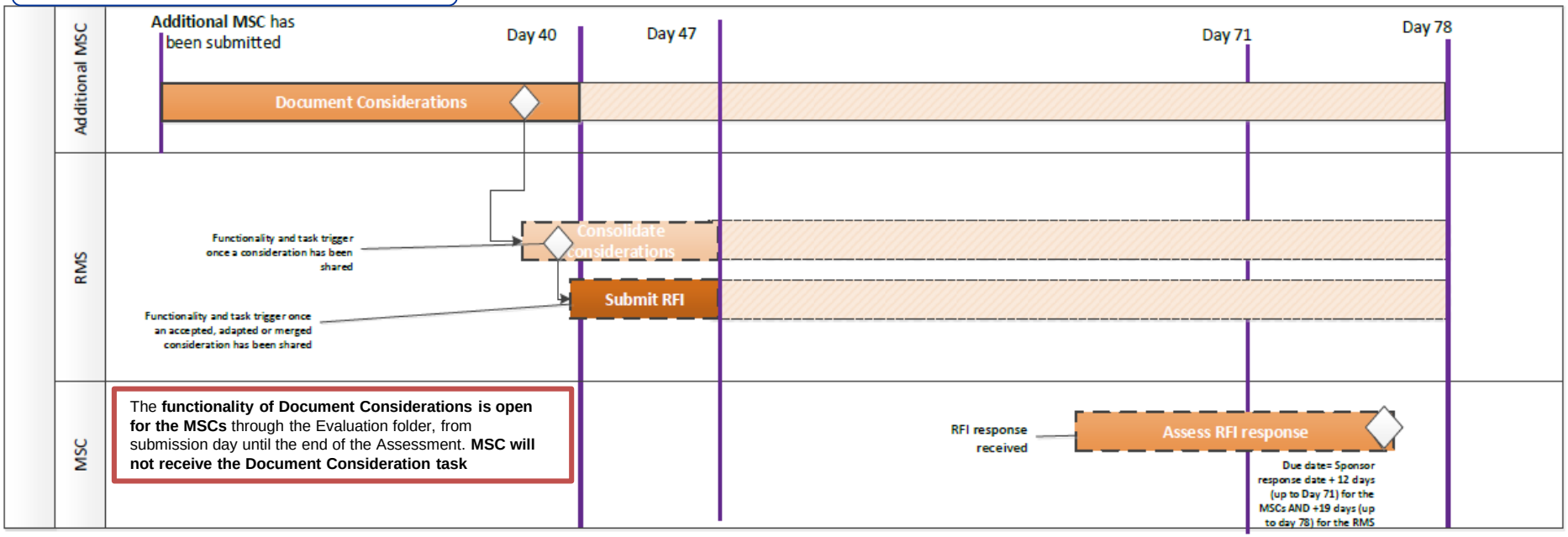
- Part II considerations directly to sponsor, Part II conclusion similar to any Part II procedure

5: Additional member states concerned (3/4)

- Disagreement - same possibility to opt out as for an initial trial application
- Where an additional Member State concerned disagrees (opting out possibilities) , it shall communicate its disagreement, together with a detailed justification, through the EU portal, to the Commission, to all Member States, and to the sponsor.
- Communicate considerations to RMS, RMS sends RFI to sponsor
- Tacit approval if no decision communicated

5: Additional member states concerned (4 /4)

Assessment Part I



Note: If the Sponsor does not respond to an RFI before the DUE date set by the RMS for the sponsor response, it will cause the Lapse of the application.

*In **Expert Group session** held on September 24, 2019, It was agreed the following statements concerning the Additional MSC application:*

- *No changes can be made to **Part I submission form** (other than translations) when the **Sponsor** responds to an **RFI** concerning Part I.*
- *No changes can be made to **Part I evaluation** (DAR & FAR) by the **RMS**, as the Part I application has already been assessed as part of the initial application.*

6: Corrective measures (1 / 2)

‘Suspension of a clinical trial’ means interruption of the conduct of a clinical trial by a Member State;

- Where a Member State concerned has justified grounds for considering that the requirements set out in this Regulation are no longer met (*), it may take the following measures on its territory:
  (a) revoke the authorisation of a clinical trial;
  (b) suspend a clinical trial;
  (c) require the sponsor to modify any aspect of the clinical trial.

- Before the Member State concerned takes any of the measures referred to above (*) , it shall, except where immediate action is required, ask the sponsor and/or the investigator for their opinion.
  That opinion shall be delivered within seven days.

6: Corrective measures (2 / 2)

- The Member State concerned shall immediately after taking a measure referred to (*) , inform all Member States concerned through the EU portal.

- Each Member State concerned may consult the other Member States concerned before taking any of the measures referred to (*)

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