EU4Health CT Cure

Best Practice Guide

Publication date: September 30th, 2024
(minor editorial changes Dec 2024)

The latest version of the Best Practice Guide (BPG) has been updated to incorporate significant revisions aimed at improving clarity, regulatory alignment, and providing practical guidance for stakeholders. This updated version also includes an annex with essential tips for working both within and outside the Clinical Trials Information System (CTIS), reflecting the most recent regulatory changes and user needs.

One of the primary updates in this version involves the incorporation of the latest references to ensure full alignment with European Union guidelines. These updates include references to the current EudraLex regulatory framework and the Clinical Trials Coordination Group (CTCG) Best Practices.

A significant portion of the update focuses on content enhancement and the clarification of procedures, particularly concerning substantial modifications (SMs) and additional Member State Concern (MSC) applications. The revised guide now clearly states that these updates apply to all substantial modification applications, not only those involving the addition of a new Investigational Medicinal Product (IMP). This change ensures that stakeholders are aware of the broader scope of SM applications and the necessary steps to remain compliant.

Additionally, corrections have been made to Table 1, ensuring that the information it contains is both accurate and up-to-date with current regulatory requirements. Visual aids in Figures 1-6 have also been further clarified, providing users with clearer guidance on navigating the various application types within the CTIS.

An important addition to this version of the Best Practice Guide is the annex, which provides practical tips for working efficiently within and outside CTIS. This annex serves as a quick-reference tool for stakeholders, offering clear, actionable advice on how to navigate the platform and manage tasks effectively. The tips outlined are designed to optimize workflows, improve user experience, and ensure regulatory compliance across all stages of clinical trial management. By streamlining both internal processes within CTIS and external regulatory activities, the annex aims to support users in fulfilling their obligations with greater ease and efficiency.

Best Practice for Member States participating in the joint action CT-CURE as RMS or MSCs in multinational COVID-19 Therapeutic Trials

The following multinational trial applications (1 and 2 below) investigating the efficacy and safety of novel COVID-19 therapeutics submitted to the Clinical Trials Information System (CTIS) under the Regulation (EU) No 536/2014 (here called the Clinical Trial Regulation, CTR) are eligible for expedited assessment and inclusion in the joint action CT-CURE under EU4Health.

Novel COVID-19 therapeutics, including those not being vaccines but intended to be used as pre-exposure or post-exposure prophylaxis, are defined as i) investigational medicinal products (IMPs) without marketing authorisation, ii) IMPs with marketing authorisation for a different indication than COVID-19-related indications and iii) COVID-19 therapeutics with a marketing authorisation used with a new posology or in novel populations, e.g. in children.

The project aims at expedited timelines for the assessment of COVID-19 therapeutics in multinational clinical trial applications. All CT-CURE participants in the expedited timelines assessment involved in the task to act as RMS or MSC in Work Package 6 are committed to follow this Work Package 5 Best Practice.

While the review will be faster for the CT-CURE applications, it should be emphasised that the expedited assessment must not compromise the quality of the scientific and ethical review as outlined in Article 4 of the CTR.

1. New initial clinical trial applications and applications adding additional Member States to an authorised CT[1]

Alternatives A and B below should both be fulfilled. Alternatives C and D describe alternative submissions to an initial full application (Part I and Part II), after the trial has been authorised in at least one MSC. Note that D is restricted to situations when the RMS raises an RFI proposed by the Additional MSC in Part I.

Member State Participants of the CT-CURE agree to expedite the assessment by RMS/MSCs, for which alternatives B-D will all be elements of the CT-CURE project Technical Work Package 6.

A. At least two Member States Concerned (MSCs)
B. **Full initial** submission (**both Part I and Part II**, see CTR Articles 6 and 7 as well as Annex I) submitted to at least one MSC
C. **Partial initial** submission (**Part I only**) to other MSCs with l**ater Part II** submission (see CTR Article 11). Note rules for these submissions described in EudraLex volume 10 Questions and Answers Document - Regulation (EU) 536/2014

[1] In cases where the CT was authorised according to the Directive 2001/20/CE related national legislation, transition to CTR according to guidance at EudraLex vol 10 is needed.

D. **Transition** of trials under the CTR into CTIS of consolidated or harmonised, earlier authorised trial Part I documents (protocol, Investigator's Brochure etc) as well as earlier authorised Part II national documents (see EudraLex volume 10 Guidance for transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation or later updates of this document and under CTCG, HMA, Key Documents List Best Practice Guide for sponsors of transition multinational clinical trials including the Annex I cover letter and Annex II on fees for transitional trials

E. **Additional MSC** submission after at least one MSC has authorised the trial through an initial application (see CTR Article 14). This option is an alternative to submit a partial initial submission (Part I only) taking into consideration that substantial modification applications are not possible in the Go-Live version of CTIS before MSCs receiving a partial initial submission have also received the later Part II submission and concluded the procedure with a decision

2. Substantial modification applications

Member State Participants of the CT-CURE agree to expedite the assessment by RMS/MSCs for all **substantial modification** applications, including those where a novel COVID-19 therapeutic in a previously authorised platform/adaptive trial.

Identification of trials suitable for CT-CURE

A. Best practice horizon scanning when sponsor seek rapid central scientific advice on new COVID-19 therapeutics. Support should be sought by EMA's Emergency Task Force (ETF)/Committee for Medicinal Products for Human Use (CHMP) to inform organisations seeking central advice at an early stage about CT-CURE in a short statement attached to the answers to the questions raised, encouraged to plan trial submission in cooperation with the intended Member States Concerned. The Member State Expert representing the Clinical Trials Coordination Group (CTCG) in ETF (WP 5 Lead) will share information via secure links among all Affiliated Member States on relevant products for which clinical trials are planned in EU/EEA.
B. Best practice horizon scanning and sharing of information via secure links among all Affiliated Member States when approached by an organisation or future trial sponsor to discuss a new COVID-19 therapeutic in national or simultaneous (organised by the EU-IN, EU Innovation Offices) national scientific advices.

C. Other events proposed by the WP 2 on Dissemination of information on the CT-CURE Project informing future clinical trial sponsors about the project.

The role of sponsors in CT-CURE

Sponsors should be encouraged to submit complete trial application dossiers, since these will not require any Validation Request For Information (RFI). In addition, high-quality

dossiers not requiring an assessment RFI on scientific and regulatory matters will benefit most from the accelerated timelines. Since CTIS implementation of Part I only submissions is not yet in line with CTR Questions and answers published at EudraLex volume 10, full dossiers including Part I and Part II are preferred. No rolling reviews or similar step-by-step submissions of trial applications are included in CT-CURE.

Sponsors are encouraged to i) seek central scientific advice at ETF ii) discuss the planned dossier with intended Member States Concerned prior to the application submission in national or simultaneous advices in several countries, iii) inform the proposed Reporting Member State as well as all other intended Member States Concerned about the planned submission date, preferably at least two weeks in advance and to submit full Part I and Part II Cs participating in CT-CURE. If sponsors include NON-CT-CURE Member States, they are recommended to check in advance if these non-members are ready to follow the CT-CURE timetable.initial applications to all MS

After validation, the assessment timeline for CT-CURE trial applications is anticipated to be substantially shortened compared with the maximum timelines provided in CTR. The variations depend on the application procedure (see Table 1). Note that the procedures without a legally defined validation in CTR reviewing the completeness of the submitted application require this step to be done early during assessment, which will appear as a less accelerated timeline but is important to allow sponsor to correct mistakes during submission.

Organisations involved in each Member State Concerned assessing and deciding upon the clinical trial applications

In each Member State clinical trial applications should be assessed and decided upon by the appropriate national organisations, e.g. the National Competent Authority and an Ethical Review Authority or other ethics committee as outlined in the Member State National law. Importantly, CT-CURE Member States should be dedicated to involving ethics committees in the accelerated timelines, both regarding Part I and Part II. If the assessment of Part II is not expedited, the decision on the trial cannot be expedited compared to the maximum timelines in CTR and the main objective of CT-CURE will not be met. Ethics Committee assessors could consider starting assessment of the application dossier already during validation in order to be able to meet the short timelines provided. Ethics Committees need to be subcontractors or affiliated organisations to receive compensation for the work performed. In order to make it possible for Ethics Committees to participate in CT-CURE and plan their assessment meetings, a fixed deadline date for all assessment subphases as shown in Figs 1-6 will be developed by the RMS to ensure maximum predictability for all parties involved (see below). This means that if an earlier subphase delivers before the specified date, the following subphase(s) dates still remain. However, the total assessment deadline should not exceed what is specified in Table 1.

Each Member State should make a single decision on the clinical trial application.
Note that Partial initial submission of a Part I only application cannot be decided upon before the later Part II submission and subsequent Part II Assessment Conclusion (see CTR Articles 7 and 8 as well as Annex I) is finalised. This CTR Article 11 procedure does not include a separate Validation Phase, why the first five days are provided for a quick RFI if validation matters regarding the Part II Dossier are identified. Also the SM Part II only does not include any legally defined Decision phase, why CTIS has reserved time for this during the last five days of the Assessment Phase.

Table 1 Number of Calendar Days used to calculate Expedited CT-CURE Assessment fixed date subphase timelines

Application procedure	Regulation (EU) No 536/2014 Maximum timeline for **Assessment** without RFI (with RFI within brackets) (days)	CT-CURE Fixed date timeline* for **Assessment** without RFI (with RFI within brackets) (days)	Reference to Figures illustrating the respective application assessment subphases	Timeline for CT-CURE expressed as a **percentage** of the Regulation maximum timeline for the Assessment phase (with RFI within brackets) (%)
Initial full of partial application (Part I) only (at least one MSC receiving a full dossier – both Part I)**	45 (76)	16 (37 including 12 days for sponsor response)	Fig. 1	36% (49%)
Later complementary Part II for initial Part I only application***	45 (76)	21(42 including 12 days for sponsor response)	Fig. 2	47% (55%)
Transition to CTR/CTIS of trials authorised under CTD/national law	45 (assessment RFI not anticipated)	5 (assessment RFI not anticipated)****	Fig. 3	(assessment RFI not anticipated)
Additional MSC***	47(78)	23 (44 including 12 days for sponsor response)	Fig. 4	49% (56%)
SM Part I and II, Part I only or Part II only*****	38 (69)	16 (37 including 12 days for sponsor response)	Fig 5 (Part I or Part I & II) Fig 6 (Part II)	42% (54%)

* Fixed timelines proposed by the RMS at the end of the Part I validation phase specifying the deadline date for each assessment subphase shown in the Figs. 1-6 enable Ethics Committees to schedule assessment meetings. If the RMS and all MSCs, including all national competent authorities and ethics committees, agree, shorter assessment timelines could apply for individual clinical trials.

**Note that CTIS has not yet fulfilled the interpretation of the CTR QnA adopted by CTAG (published at EudraLex Volume 10) that both MSCs receiving Part I & Part II and Part I only should be involved in reviewing a later Part I substantial modification. At present, sponsors are blocked from submitting an SM Part I application before all initial MSCs have received full dossiers. For this reason, sponsors are encouraged to submit both Part I and Part II dossiers to all MSCs participating in CT-CURE until an acceptable work-around is implemented.

*** Procedure without legally defined validation phase may require an early additional assessment RFI with a short sponsor response time if the application is not complete (valid), which means that the sponsor has a chance to correct this aspect before the main, scientific assessment RFI. For all other procedures (without ***) a separate validation procedure (10 days for initial application and 6 days for substantial modification applications) is defined in the Regulation, prolonging the validation phase with an additional 15 days if a validation RFI is sent by the RMS including time for the sponsor to respond (10 days).

**** In 2024 modified as described in the CTCG Recommendations to sponsor on Transition of trials from CTD to CTR applying a single step review without any assessment phase allowing decision on earlier approved CTD documents to be made directly after validation.***** Procedure without legally defined decision phase, implemented in CTIS as setting aside the last five days of the assessment to the decision.

Fig. 1 NEW TRIAL APPLICATION (PART I AND PART II OR PART I ONLY)

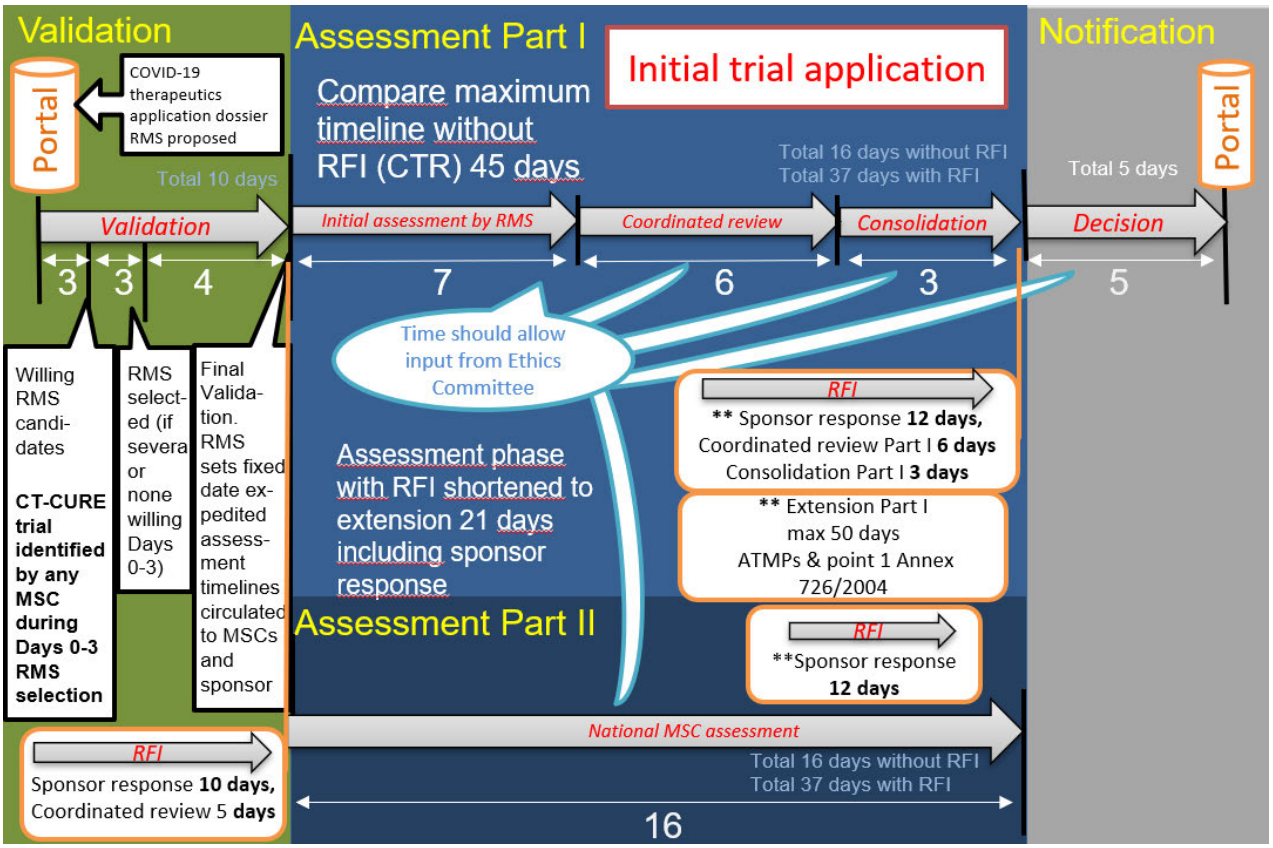


Fig. 2 LATER PART II SUBMISSION

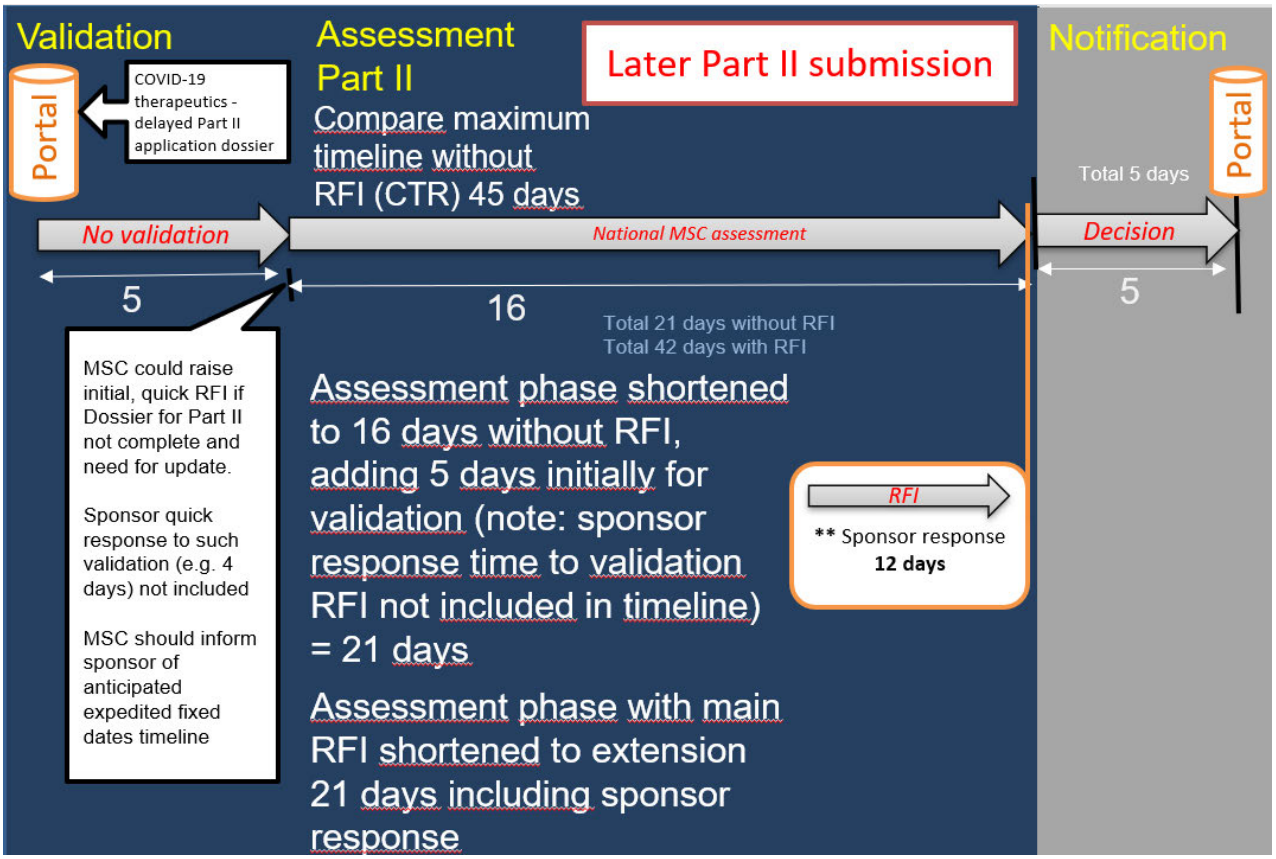


Fig. 3 CTR TRANSITION OF TRIALS AUTHORISED UNDER CTD/NATIONAL LAWS

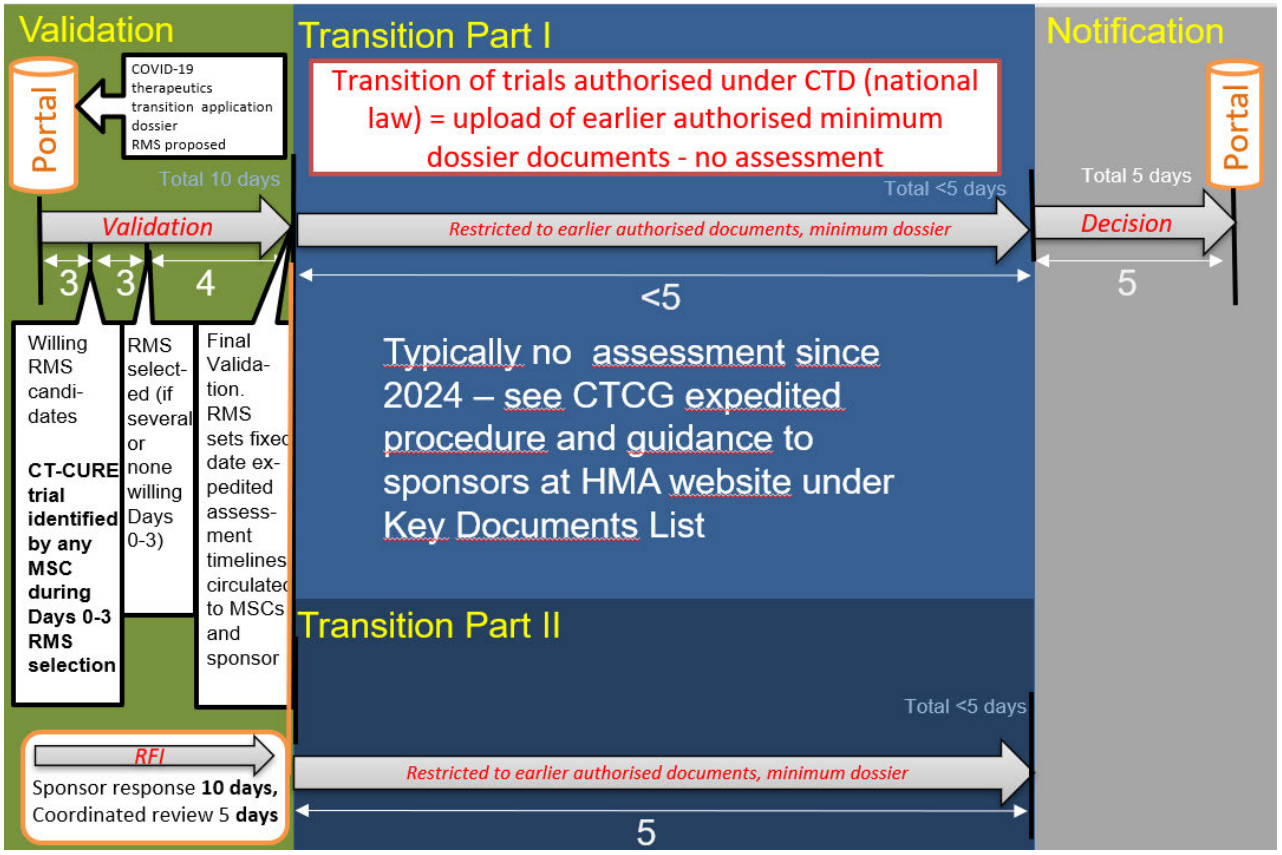


Fig. 4 ADDITIONAL MEMBER STATE CONCERNED

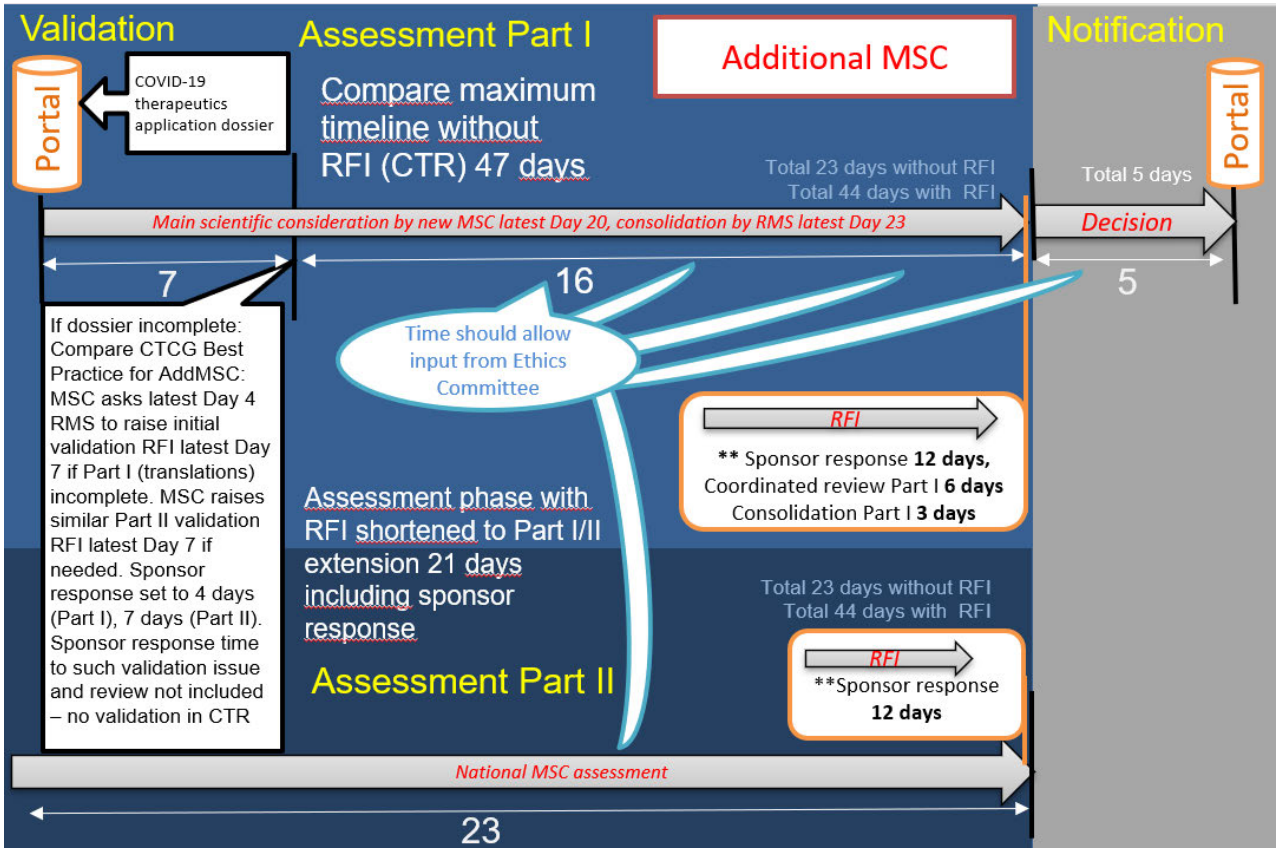


Fig. 5 SUBSTANTIAL MODIFICATION PART I AND PART II OR PART I ONLY

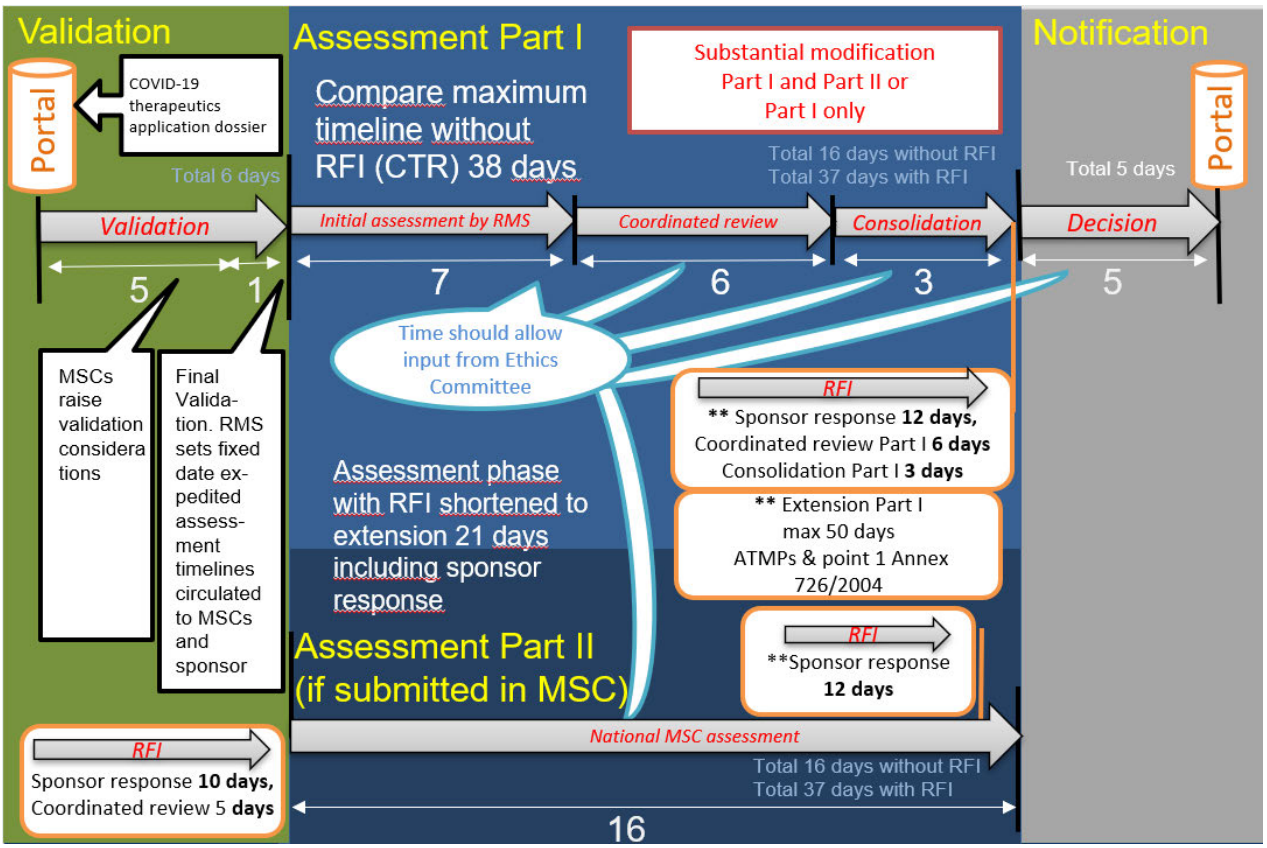
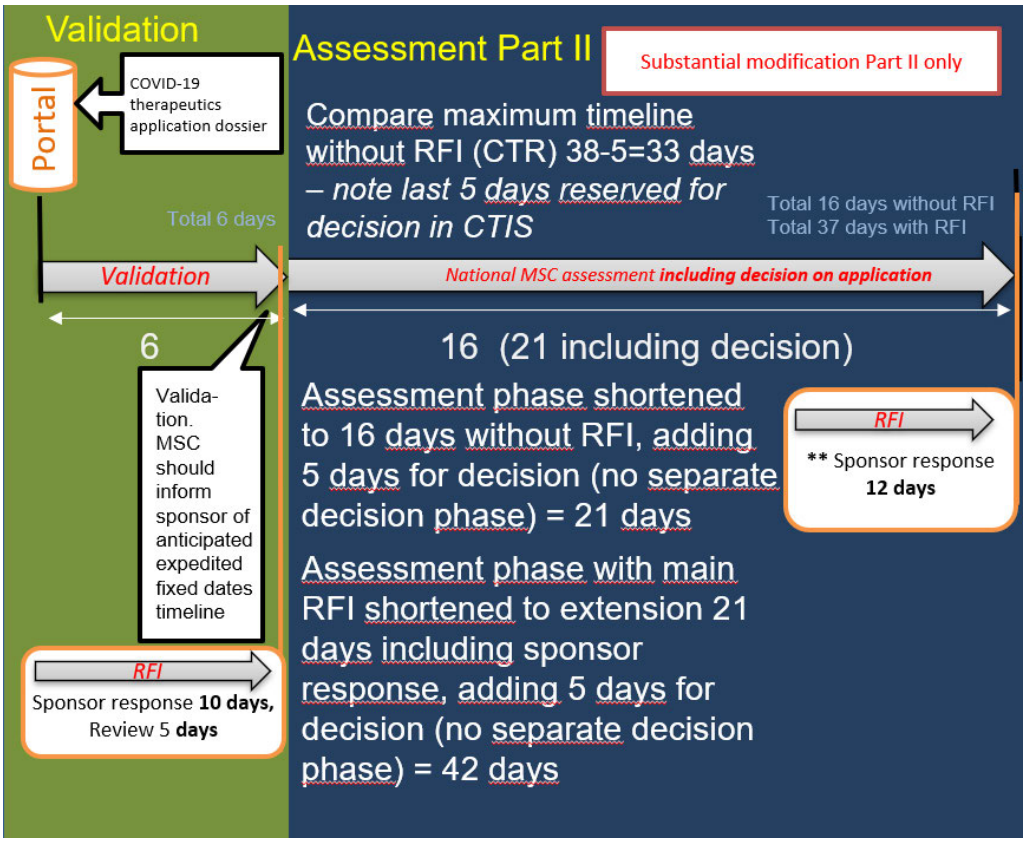


Fig. 6 SUBSTANTIAL MODIFICATION PART II ONLY



Decision on eligibility and inclusion of trials in CT-CURE, selection of Reporting Member State during the initial application validation phase and preparing a fixed timeline for the expedited assessment subphases

Decisions on CT-CURE inclusion of a particular clinical trial application (see criteria above –) will be made during the first 6 days selecting a Reporting Member State with the task to coordinate Part I during the Part I and Part II common validation phase, as outlined for new clinical trial applications in CTR Article 5. Importantly, if only one MSC is willing to be RMS, this time window is shortened to three days, see below.

When selecting the RMS, reaching a balanced work-sharing between CT-CURE Member States for this task should be taken into consideration, in line with the algorithm for work-sharing of RMS-ships in CTIS. If another MSC participating in CT-CURE with a lower workshare for RMS-ships than the one proposed as RMS by the sponsor is willing to act as RMS, this should be the preferred choice to avoid that only a limited number of MSCs will get experience to act as RMS in the CT-CURE project. The willing RMS candidate does not have to receive a full Part I and Part II application, but at least one MSC among the MSCs receiving the initial application should receive a full trial application. Later Part II application submission to MSCs receiving Part I only should be done promptly not to block subsequent SM applications.

When an MSC considers the application to be eligible for CT-CURE and expresses willingness to be RMS during Days 0-3 after the initial clinical trial submission, that MSC should communicate this in CTIS using the 'justification free text box' and also explain that an accelerated assessment according to the CT-CURE Best Practice applies. Note that MSCs not willing to be RMS should still communicate that the trial has been identified as eligible for CT-CURE in the 'justification free text box'.

If only one MSC is willing to be RMS at the end of Day 3 after trial submission, this MSC will be selected immediately, and the validation phase will proceed.
If several CT-CURE Member States are willing to act as RMS, the decision is taken during Days 4-6 after the application submission. If no agreement is reached, the MSC proposed by the sponsor is selected. Preferably, CT-CURE Member States should not object to another CT-CURE Member State willing to act as RMS in respect of the work-sharing algorithm. The RMS controls when considerations are sent to the sponsor as a Request for Information (RFI) during the Assessment Phase for Part I, why it is preferable that a Member State participating in CT-CURE will act as RMS to succeed in accelerating assessment timelines. At the same time, a non-participant Member State could agree to follow the CT-CURE Best Practice. All MSCs participating in CT-CURE have the responsibility to follow the CT-CURE accelerated timelines for Part II assessment.

The RMS should inform all MSCs, also those outside the Member States participating in CT-CURE, about the anticipated target dates in line with this Best Practice document for the Part I and Part II assessment phase already during the validation phase (preferably both in an e- mail to the respective MSC national contact point at the end of validation and as an early assessment regulatory consideration shared with all MSCs already Day 1 of the assessment phase) and add this list of fixed due dates for assessment subphases as a separate document named Expedited Assessment Subphase Fixed Dates to Draft Assessment Report using upload slot for Introduction DAR template. A fixed timeline specifying the dates for the expedited assessment subphases shown for the different procedures in Figs. 1-6 should be prepared by the RMS and shared with all MSCs and the sponsor via secure Eudralink communication.

When selecting these dates, the timelines specified in Figs. 1-6 should be respected and no task should fall on a weekend or official holiday of the RMS (see below under Calculation of due dates based on the agreed accelerated assessment timeline),

Note that the RMS should always wait until all MSCs have entered their validation considerations relating to Part I and Part II, i.e. Day 7 after the application submission unless the task has been completed by all MSCs earlier. Speeding up the procedure before MSCs confirm that they completed their validation is counterproductive, since this prevents both CT-CURE Member States and non-CT-CURE Member States to carefully validate the Part I and submitted Part II dossiers. Taken together, this means that the Validation phase has not been agreed to be substantially shorter in CT-CURE applications compared to other submissions.

Assessment of eligible trial applications – non-CT-CURE Member States as MSCs

Note that Member States outside the CT-CURE participant Member States acting as RMS/MSC for CT-CURE trials (Work Package 6) have not formally agreed to the accelerated timelines for Part I and Part II assessment in this Best Practice. As for Part I, the RMS decides on the timeline for assessment, whereas for Part II, and as a consequence, for the decision based on the conclusions on Part I and Part II, no such expedited timelines have been agreed beyond the 15 Member States that are represented in this Joint Action Consortium.

Broad agreement on the expedited timelines should be sought for trials on COVID-19 therapeutics also involving Member States not participating in the Joint action CT-CURE, but these MSCs decide independently if they intend to follow the accelerated assessment timelines for Part II or not. As stated above, sponsors are encouraged to discuss with non-CT CURE Member States before choosing to include them in a CT-CURE application as Member States concerned. Best Practice Updates are shared with CTCG and CTEG/CTAG and used in Training of assessors from National Competent Authorities and Ethics Committees.

The accelerated timelines for Part II and the decision on the application are likely only to be respected by Member States participating in CT-CURE. At the same time, it is expected that all Member States are willing to support the expedition of the assessments of high-quality, well-constructed applications for critical trials with promising novel COVID-19 therapeutic products.

Calculation of due dates based on the agreed accelerated assessment timeline

All timelines are calendar days counted in the same way as for other due dates in CTR taking Regulation (EEC, Euratom) No 1182/71 into consideration. This means that the task is moved to the next working day if it falls on a weekend or on an official holiday/legally defined vacation day. The RMS national calendar applies during the assessment Part I phase, whereas during the decision phase and Part II assessment phases each MSC applies its own national calendar. Another rule for this way of calculating due dates is that each task spanning over several days should always include at least two consecutive working days. Note that for the CT-CURE project a fixed timeline defining the dates of all deadlines for the respective Part I assessment subphase will apply. This means that if a task is fulfilled earlier, the already fixed date for the subsequent subphase still applies.

Timelines not possible to follow due to problems with CTIS

As applicable for CTIS, critical database problems with an impact on the workflow as well as any substantial downtime of the system during working days will result in prolonged timelines. At the same time, both the RMS and MSCs should seek work-around opportunities trying to adhere to the agreed timelines if possible.

Rules for considerations and Requests for Information during validation and assessment

All participants in the task acting as RMS/MSC in WP 6 are expected to follow the CTCG Best Practice on considerations/RFIs, which describes that these should be restricted to issues that could lead to the rejection of the application or, in exceptional cases, to an authorisation with a condition, which should explicitly describe how the sponsor should proceed (via a non-substantial substantial modification or a substantial modification application).

Agreement on circulation of the Draft Assessment Report by the RMS to all MSCs and on the Draft Assessment Report and Final Assessment Report contents

The CTCG Best Practice relating to the Draft Assessment Report (DAR) and the Final Assessment Report (FAR) should be followed, which sets a common understanding for what should be included in the assessment report. However, for the expedited assessment timelines in CT-CURE, no other agreements on the application assessment phases should apply, i.e. for an initial trial application the i) initial assessment phase when the RMS circulates the DAR should end Day 7 after the Validation Date instead of Day 26, ii) the coordinated review providing considerations from all MSCs should end Day 13 and be followed by iii) a consolidation phase for the RMS/MSCs ending Day 16 after the coordinated review (calendar days after validation). This means that considerations by MSCs later than Day 13 will not be forwarded in an RFI to the sponsor.

All assessment subphase procedures are clarified in the Table 1 and Figs. 1-6. See also the Annex - Practical tips from CT-CURE on how to work within and outside the Clinical Trials Information System (CTIS) assessing trial applications with expedited timelines.

If the RMS decides to send considerations to the sponsor as a Request for Information (RFI), the maximum CTR timeline for the sponsor’s response still applies (12 days), but the subsequent assessment of the response by the RMS and MSCs is accelerated as shown in Figs 1-6.

Importantly, a late response by the sponsor should not impact the RMS/MSCs fulfillment of this CT-CURE best practice. Also, a maximum 50 days extension of the assessment timelines for consultation with experts should be possible for e.g. Advanced Therapy Medicinal Products (ATMPs) and Products listed in point 1 of the Annex to 726/2004.

Decisions on clinical trial applications

Decision phase timelines follow the maximum timelines implemented in CTIS according to CTR. Note that if an MSC receives an initial Part I only submission, this MSC cannot make a decision on the trial before a subsequent Part II submission has been received and assessed. Thus, this Best Practice should be considered to be fulfilled already at the notification of the first decision by an MSC that received the full application for such Part I only initial submissions.

Annex - Practical tips from CT-CURE on how to work within and outside the Clinical Trials Information System (CTIS) assessing trial applications with expedited timelines

Practical tips on how to identify CT-CURE trials and how to communicate between RMS, MSCs and sponsor. These recommendations are based on testing the CT-CURE Best Practice on expedited assessment in the CTIS Sandbox/Training Environment.

Practical tips from CT-CURE on how to work within and outside the Clinical Trials Information System (CTIS) assessing public health emergency trial applications with expedited timelines

Ann Marie Janson Lang

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LÄKEMEDELSVERKET SWEDISH MEDICAL PRODUCTS AGENCY

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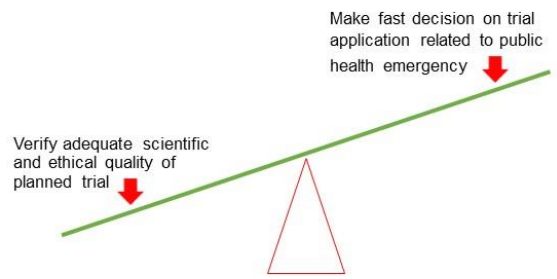
Member State Assessment Timelines in Clinical Trials Regulation – public health emergency applications

Clinical Trials Regulation – preamble (8): all timelines are maximum in order to allow faster assessment of trials in public health crisis



Article 3

General principle

A clinical trial may be conducted only if:

(a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and

(b) it is designed to generate reliable and robust data.

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CTIS lacks important functionalities required for review of Public Health Emergency trial application

CTIS generates tasks for Member States Concerned specifying due dates in line with CTR maximum timelines

The following additional CTIS functionalities could ensure a more efficient accelerated Public Health Emergency trial application review:

- Necessary **overview for MSCs and sponsor of fixed due dates set by the RMS for accelerated assessment subphases**
- **Additional assessment tasks/notifications and MSC completion status notification** should be generated if a **second assessment RFI sent to the sponsor**, e.g. to facilitate expedited procedures without validation phase
- **Name of Added Member State** should appear on **tasks and notifications** – required for overview if several Additional MSC procedures at the same time

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Proposed alternative ways to communicate within and outside CTIS as workarounds

CT-CURE identified alternative ways to communicate within and outside CTIS on agreed application procedures with expedited assessment (below *entity performing action within parenthesis*)

- **Communicate identified 'public health emergency trial status' to all MSCs in CTIS free text fields (justification, discussion) during RMS Selection (*each MSC*)**
- **Inform MSC national contact points and sponsor about fixed dates for expedited assessment subphases secure Eudralink at end of validation phase (*RMS*)**
- **Communicate list of fixed dates for expedited timelines in *document* uploaded to CTIS (*RMS*)**
  1. **associated document with an early assessment consideration preferably Assessment Day 1 (category 'regulatory', 'clock stop'). Not sent to sponsor if no other consideration raised in RFI to avoid assessment phase prolongation**
  2. **added separate additional document named *Expedited Assessment Subphase Fixed Dates* to Draft Assessment Report using upload slot for Introduction DAR template**

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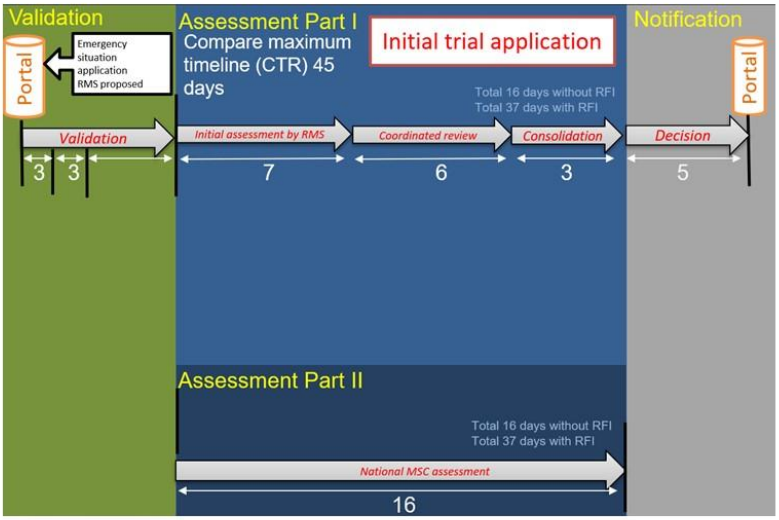
Initial trial application – Part I and Part II or Part I only



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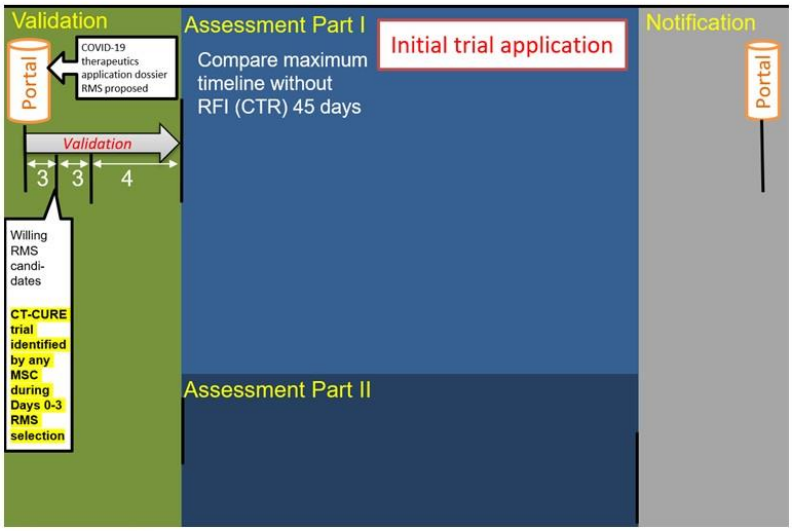
Initial trial application – Part I and Part II or Part I only



ALL MSCs during initial 3 days of validation (RMS selection):

- **Check application dossier (cover letter, trial details including central/national scientific advice)**
- **Notify all MSCs national contact points on emergency situation trial application in CTIS using the justification field for providing willingness or unwillingness to be RMS**

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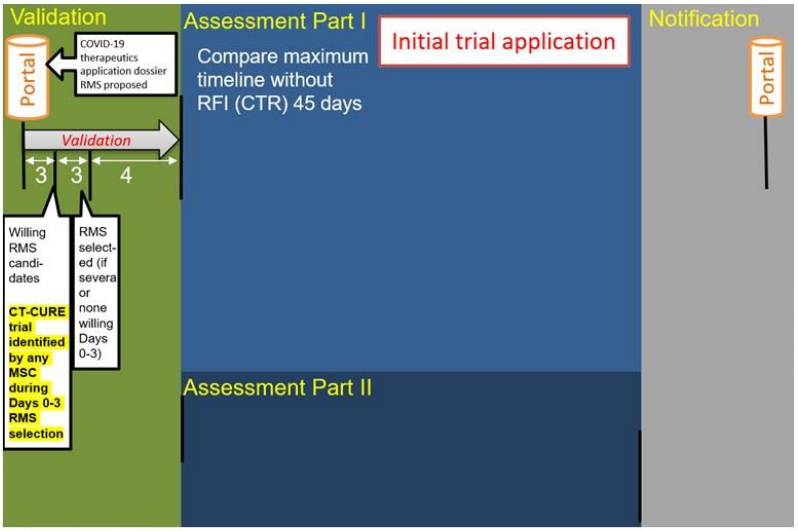
Initial trial application – Part I and Part II or Part I only



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RMS willingness: If > 1 MSC willing or none willing:

- **Communicate in free text field 'discussion with MSCs' that the application is a PHE trial**
- **Note that only those assigned to the task 'agree RMS' will see the discussion field!**

After selection, RMS sends an e-mail/Eudralink to all MSCs national contact points on application status: public health emergency (PHE) trial application

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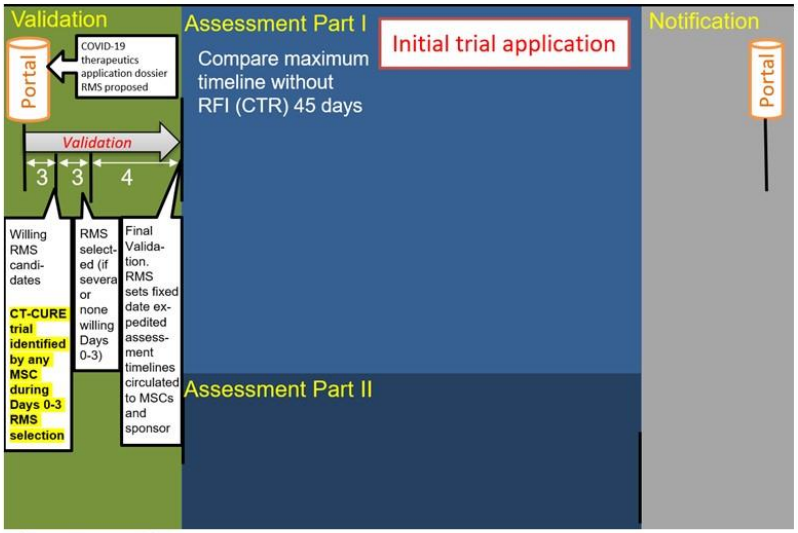
Initial trial application – Part I and Part II or Part I only



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All MSCs should inform RMS if the 'document validation consideration' step completed (not before RMS selection) = allowing RMS an overview with information if all MSCs finished before the due date (Day 7)

RMS should communicate via e-mail/Eudralink when validation *fixed dates for expedited assessment subphases* ended. Send to:

- **CTR national contact point at EudraLex volume 10 and**
- **sponsor (see contact address in application)**

No subphase due dates on weekends or RMS national holidays (Regulation (EEC, Euratom) No 1182/71)

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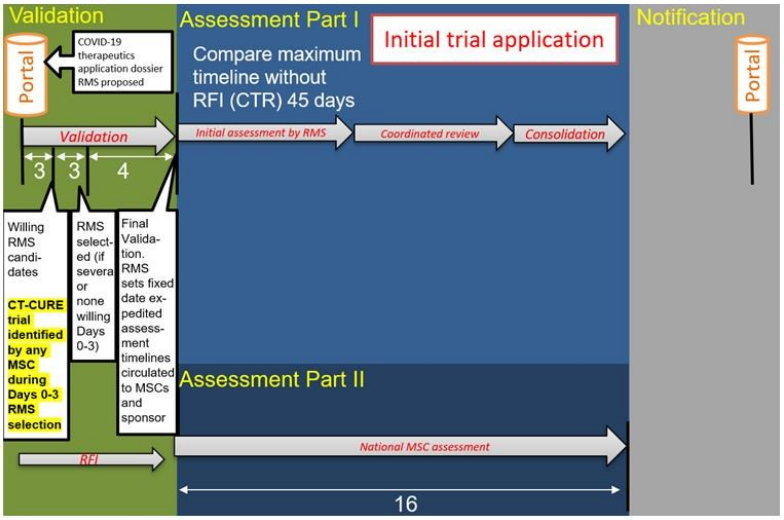
CTR national contact point at EudraLex volume 10

Initial trial application – Part I and Part II or Part I only



When the assessment phase starts, the RMS should upload the fixed dates subphase due dates Day 1 of the assessment (same as communicated by mail/Eudralink at end of validation) using the consideration category 'regulatory' / 'clock-stop' = ensuring that time table can also be found within CTIS

If there are other assessment considerations, an RFI will be sent to the sponsor including the expedited assessment dates in the main RFI sent to the sponsor Day 16. If there are no other considerations to the sponsor, the initial consideration with the expedited assessment timetable should not be sent, since this prolongs the assessment phase

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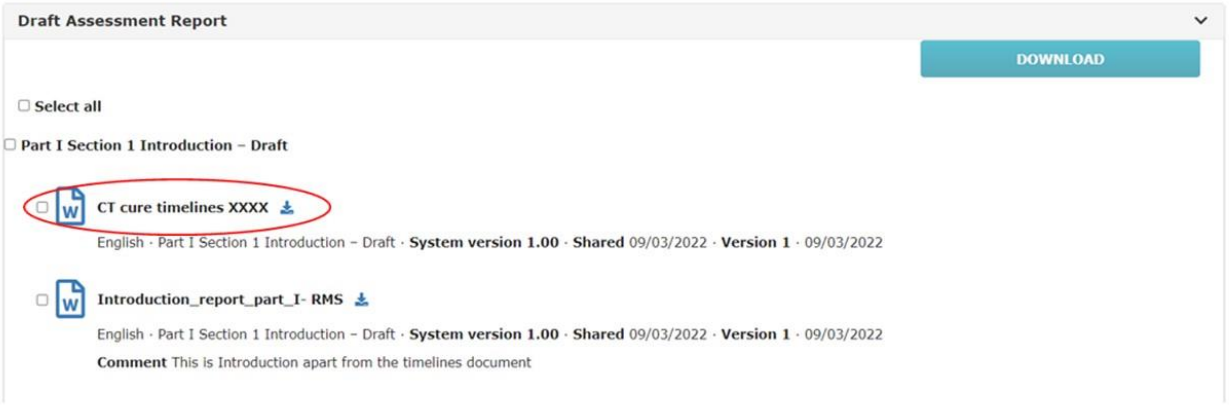
At first DAR upload to CTIS, RMS recommended to add a separate document with the Expedited Assessment Timetable

The same fixed date timetable on expedited timelines should also be uploaded by the RMS as a separate Introduction DAR document



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RMS also recommended to add comment on expedited assessment in the discussion field on DAR

The RMS also encouraged to mention the expedited assessment phase for the trial applicaiton (but not the entire timeline) in the free text field for DAR discussion (note field incorrectly labelled discussion WITHIN MSC):

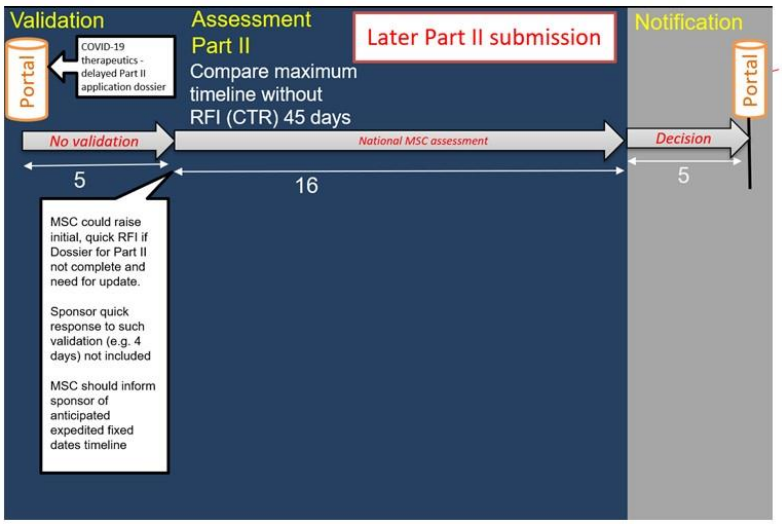
If an MSC find a critical omission in the DAR this could be comunicated in the same field (above) to alert the RMS

MSCs should inform RMS on completion of their considerations – RMS proceeds to consolidation after 6 days

MSCs should inform the RMS that they have completed their assessment considerations

If the fixed timeline date for the agreed expedited 6-day time window for timely assessment considerations by MSCs is not respected, the RMS will proceed to the consolidation phase

Later Part II submission if initial application Part I only (partial initial submission)



Task for MSC:
Notify sponsor, preferably latest Day 5 (together with validation consideration if any) about expedited fixed dates for assessment of main Part II RFI

If no validation consideration, notify timetable in e-mail/Eudralink to sponsor sponsor (see contact address in application)

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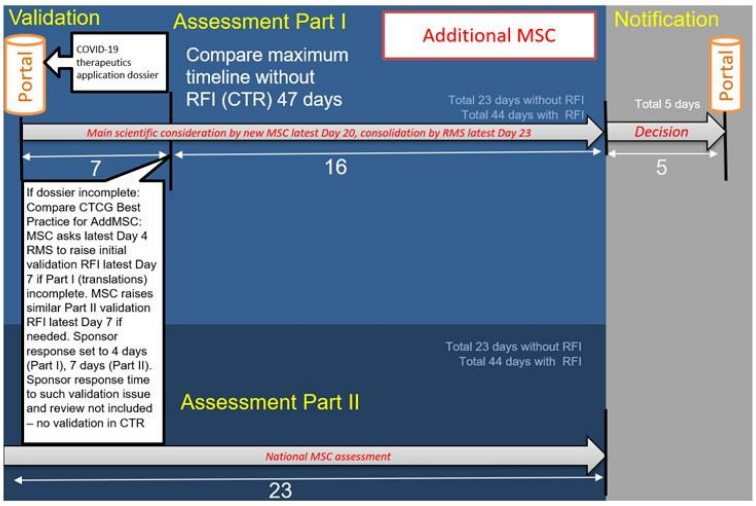
Additional MSC



Tasks for additional MSC:
Check if emergency situation trial (Cover letter, final version of DAR)

Notify RMS in early consideration 'Regulatory – clock-stop' latest Day 4 asking RMS to set up fixed dates expedited timeline for Part I. Any Validation consideration Part I should be sent the same day

Note that the RMS cannot draw up any new consideration, only modify or add a document to a consideration (e.g. attaching a fixed date expedited timetable to consideration raised by the AddMSC)

Also notify the RMS latest Day 4 by e-mail/Eduralink to CTR national contact point at EudraLex volume 10

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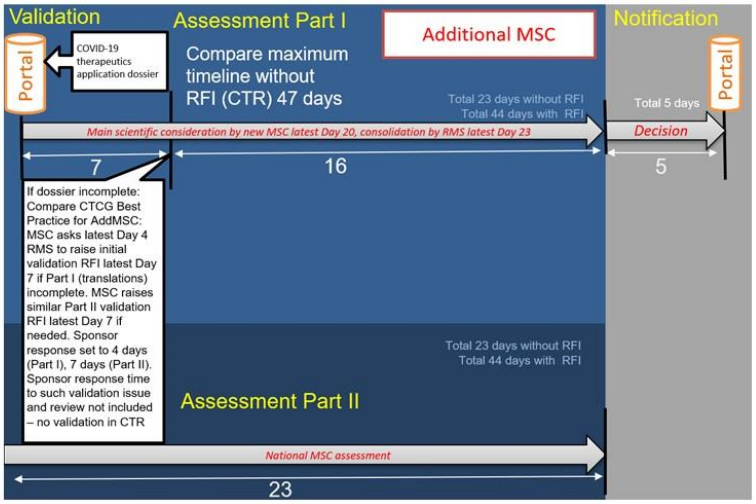
CTR national contact point at EudraLex volume 10

Additional MSC



Task for RMS:

RMS should send any Part I Validation RFI raised by the AddMSC latest Day 7 and require sponsor response latest Day 11

By Day 7 the RMS should also send the fixed dates for the expedited assessment including the main RFI to the sponsor by e-mail/Eudralink (see contact address in application)

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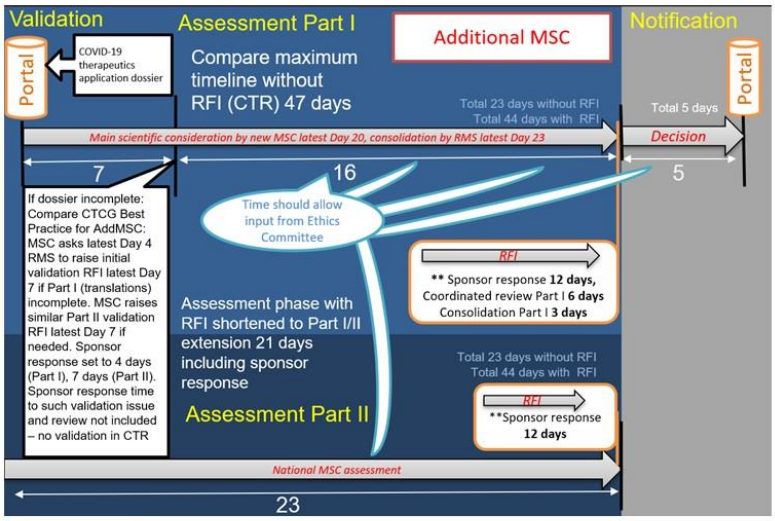
Additional MSC



Any main scientific consideration by AddMSC should be uploaded to CTIS latest Day 20 after the application submission

The RMS consolidates and sends an RFI to sponsor latest Day 23

All MSCs from the initial application have the option to join the coordinated review Part I reviewing the sponsor response

For more details on the procedure, see the CTCG Best Practice on Additional MSC

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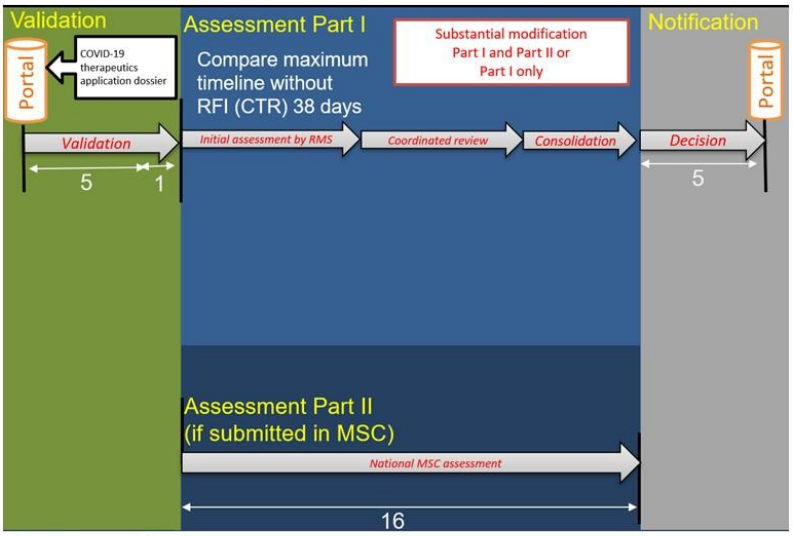
Substantial modification Part I only, Part I and Part II



Substantial modification Part I only or Part I and Part II (to some MSCs)

Part I communication by RMS similar to initial application

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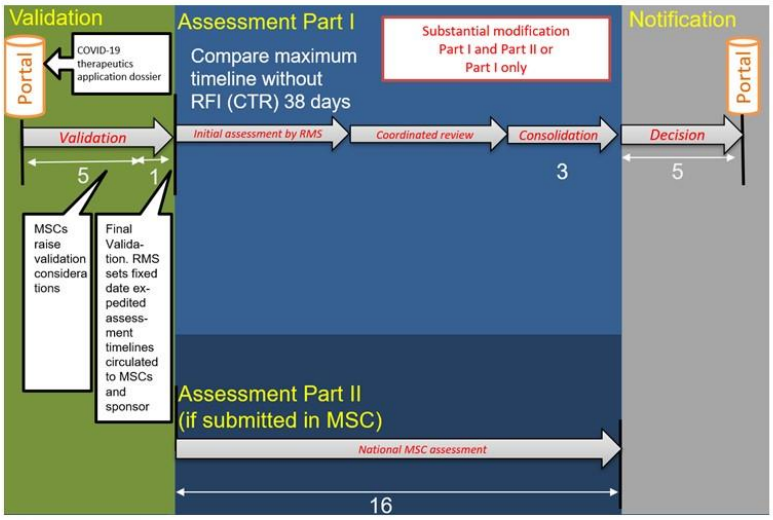
Substantial modification Part I only, Part I and Part II



RMS communicates *fixed dates for expedited assessment subphases for* SM applications including scope Part I

Send e-mail/Eudralink to:

- **CTR national contact point at EudraLex volume 10 and**
- **sponsor (see contact address in application)**

No subphase due dates on weekends or RMS national holidays (Regulation (EEC, Euratom) No 1182/71)

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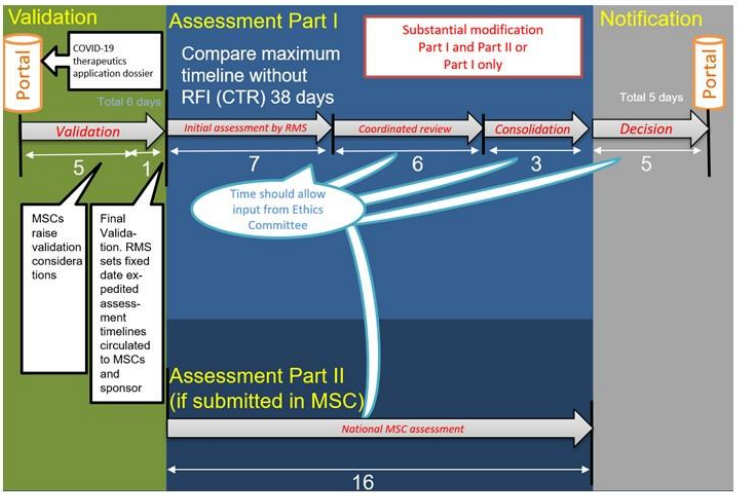
CTR national contact point at EudraLex volume 10

Substantial modification Part I only or Part I and Part II



When the assessment phase starts, RMS should upload the fixed dates subphase due dates Day 1 of the assessment (same as communicated at end of validation – best consideration category 'regulatory' and 'clock-stop' = ensuring that time table is also uploaded to CTIS)

If there are other assessment considerations this consideration will be sent to the sponsor included in the main RFI sent to sponsor Day 16.

If there are no other considerations to the sponsor, the consideration with the expedited assessment timetable should not be sent, since this would prolong the assessment phase

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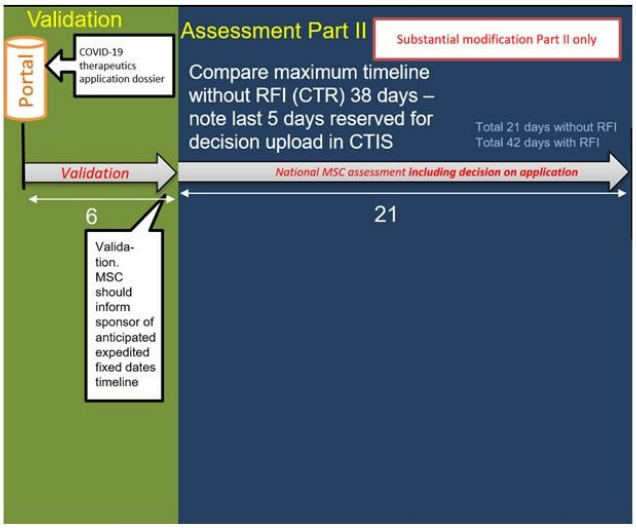
Substantial modification Part II only



SM Part II only – MSC communicates fixed dates for expedited timeline directly to sponsor at end of validation

Note that there is no decision phase (five days) defined in CTR. The last five days of the assessment are set aside for the decision

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CONCLUSION ON CTIS FUNCTIONALITIES RECOMMENDED TO BE DEVELOPED

CTIS lacks important functionalities required for efficient accelerated review of Public Health Emergency trial applications

Workarounds developed in CT-CURE to ensure expedited assessment communication can be used but are burdensome. Solutions below for additional CTIS functionalities have also been endorsed by CTR Collaborate (CTCG, MedEthicsEU Members)

Additional CTIS functionality should ensure	Proposed solution
Necessary overview for MSCs and sponsor of fixed due dates set by the RMS for accelerated assessment subphases	• *add document upload slot when validation finalised* • *allow RMS to set accelerated subphase fixed dates in CTIS for procedures agreed by NCAs and ECs to be expedited*
Additional assessment tasks/notifications and an MSC completion status notification should be generated if a second assessment RFI will be sent to the sponsor to facilitate expedited procedures without validation phase	• *develop functionality generating MSC tasks, notifications and completion status for sequential RFIs sent by the RMS, not only the first one*
Name of Added Member State should appear on tasks and notifications – required for overview by RMS if several Additional MSC procedures overlap or start at the same time	• *add Member State acronym to Additional Member State tasks/notifications*

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