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 investigating the efficacy and safety of novel COVID-19 therapeutics submitted to the Clinical Trials Information System (CTIS) under the Regulation (EU) 536/2014 (here called the Clinical Trial Regulation, CTR) are eligible for inclusion in the joint action CT-CURE under EU4Health.

Novel COVID-19 therapeutics 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 the Technical WP 6 are committed to follow this WP 5 Best Practice.

At the same time, it should be emphasised that the expedited assessment should 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 and 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 submission (both Part I and Part II dossiers, see CTR Articles 6 and 7 as well as Annex I) submitted to at least one MSC
C. Partial submission to other MSCs with later 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 – Version 6 (April 2022) or later updates of this document

[1] In cases where the CT was authorised according to the Directive 2001/20/CE related national legislation, prior transition to CTR according to section 11 in Q&A document in Eudralex vol 10 is needed.

D. Additional MSC submission restricted to those requiring a multinational coordinated review where the Additional MSC raises a consideration and this is sent by the RMS as a Part I RFI to the sponsor 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 modifications to include a novel COVID-19 treatment in a previously authorised platform/adaptive trial, e.g. transitioned to the Clinical Trial Information System.

Trials transitioned, authorised under earlier applicable national laws on clinical trials, e.g. those undergoing the *Voluntary Harmonisation Procedure* of CTFG (Clinical Trials Facilitation and Coordination Group) under HMA (Heads of Medicines Agencies). Note that expedited transitions in CT-CURE are restricted to platform/adaptive trials where a novel Investigational Medicinal Product (defined as described in the introduction to this document) is intended to be added in a substantial modification application, alternative C. below.

Member State Participants of the CT-CURE agree to expedite the assessment by RMS/MSCs, for which alternatives C-D will be considered elements of the CT-CURE-project Technical Work Package 6. Typically, alternative B does not include any assessment beyond e.g. agreeing to categories chosen by the sponsor regarding transparency[2] of trial information for deferring publication but focuses on selecting a Reporting Member State Concerned coordinating future Part I applications, although the Clinical Trial Information System (CTIS) functionality for a new initial application applies for this procedure. The novel COVID-19 therapeutic will be added in alternatives C and D.

A. At least two Member States Concerned (MSCs)
B. Transition of platform/adaptive design 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 Questions and Answers Document - Regulation (EU) 536/2014 – Version 6 (April 2022) or later updates of this document and under CTFG, HMA, Key Documents Best Practice Guide for sponsors of transition multinational clinical trials

[2] EMA/228383/2015

C. Substantial modification applications, e.g. for transitioned platform/adaptive trials, with the intention to add a novel COVID-19 therapeutic in a new treatment arm
D. Additional MSC submission restricted to those requiring a multinational coordinated review where the Additional MSC raises a consideration after adding a new investigational medicinal product (see C above) to the platform/adaptive trial (see CTR Article 14)

Identification of trials suitable for CT-CURE

A. Best practice horizon scanning when sponsor seek rapid central scientific advice on new COVID-19 therapeutics. If agreed by CHMP/SAWP, the organisation seeking central advice should be informed 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, earlier CTFG) in the EMA Pandemic Task Force (ETF) (WP 5 Lead) will share information via secure links among all Affiliated Member States.

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. Rolling reviews or similar step-by-step submissions of trial applications are not possible.

Sponsors are encouraged to i) seek central scientific advice ii) discuss the intended dossier with intended Member States Concerned prior to the application submission in national or simultaneous scientific advices (see above), iii) inform the proposed Reporting Member State as well as all other intended Member States Concerned about the planned submission time, preferably at least two weeks in advance and to submit full Part I and Part II initial applications to all MSCs 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.

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 I). Note that the procedures without a legally defined validation in CTR require this step, which will appear as a less accelerated timeline but is important to allow sponsor to correct mistakes during submission.

Agreed accelerated CT-CURE timelines for RMS and MSC assessment – Table and Graphs

Table 1 Assessment 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)	References to Figures illustrating the respective application assessment subphases	Timeline for CT-CURE expressed as a **percentage** of the Regulation maximum timeline for the Assessment step (with RFI within brackets) (%)
Initial full application Part I and Part II for at least 1 MSC and Partial Part I to the rest**	45 (76)	16 (37 including 12 days for sponsor response)	Fig 1	36% (49%)
Later complementary Part II for initial application	45 (76)	21(42 including 12 days for sponsor response)	Fig 2	47%*** (55%)
Additional MSC restricted to trials with coordinated Part I review on other matters than translations	47(78)	21(42 including 12 days for sponsor response)	Fig 3	45%*** (54%)
Transition of adaptive/platform trials authorised under national law (before regulation)	45 (assessment RFI not anticipated)	5 (assessment RFI not anticipated)	Fig 4	11% (assessment RFI not anticipated)
SM Part I and II or Part I only restricted to trials proposing to add a novel COVID-19 therapeutic treatment arm	38 (69)	16 (37 including 12 days for sponsor response)	Fig 5	42% (54%)
SM Part II only if related to an earlier submitted SM Part I adding a novel treatment arm	38 (69)	16 (37 including 12 days for sponsor response)	Fig 6	55%** (54%)

* Fixed timelines proposed by the RMS during 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. However, 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 Partial initial submission (Part I) does not permit decision before later Part II submission assessment is complete. Sponsors are encouraged to submit full Part I and Part II dossiers to MSCs participating in CT-CURE
*** Procedures without legally defined validation include chance for sponsor to correct application dossier early during assessment. For all other procedures (without **) listed a separate validation procedure is described in the Regulation.

UPDATE FIGs below

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

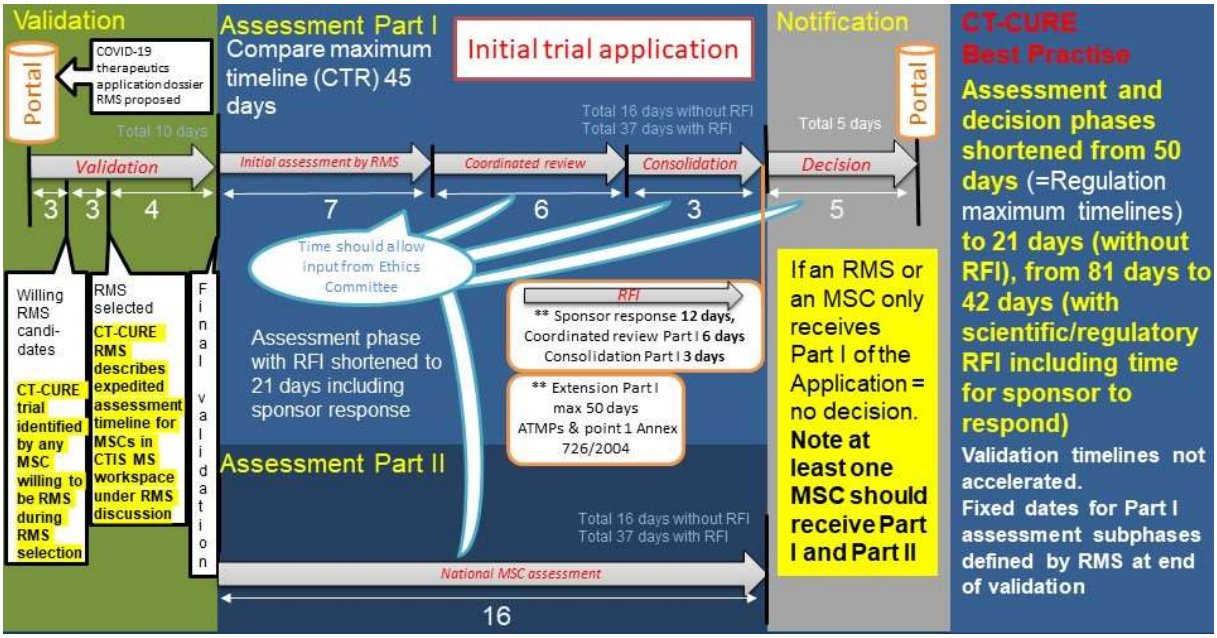


FIG 2 LATER PART II SUBMISSION

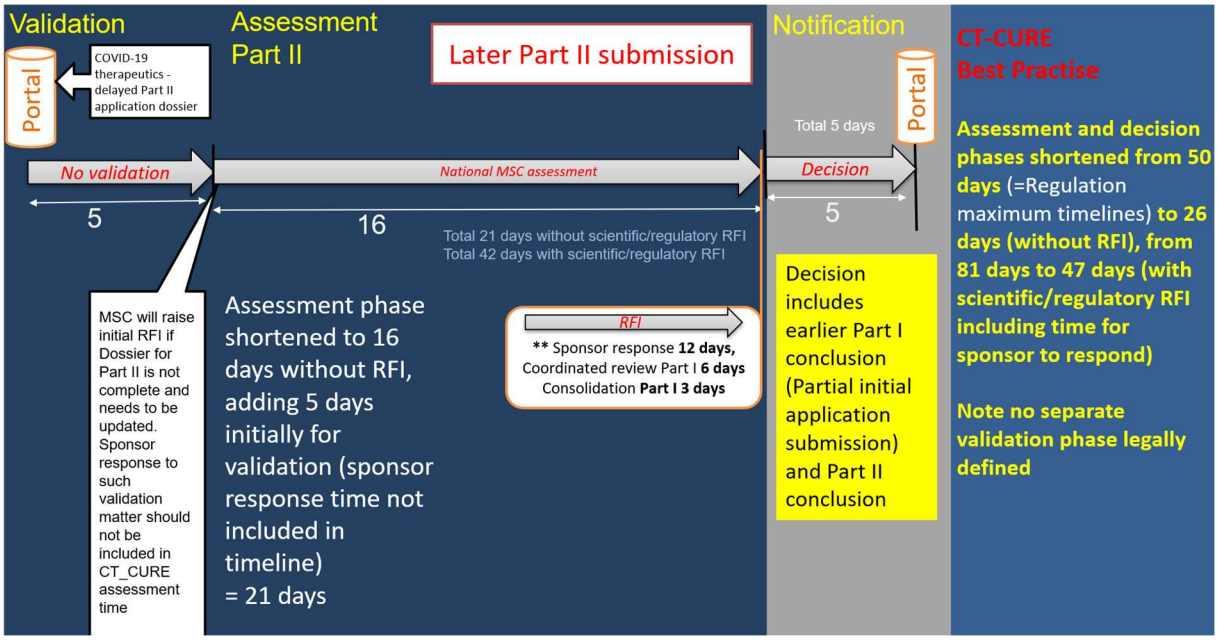


FIG 3 ADDITIONAL MEMBER STATE CONCERNED

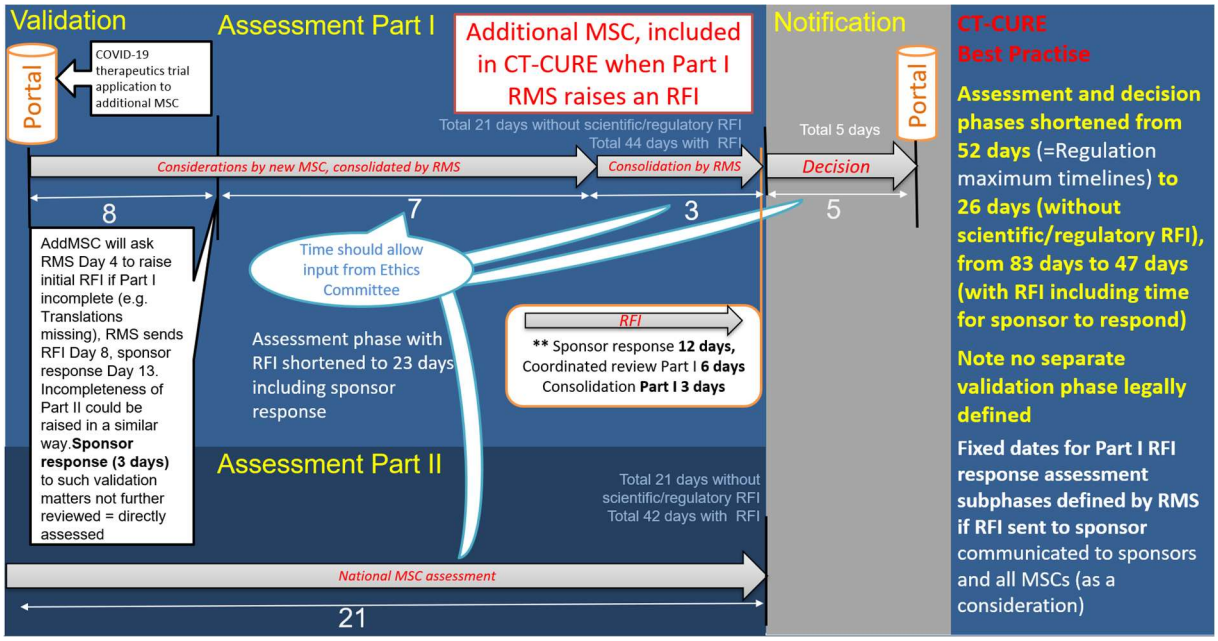


FIG 4 TRANSITION OF TRIALS AUTHORISED UNDER NATIONAL LEGISLATION BEFORE CTR APPLIES

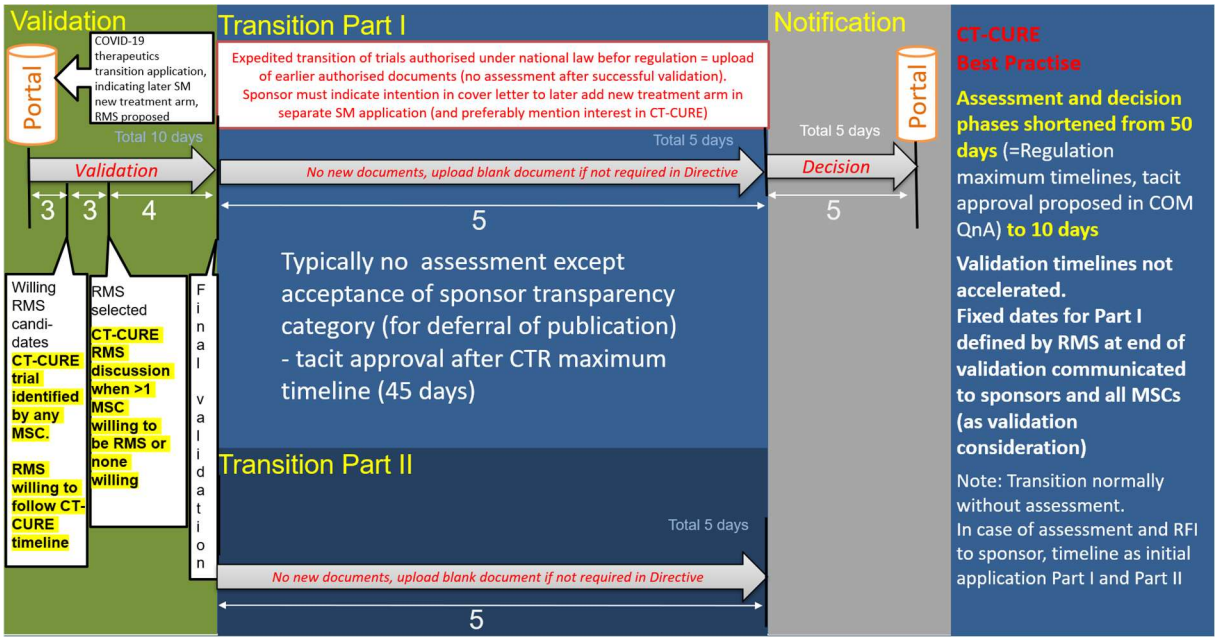


FIG 5 SUBSTANTIAL MODIFICATION PART I AND II AND PART I ONLY

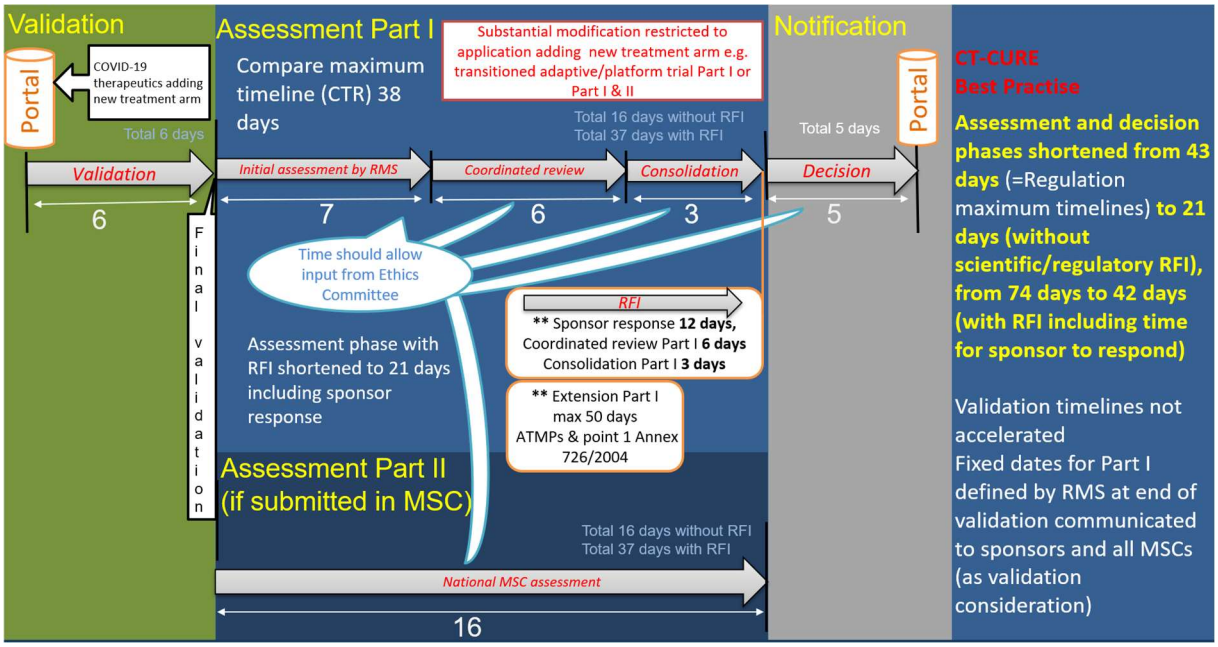
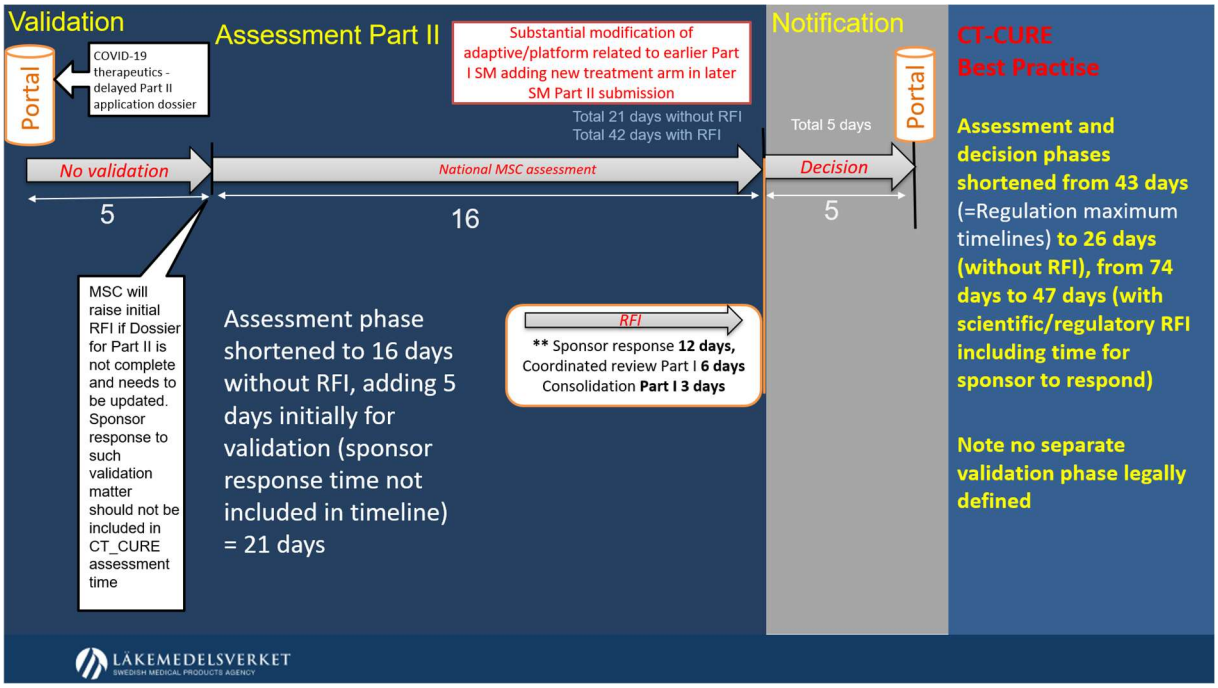


FIG 6 SUBSTANTIAL MODIFICATION PART II ONLY



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 JA will not reach its main objective. 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 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.

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 – new trial application or transitioned trial with a subsequent substantial modification application adding a new IMP to the platform/adaptive trial) 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.

When selecting the RMS, reaching a balanced workshare between CT-CURE Member States for this task should be taken into consideration, in line with the algorithm for worksharing 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 initially as well as applications to additional Member States can only take place after the trial has been authorised by at least one MSC based on a full application submission with both Part I and Part II Dossiers.

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.

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 worksharing 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 (either using the RMS selection discussion free text field or described in a consideration during validation shared with all MSCs)[3]. A fixed timeline specifying the dates for the expedited assessment subphases shown in Figs. 1-6 should be prepared by the RMS and shared with all MSCs. 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 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 Part II dossiers submitted. Taken together, this means that the Validation phase should not be substantially shortened in respect of this first version of Best Practice for CT-CURE.

[3] At a CT-CURE feasibility test in March 2022, it was recommended to communicate via e-mail as well as within CTIS, e.g. documenting regulatory considerations or adding a section to the Introduction of the Draft Assessment Report

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 of Work Package 6 have not 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.

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 want 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 should be shared with representatives in CTCG) and CTEG.

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 would be willing to support the expedition of the assessments of high quality 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 1182/1971 into consideration. This means that no task is due during 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 phase each MSC applies its own national calendar. Another rule for this way to calculate due dates is that each task spanning of 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.

Timelines not possible to follow due to problems with CTIS

As applicable for the EU Portal and Database, 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 possibilities 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 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 a condition of the authorisation if the sponsor cannot provide an acceptable response.

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 CTFG 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. the i) initial assessment phase when the RMS circulates the DAR should end Day 7 after the Validation Date instead of Day 24±2, 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 (Days expressed as time after validation).

All procedures shortened are clarified in the Figs. 1-6.

If the RMS decides to send considerations to the sponsor as a Request for Information (RFI), the maximum timeline for the sponsor's response apply (12 days), but the subsequent assessment of the response 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. Future drafts of this CT-CURE Best Practice could seek further expedited assessment building on the experience gained.

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 submission, this MSC cannot make a decision on the trial before a later 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 a MSC that received the full application for such Part I only initial submissions.

Annex

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 Training Environment.