EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Clinical Trial Life-Cycle Applications, Notifications and Report Submissions

SMEs and Academia Webinar on the EU CTR and CTIS 29-Nov-2021

Presented by:
Maria Elgaard Sørensen, Danish Medicines Agency, CTIS Member State Product Owner
Rüdiger Pankow, Parexel Germany, CTIS Sponsor Product Owner

Origin of materials

The training material in this presentation is derived from material previously prepared by EMA.

Module 19 of the online training programme published on EMA website has been developed in particular for sponsors representing SME and academia with contribution from this group of stakeholders: CTIS for SMEs and academia

Table of contents

Clinical trial life-cycle CTIS data flow

Initial application

Update of an initial application

Notifications

Ad-hoc assessments and requests for opinion on intended corrective measures

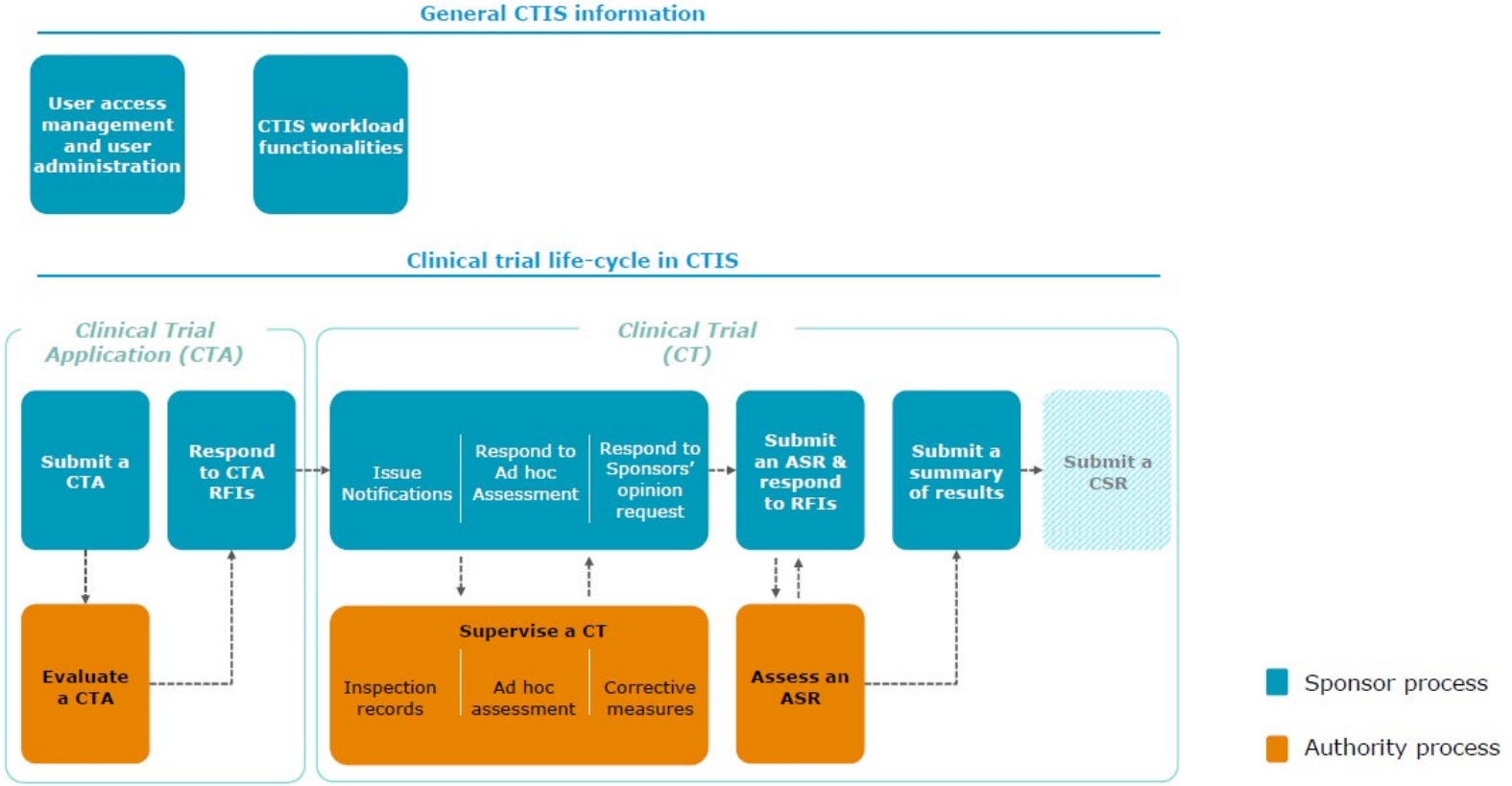
Submission of results

Clinical trial life-cycle CTIS data flow

Clinical trial life-cycle CTIS data flow

EUROPEAN MEDICINES AGENCY

All communication between sponsor and Member States Concerned in the trial occur solely within and via CTIS.

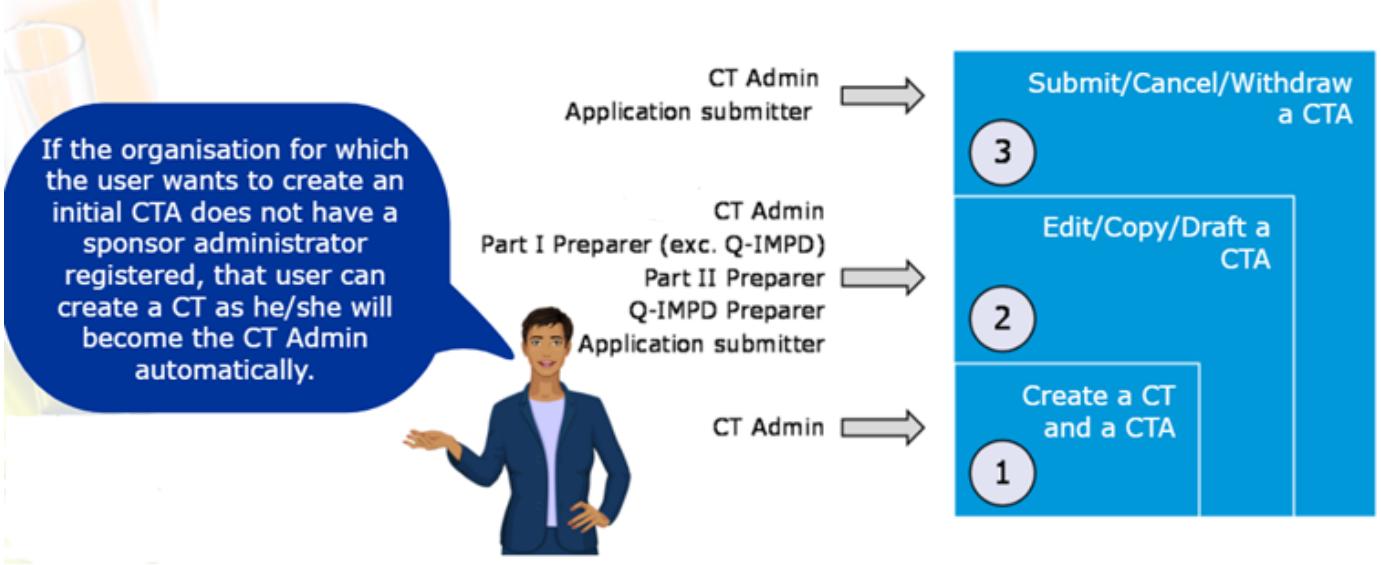


Clinical trial life-cycle CTIS data flow

EUROPEAN MEDICINES AGENCY

Actors must be logged into CTIS to receive notices and alerts and perform tasks according to their user role permissions.

The CT admin is the only role able to create a CTA and all the subsequent applications. Five roles are involved in the edition and drafting of the CTA, and only two roles can submit or cancel a draft CTA and withdraw it after it has been submitted.



Initial application

Content and structure of the CTA dossier

The application dossier consists of multiple sections.
Article 26 'Language requirements': " The language of the application dossier, or parts thereof, shall be determined by the Member State concerned."

Form: set the trial category and define the timelines for the publication of data/documents

MSC: choose the Member States Concerned (MSC)

Part I: contains data/documents, subject to common assessment led by the Reporting Member State (RMS) in collaboration with the MSC

Part II: contains data/documents, of pertinence of the individual MSC assessment

Evaluation: section where sponsor users can access RFI and conclusions on the assessments done by the RMS/MSC including the assessment reports for part I and part II and the decision

Timetable: projection on the timelines for evaluation of the application

Source database for organisations in the trial

EUROPEAN MEDICINES AGENCY

Details of any organisation captured in CTIS are retrieved from EMA's Organisation Management System (OMS) – therefore it is important that sponsor users submit the desired information in OMS first, so that they can use it in CTIS.

- Data for organizations associated to the trial must be preregistered records
  - **Trial sponsor** provided at the time of the creation of the initial application
    - **Note: If the organisation does not exist in OMS it cannot become a main sponsor for a new clinical trial**
  - **Legal Representative,** any **co-sponsor** and **third parties** to whom tasks have been delegated and specify those tasks
  - **Trial site(s) details**, where the trial is going to be conducted per MSC
    - **Note: If a trial site is not in OMS the user can still create a new record in OMS at the time of completion of the CTA and progress with the submission of the application**

Source database for products in the trial

Details of any medicinal product captured in CTIS are retrieved from the Extended EudraVigilance Medicinal Product Dictionary (XEVMPD) – therefore it is important that sponsors users register the desired information in XEVMPD first

- Data on medicinal products used in the trial must be preregistered records
  - All data for **medicinal product(s)** used in the trial as test / comparator / auxiliary / placebo are derived from preregistered records in **XEVMPD**
    - **Exception: Placebo products may be manually entered directly in the application dossier in CTIS**

Submission of a clinical trial application

EUROPEAN MEDICINES AGENCY

For a multinational clinical trial sponsor proposes Reporting Member State (RMS) and has the option to submit part I and II together (article 5) or limited to part I and subsequently part II (article 11)

- For multinational clinical trial sponsor proposes Reporting Member State (RMS)
- The initial application can be submitted by two approaches:
  - Full initial: all the MSC receive part and part II (Article 5)
  - Partial initial: all MSC receive part I and some, or none, of the MSC receive part II (Article 11)
  - The outstanding part II for the MSC shall be submitted by the sponsors within 2 years from the reporting date

Application evaluation

During application evaluation the RMS and MSC may raise one or more requests for information (RFI) during each evaluation phase (validation, assess part I, assess part II) and each of those may have different timelines

- RMS may raise RFI at the time of validation and for part I assessment
- MSC may raise an RFI for part II assessment (and validation for SM part II)
- If an RFI response requires a change in the application dossier, a new version of the dossier will be created and submitted with the RFI response
- Where sponsor does not respond within the timeline, the application will be deemed lapsed

Timelines and due dates in CTIS

Calculation of due dates are based on the rules defined in the Euratom Regulation (EEC, EURATOM) No 1182/71 OF THE COUNCIL of 3 June 1971 determining the rules applicable to periods, dates and time limits

- CTIS Time Zone – Central European Time (CET)
- Start of task timer – 00:00:01 of next calendar day following the creation of a task
- End of timer – 23:59:59 on the due date day, but **cannot fall on a Saturday or Sunday**
- CTIS allows for one or more **Request(s) For Information (RFI)** to be raised during each application evaluation phase, i.e. validation, assess part I, assess part II
- Irrespective of the number of RFI raised, the extension of the timelines for each evaluation phase will only occur once
- Sponsors can be given a timeframe to reply to an RFI shorter than maximum one stipulated in the Regulation but of at least one day

If a timeline for responding is not met, the application will lapse

Update of an initial application

Substantial modification (SM) applications

EUROPEAN MEDICINES AGENCY

Business situation when to select this application type

- **Change** to any aspect of the clinical trial **likely to have a substantial impact on the safety or rights of the subjects or reliability and robustness of the data** (Article 2 (13))
  → Examples see EudraLex Volume 10 Chapter V Q&A
- Addition of a **new clinical trial site** or **change of a principal investigator** (Article 15)
- Extension to **start trial recruitment in an MSC beyond 2 years** (Article 8 (9))
- **Request restart for temporary halted trial** for reasons of subject safety and/or benefit-risk balance (Article 38 (2))
- Extension to **restart temporary halted trial in a MSC beyond 2 years** (Article 37 (7) and 38 (2))

Non-substantial modifications (NSM) acc. Article 81.9

EUROPEAN MEDICINES AGENCY

Business situation when to select this application type

- **Changes to the clinical trial** which are **not substantial modifications** but are **relevant for the supervision** of the clinical trial **by the Member States concerned** (Article 81 (9))

- Not in scope of this functionality are changes **to the clinical trial** which are **not substantial modifications <u>but not</u> relevant for the supervision** of the clinical trial **by the Member States concerned** (Article 81 (9))
  → These should be included as non-substantial changes in the next substantial modification application dossier

Additional MSC applications (AM)

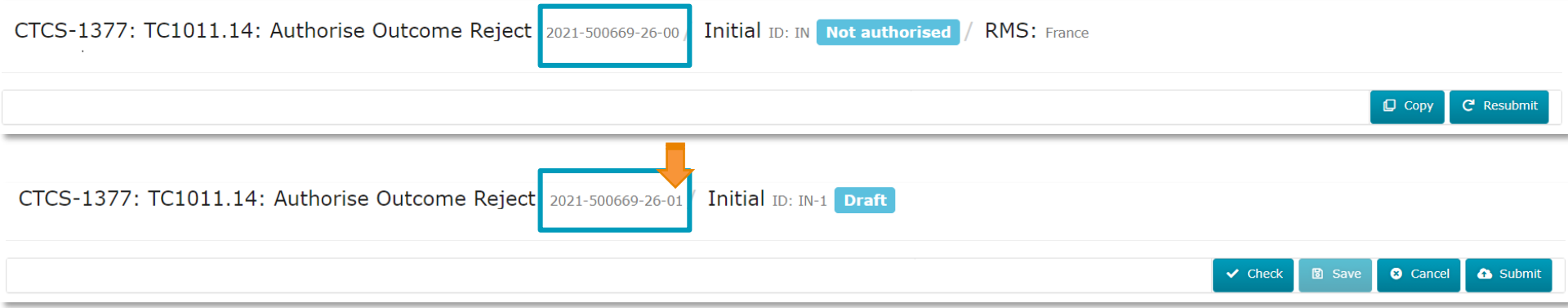
Business situation when to select this application type

- **New MSC not concerned** in the initial request for authorisation
- **Reinclude MSC** for which initial application or additional MSC application was **withdrawn** or **lapsed**, or **not authorized**
- **Reinclude MSC** for which **trial authorisation expired**, i.e. start of recruitment for that MSC not within 2 years after clinical trial authorization date

Resubmission

The resubmission allows the sponsor to submit a new application for authorisation as a new clinical trial, when the initial application has lapsed or been withdrawn entirely, or the authorization refused by all Member States Concerned. The last two digits of the EU CT number denote the resubmission number for such clinical trial.

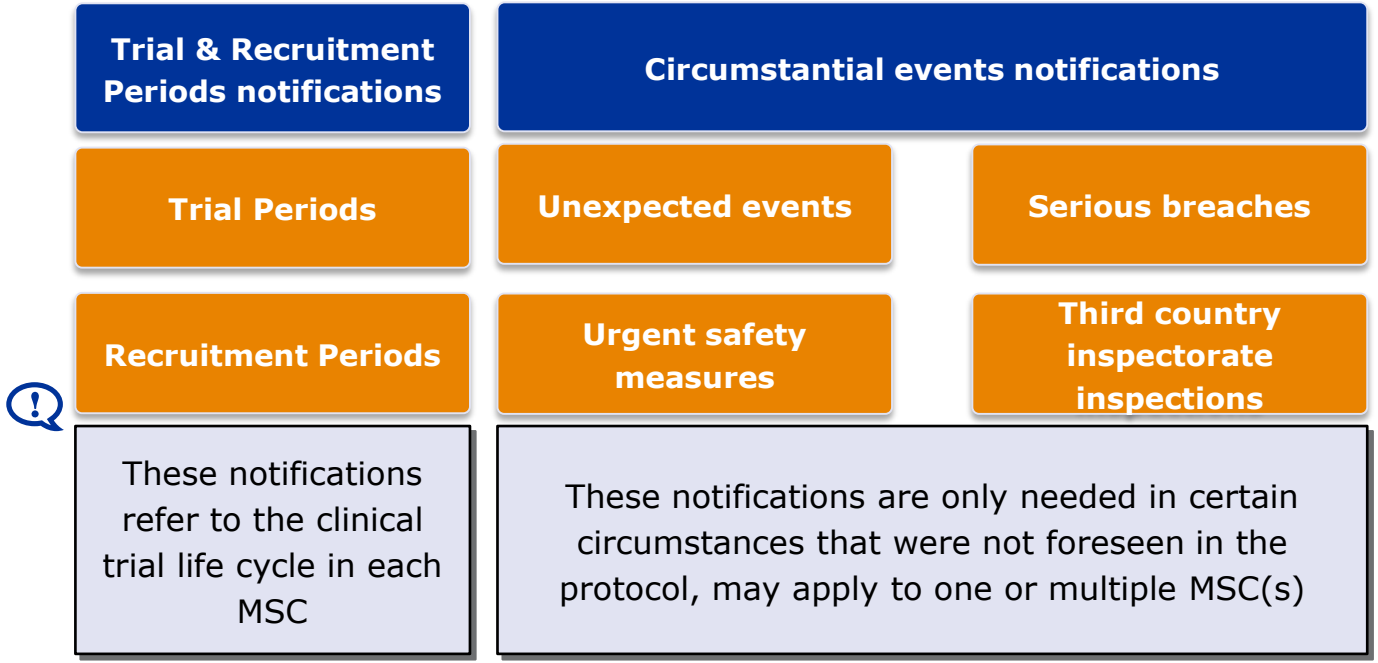
- **Initial application** or latest resubmission of the initial application **withdrawn, lapsed, or not authorized in <u>all</u> Member States concerned**



Notifications

Notifications

Notifications allow sponsors to notify MSC(s) of relevant events during a clinical trial life cycle. Those events can be classified in two main groups.



Trial & recruitment periods

EUROPEAN MEDICINES AGENCY

Start trial

The first act of recruitment of a potential subject for a specific CT

It could be the date of initiation of the clinical trial in the first site, or the date when the first trial specific advertisement is published

Start recruitment

The first visit of the first subject.

Recruitment shall begin within 2 years from trial authorisation

To extend start recruitment beyond 2 years, substantial modification requires to be authorized before initial timeline expires

End recruitment

The act of not recruiting subjects anymore in a MSC

End trial

The last visit of the last subject, or a later point in time as defined in the protocol

*Includes **also early terminations** and whether related to a matter of subject safety and/or benefit-risk balance, or not*

Trial & recruitment periods

Temporary halt

An interruption not provided for in the protocol of the conduct of a trial by the sponsor with the intention to resume it

There are two types depending if the temporary halt is related to subject safety and/or benefit-risk balance, or not

A halted trial is automatically ended if not restarted within 2 years

For an extension to restart the halted trial beyond 2 years, substantial modification requires to be authorised before initial timeline expires

Restart trial

The act of restarting the trial after a temporary halt, or after suspension of the trial by an MSC

If temporary halt is related to subject safety and/or benefit-risk balance, a **prior substantial modification must be submitted and authorised** to enable notification

Restart recruitment

The act of restarting the recruitment of subjects

The trial must be restarted to enable restart the recruitment notification

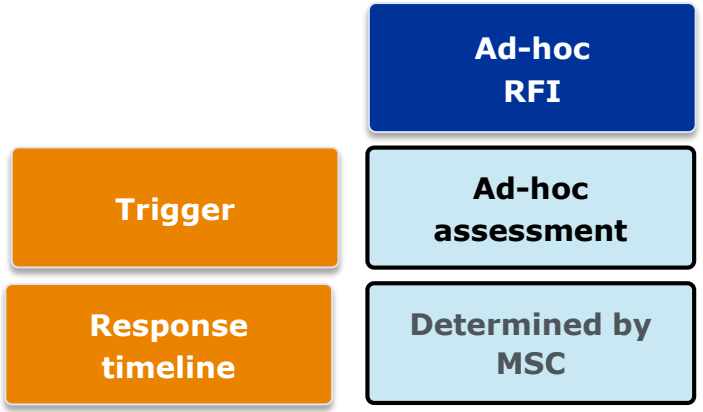
Ad-hoc assessments and requests for opinion on intended corrective measures

Ad-hoc assessments

Ad hoc assessments enable the MSC(s) to assess information relevant to the supervision of the trial. They may be triggered upon different situations as outlined and may require additional information from the sponsor via ad-hoc RFI(s). When submitting a response to an ad-hoc RFI the sponsor neither submit updates to the clinical trial dossier, nor update the notification that has caused the ad-hoc assessment.

Ad-hoc assessment related to a notification
e.g. temporary halt, serious breach, unexpected event or urgent safety measures.

Ad-hoc assessment related to other aspects of a CT
e.g. safety submission made for the same or another CT using the same medicinal product, etc.

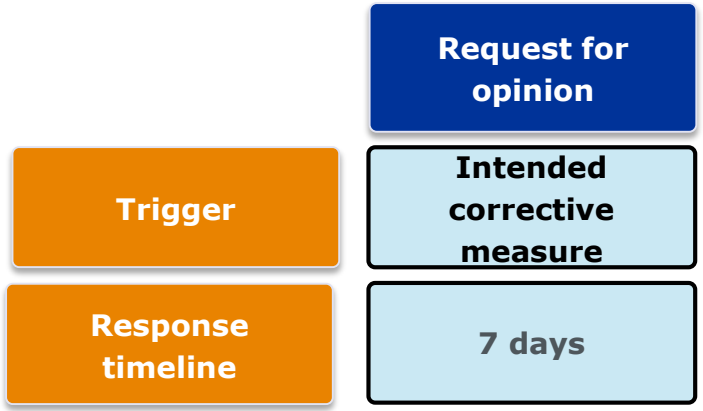


Request for opinion on intended corrective measure

Where an MSC has justified grounds according to article 77 of Regulation (EU) 536/2014 they may take corrective measures. Unless where immediate action is required, the MSC must ask the sponsor and/or investigator for their opinion before taking (applying) the corrective measure. Based on sponsors response, the MSC may then decide to cancel the intended corrective measure or apply the corrective measure.

Intended corrective measure

Request for sponsor opinion before an intended corrective measure to ***require modification***, ***suspend the clinical trial***, *or* ***revoke authorization*** *is applied*



Submission of results

Submission of results

Sponsors have an obligation to submit results, lay summaries of results and (where applicable) a clinical study report for the clinical trial

- Intermediate data analysis
  - Within 1 year after intermediate analysis date
- Summary of Results / Summary of Clinical Trial Results for Laypersons
  - Within 1 year after end of trial in EEA (or after global end of trial if justified in protocol)
  - Within 6 months for trials under PIP and including paediatric trial subjects
- Clinical Study Report (CSR)
  - to all MSC
  - Within 30 days after the marketing authorization has been granted, the procedure for granting the marketing authorization has been completed or withdrawn

Any questions?

Further information

emaevents@diaglobal.org (CTIS sponsor Master Trainer programme)
CT.Sponsortraining@ema.europa.eu (general queries on other (sponsor) training)

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Telephone +31 (0)88 781 6000
Send us a question Go to www.ema.europa.eu/contact

Follow us on **@EMA_News**