Guidelines for Submitting a Clinical Trial in the Clinical Trial Information System (CTIS)

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ABBREVATION LIST

AE	Adverse Event
ACT EU	Accelerating Clinical Trials in the EU
ATMP	ATiMP Advanced Therapy Investigational Medicinal Product.
AxMP	Auxiliary Medicinal Product
CCI	Commercial Confidential Information
CT	Clinical Trial
CTA	Clinical Trial Application
CTAG	Clinical Trials Coordination and Advisory Group
CTCG	CTCG Clinical Trials Coordination Group
CTD	Clinical Trials Directive
CTEG	Clinical Trials Expert Group
CTIS	Clinical Trials Information System
CTR	Clinical Trials Regulation
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GDP	Good Distribution Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
MS	Member State
MSC	Member State Concerned
RFI	Request for Information
RMS	Reporting Member State
XEVMPD	eXtended EudraVigilance Medicinal Product Dictionary

Clinical Trials with Medicinal Products

National or multinational: general information

- The Clinical Trials Regulation (CTR) applies to both national and multinational clinical trials.
- National trials are assessed by the Member State (MS) where the trial is conducted.
- Multinational trials involve coordinated assessment by all Member States where the trial is conducted.
- Multinational trials can start as national trials and add more Member States later via the "Addition of MS" procedure, which can only begin after authorization in at least one Member State.

One Application:

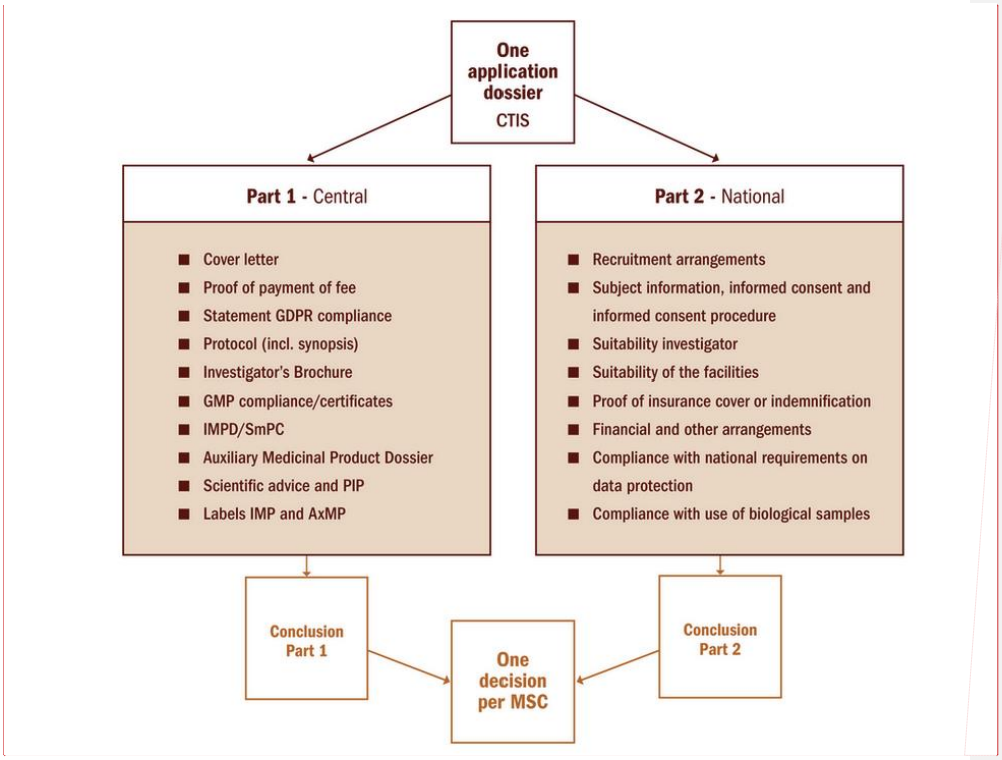
There is one single point of entry for all clinical trials conducted in the EEA: **the Clinical Trial Information System (CTIS).** The clinical trial application consists of part I (same documents for all MSC) and part II (national documents per MSC).

In case of **multinational clinical trials**:

- The application consists of Part I (common documents for all MSC) and Part II (national documents per MSC).
- Part I is jointly assessed by all MSC with a single conclusion valid for all MSC, coordinated by a Reporting MS (RMS).
- Part II is assessed nationally with conclusions valid only in the specific MS.

A **national clinical trial** application also consists of a part I and a part II and is assessed by the MS concerned. This Member State is the RMS for this clinical trial by default.

See figure below for an overview of the Part 1 and Part II components:



Commenté [ST1]: à**Part I** consisting of trial details à**Part II** consisting of clinical trial site details and placeholders for documents part II (recruitment arrangement, informed consent form, CV for principal investigator etc.).

Part I *consisting of trial details;* ***Part II*** *consisting of clinical trial site details and placeholders for documents part II (recruitment arrangement, informed consent form, CV for principal investigator etc.).*

Clinical Trial Information System (CTIS)

The CTR requires a single-entry point through CTIS for all clinical trials in the EU/EEA.

Information and access to CTIS are available on the EMA website, which also offers a comprehensive training program for CTIS users, including guidance, instructions, videos, and FAQs: Go to CTIS training programme *(Find also a Guide to CTIS Training Catalogue can be found and help you to organize your training :* Training Catalogue)

Sponsors should carefully assess the pertinence and feasibility of the planned CT. The protocol and the rest of the CT dossier should be prepared, an insurance/compensation should be in place and the safety surveillance and capability for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting to EudraVigilance should be organized.

To be prepared for submitting applications and notifications via CTIS, sponsors are advised to check the training modules for CTIS.

Registration CTIS

An EMA account is required to access the CTIS sponsor workspace.

Users of other EMA applications (Eudralink, SPOR, IRIS, Eudravigilance, OMS) can use the same EMA account. New users must create an EMA account through self-registration (The self-registration process is described in module 03 of CTIS training material catalogue).

To access the CTIS sponsor workspace, a user will need to have an EMA account.

Organizations have to be registered in the organisation management system and medicinal products have to be registered in the medicinal product dictionary (see more details below).

!!!! Make sure that 'Scientific Contact Point' and 'Public Contact Point' in the section sponsor are completed, otherwise the application will not pass the final check on submission application in CTIS.

How to register additional users to one study (provide access to multiple users within one study)

You can register at EMA with the following link:
https://register.ema.europa.eu/identityiq/help/selfregister.html

After registering, you receive an email with your account name. Using this name, you can log in to the CTIS workspace.

To ask for permission to a study, see CTIS – M07 How to request roles and how to assign roles to registered users in CTIS - YouTube

- You need to obtain 3 items from a colleague that should give you access:
  1. Trial number (that is a 14 numbered code)
  2. Name organization
  3. Organization ID
- You can choose the required role for yourself (usually CT admin).

After you've submitted your request, the colleague who has access to the study in CTIS has to grant you permission to access the study. As confirmation, you will receive an email.

Medicinal Product Registration

Before completing the clinical trial application in CTIS, the sponsors of clinical trials should ensure that the details of the medicinal products used in the clinical trial are already registered in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD). The dictionary includes all medicinal products that are authorised in the EU/EEA and also development products that are associated with clinical trials.

A placebo can be added manually without resorting to a registration in XEVMPD necessarily.

For each trial in CTIS, the sponsor has to associate at least one test product. Other product types that can be associated in CTIS are: comparator, placebo and auxiliary medicinal product.

In CTIS, the product information is retrieved from XEVMPD and this is enabled by a search and selection process for an authorised product (product with a marketing authorisation from the EU/EEA), development product, an active substance or an ATC code.

For more information, see CTIS training module 10 including video: CTIS – M10 How to submit an initial CTA in the CTIS – Fill in the Product details of Part I section. See also chapter 5 of the CTIS Sponsor handbook on "Product management in CTIS".

Structure research dossier in CTIS

The application dossier consist of a Part I and a Part II. The list of required documentation and information is set out in Annex I of the CTR.

!!! Documents should be searchable and titled according to the structure in CTR Annex I (Use the codes and filenames as given in the Document codes and titles in CTIS).

In the document Instruction on uploading, naming and changing documents in CTIS is specified how to change your clinical trial application in CTIS if an RFI requests new documents or document changes (Also, see CTTM11 - Step-by-step guide (europa.eu) on how to respond to a RFI)

Commenté [vdWM(2)]: Also, see CTTM11 - Step-by-step guide (europa.eu) on how to respond to a RFI

Completion Process – Section Form and MSC

CTIS contains two sections (Form, MSC) that must be completed for an initial application.

Form:

- **Cover letter:** Placeholder to upload cover letter (Templates available: OpenDocument Text Format; PDF Format)
- **Proof of payment of fee:** for clinical trials with medicinal products that are conducted entirely or predominantly without influence from pharmaceutical companies (non-commercial trials)* and for commercial phase I trials. Non-commercial clinical trials are exempt from fees for initial applications and substantial modification requests to national regulation (please refer to national support initiatives (map) to guide you in this process)
- **Compliance with Regulation (EU) 2016/679:** Placeholder to upload statement; A statement by the sponsor or his or her representative that data will be collected and processed in accordance with the GDPR shall be provided. The application does not require a signed Statement GDPR compliance. If a signed version is submitted (unredacted version, not for public disclosure), an unsigned version must also be submitted (redacted version, for public disclosure).
- **Deferral publication date:** Trial category 1,2 or 3 has to selected for the publication date of trial information, including a justification for the selected category (see transparency rules). Deferral of publication date is possible by indicating a new publication date.

Research dossier Part I

Please refer to The Central Committee on Research Involving Human Subjects (CCMO) website for guidance and documentation (templates for each document to provide are available) : https://english.ccmo.nl/investigators/clinical-trials-with-medicinal-products-ctr/preparation-ctr/research-dossier-part-i

Research dossier Part II

Please refer to The Central Committee on Research Involving Human Subjects (CCMO) website for guidance and documentation (templates for each document to provide are

available): https://english.ccmo.nl/investigators/clinical-trials-with-medicinal-products-ctr/preparation-ctr/research-dossier-part-ii

Submitting and assessment

Proposal for reporting Member State

The sponsor proposes a Member State to act as reporting Member State (rMS).

In case of a low-intervention clinical trial where the use of the IMP is evidence based, the sponsor shall propose a MS concerned (MSc), where the use is evidence-based, to act as rMS.

Timelines

Strict timelines are enforced, with each phase (validation, assessment, decision) having specific limits (follow the rules as set in Regulation 1182/71). This means that the due date can never fall on a weekend day or an official holiday. Neither can a time period be shorter than two consecutive working days. For multinational trials, official holidays of rMS and/or MSc are taken into account depending on the hard task of rMS/MSc . The timelines are visible in CTIS.

Christmas clock stop: The Christmas clock stop is observed between December 23 and January 7 for all trials. There are no other clock stops within the procedures.

Withdrawal

The sponsor has the option to withdraw an application for a clinical trial until the decision is made.

In cases of withdrawal of an application before the reporting date of part I, the withdrawal will apply to the entire application in all MSc. After the reporting date, but before the decision is taken by a particular MSc, the sponsor has the option to withdraw the application in one, two or all MSc. Once the decision regarding an application is taken, a sponsor no longer has the possibility to withdraw the application.

After a withdrawal has taken place, resubmission is possible. A resubmission is also possible following the refusal to grant an authorization.

If a clinical trial does not start and the sponsor decides not to carry out the clinical trial in a MSc, the application will expire after 2 years from the date of decision. Otherwise, once the

clinical trial has been started, it may be an early termination if the clinical trial does not proceed.

Validation phase: general information

The maximum period for the validation phase is **25 days** including 15 days for the MS (10 plus an additional 5 in case of the rMS requests for information), and 10 days for the sponsor to complete the application dossier.

During the validation phase, the rMS is selected for multinational clinical trials (see more details below). If a MS does not meet its time limits, there will be a tacit approval (the clinical trials fall within the scope and the application dossier is complete). If a sponsor does not meet its time limits the application auTomatically lapses.

The procedure of selection of a rMS in a multinational clinical trial is not fully presented here. See for complete procedure CTIS training module 6 Selection of reporting Member State (RMS) and validation of the clinical trial application.

Selection of reporting Member State

For a national clinical trial, the reporting Member State (rMS) is the MS to which the clinical trial application is submitted. For multinational trials, the sponsor proposes a rMS but it is up to the MSc to express their willingness to become rMS during the first 3 days of the application.

Between day 3 and 6 the selection of the rMS takes place among the MSc willing to be rMS. If more than one MSc is willing, the MSc with the lowest workshare proposes a candidate rMS (from the pool of willing MS). The workshare is primarily based on an algorithm of work sharing taking into account the number of multinational clinical trials where the MS acts as a rMS and the total number of multinational clinical trials where the MS participates. If no MSc is willing to be rMS, the MS proposed by the sponsor will be the rMS or may propose another MS to be rMS.

The CTR does not provide for a procedure to change the rMS. However, it may be possible for a rMS to delegate/contract out the work to another MSc, but the responsibility will still lie with the original rMS.

Validation

The rMS will validate whether the clinical trial falls within the scope of the CTR and whether the application dossier is complete

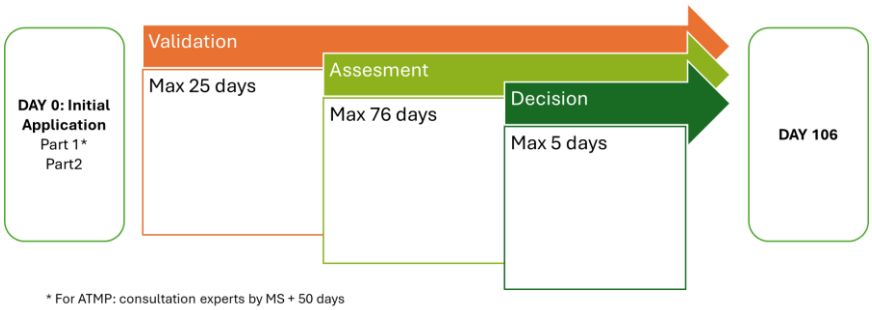
If the rMS has not notified the sponsor within the timelines set, the application will be tacitly valid. If the sponsor has not replied within the timeline set, the application will automatically lapse.

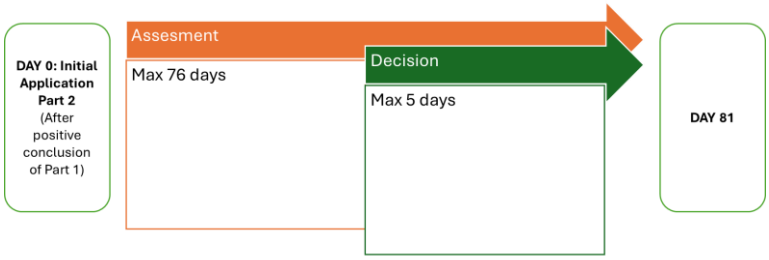
Validation date: The validation date is the date on which the sponsor is notified about the conclusion of the validation phase or in case the sponsor is not notified the last day of the validation period.

Assessment phase

The assessment period starts from the date of validation and depends on the type of application.

The timelines for the assessment of part I and part II are similar except in case of clinical trials involving ATMPs, the rMS can extend the assessment period by an additional 50 days for consulting with experts *(see more details below "Extended assessment")*;

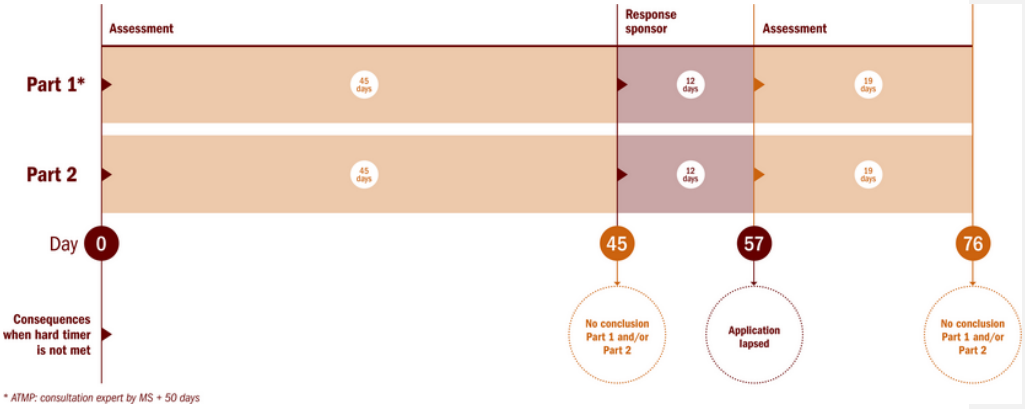




Maximum assessment time is 45 days, extendable by 31 days for additional information requests (12 days for the sponsor and 19 days for the MS) in case the rMS send a request for information (RFI). The sponsor shall submit the requested additional information within the period set by the rMS (maximum 12 days).

The rMS can send multiple RFI to the sponsor as long as the maximum timeline is not exceeded. This means that during the initial 45 days multiple RFI can be submitted trough CTIS at any time. However, the aim is to have only one RFI for a clear and transparent process.

If a MS does not meet its timelines for the part I assessment there is no assessment report and no conclusion on part I. This means that no MS can take a decision. In that case, the sponsor has to resubmit its application dossier. If a sponsor does not meet its timelines the application will automatically lapse.



Multinational clinical trials

For multinational clinical trials, the 45 days of the assessment of part I is divided into three phases:

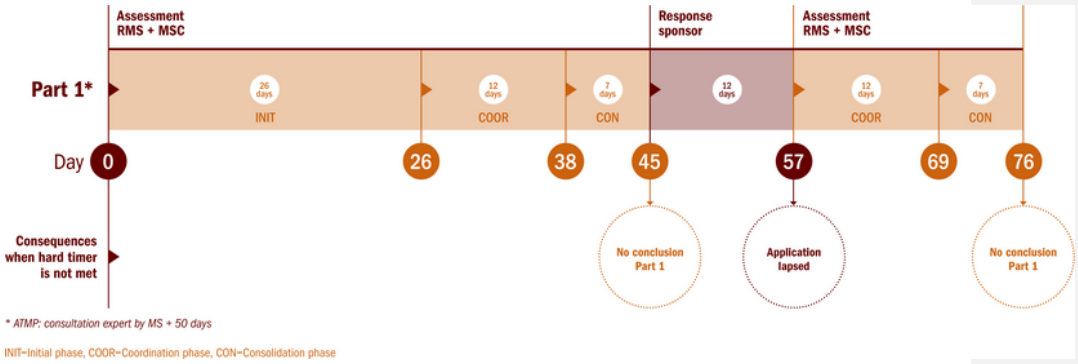
- An initial assessment phase performed by the rMS (max 26 days);
- A coordinated review phase involving all MSc (max 12 days);
- A consolidation phase performed by rMS (max 7 days).

In case of RFI, the sponsor has maximal 12 days to respond on the RFI. The additional information is reviewed by all MSc. The 19 days review are divided in two phases:

- A coordinated review phase involving all MSc (max 12 days);
- A consolidation phase performed by rMS (max 7 days).

MSc can submit their considerations via CTIS within the timeline set of the coordinated review phase. These considerations have to be taken into account by the rMS. The rMS finalises the assessment report part I and distributes the report together with its conclusion via CTIS. The date on which the final assessment report Part I is submitted to the sponsor and the MSc is the reporting date.

The MSc finalises the assessment report part II for their MS and distibutes the report together with its conclusion via CTIS.



Extended assessment

For clinical trials involving **advanced therapy investigational medicinal products*** or **medicinal products*** allows the rMS to extend the assessment period for part I by an additional **50 days**, for the purpose of consulting with experts. However, the extension of the timelines for the assessment of part II is not provided for by the legislation.

** These are medicinal products developed by means of one of the following biotechnical processes:*

- *Recombinant DNA technology;*
- *Controlled expression of genes coding for biologically active proteins in prokaryotes amd eukaryotes including transformed mammalian cells;*
- *Hybridoma and monoclonal antibody methods.*

Conclusion, decision and appeal

Each member states draws separate conclusions for part I and II. After both conclusions, a decision is taken.

Decision

Each MS makes separate conclusions for Part I and Part II (within five days from the reporting date or from the last day of the assessment part II), leading to one of the following decisions:

- The clinical trial is authorized;
- The clinical trial is authorized subject to conditions*;
- The clinical trial is refused.

** An authorization of a clinical trial subject to conditions is restricted to conditions which by their nature cannot be fulfilled at the time of that authorization, e.g. submission of the minutes of the Data Safety Monitoring Board meetings*

In case a MSc does **not submit** the decision in CTIS within 5 days, then a **tacit Decision** will automatically be generated:

- If both part I and II conclusions are acceptable or acceptable with conditions, the application is automatically **authorized**.
- If part I conclusion is acceptable or acceptable with conditions and part II conclusion is not acceptable or lacking, the application is automatically **authorized**.
- If part I conclusion is not acceptable and part II conclusion is acceptable or acceptable with conditions, not acceptable or lacking, the application is automatically **not authorized**.

If part I conclusion is lacking and part II conclusion is acceptable or acceptable with conditions, not acceptable or lacking, the application is automatically still under evaluation.

Appeal

Appeals against refusals can be made to an administrative court.

For detailed procedures, please refer to the CTIS training modules and relevant sections of the CTR and EMA guidelines.

Modifications during the trial, after approval

During the trial, the sponsor may modify the clinical trial. It is up to the sponsor to decide whether a modification is to be regarded as substantial or not, based on the definitions given in the CTR.

Substantial or non-substantial?

A substantial modification (SM: is defined as "any change to any aspect of the clinical trial which is made after notification of a decision referred to in Articles 8, 14, 19, 20 or 23 of the CTR and which is likely to have a substantial impact on the safety or rights of the subjects or on the reliability and robustness of the data generated in the clinical trial". Modifications to a trial are regarded as 'substantial' when they are likely to have a significant impact on: the safety or rights of the subjects and/or the reliability and robustness of the data generated in the clinical trial. For information on the documents that need to be uploaded for a SM, see Annex II of the CTR and the CCMO website.

A non-substantial modification: is a modification without substantial impact on the safety or rights of the subjects and/or the reliability and robustness of the data, and the information is not necessary for oversight. This modification should not be reported as such. The non-substantial changes should be listed and identified as such in the cover letter of the next substantial modification application, but they do not have to be described in detail. Sponsors can provide non-substantial changes whenever the scope of the non-substantial changes matches with the scope of the application under evaluation.

In case the SM application is rejected and the documents with non-substantial modifications are reverted, these changes should be resubmitted with the next SM application. In the meantime, the non-substantial modifications will have to be recorded in the Trial Master File and made available on request for inspection purposes as appropriate.

Non-substantial modifications that should be notified: Information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trials by the MSc shall be permanently updated in CTIS by the sponsor, in line with Article 81(9) of the CTR.

MORE SUPPORT

Map of national support initiatives for non-commercial sponsors

Access the map of national initiatives for non-commercial sponsors here: National Initiatives ; This map will assist you in incorporating national specific requirements into your application dossier when needed.

EMA's CTIS Helpdesk

The EMA provides a helpdesk service for users who need assistance with using the CTIS system. The helpdesk can be contacted through email or phone, and provides support in several languages : https://euclinicaltrials.eu/training/

Guidance, instructions, videos, and FAQs: Go to CTIS training programme *(Find also a Guide to CTIS Training Catalogue can be found and help you to organize your training :* https://www.ema.europa.eu/en/documents/other/guide-ctis-training-material-catalogue_en.pdf