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Clinical Trials Regulation (EU) No 536/2014 in practice

Quick guide on the rules and procedures of the EU Clinical Trials Regulation drawn up by the Clinical Trials Coordination and Advisory Group (CTAG) as its members are the National Contact Points defined in the abovementioned Regulation.

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Important notice: The objective of this document is to provide sponsors and investigators a quick guide on the rules and procedures of the Clinical Trials Regulation (EU) No 536/2014 with a view to facilitating its implementation. This document should be read in combination with the legislative text. Ultimately, only the European Court of Justice can give an authoritative interpretation of Community law.

More specific documents published on Eudralex 10: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en

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ABBREVATION LIST

AE	**Adverse Event**
ACT EU	**Accelerating Clinical Trials in the EU**
ASR	**Annual Safety Report**
ATiMP	**Advanced Therapy Investigational Medicinal Product. An ATMP is defined as either a gene therapy 'medicinal product' (GTMP), a somatic cell therapy 'medicinal product' (sCTMP) or a tissue-engineered product (TEP)**
AxMP	**Auxiliary Medicinal Product**
CCI	**Commercial Confidential Information**
CT	**Clinical Trial**
CTA	**Clinical Trial Application**
CTAG	**Clinical Trials Coordination and Advisory Group**
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**
GMO	**Genetically Modified Organism**
GMP	**Good Manufacturing Practice**
IAM	**Identity and Access Management system**
IB	**Investigator's Brochure**
ICH	**International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use**
IMP	**Investigational Medicinal Product**
IMPD-Q	**Investigational Medicinal Product Dossier on Quality data**
IMPD SE	**Investigational Medicinal Product Dossier on Safety and Efficacy data**
IVDR	**In Vitro Diagnostic Medical Devices Regulation**
MFA	**Multi-Factor Authentication**
MS	**Member State**
MSC	**Member State Concerned**
OOS	**Out of Specification**
Q&A - CTR	**Question and Answer document on CTR, see reference 3**
RFI	**Request for Information**
RMS	**Reporting Member State**
SAE	**Serious Adverse Event**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
XEVMPD	**eXtended EudraVigilance Medicinal Product Dictionary**

Clinical Trials Regulation (EU) No 536/2014 in practice

1. Introduction

This is a quick guide on the main rules and procedures of the Clinical Trials Regulation (EU) No 536/2014 (CTR) [1] for sponsors who wish to conduct clinical trials (national and multinational) in the European Union (EU) / European Economic Area (EEA) or have ongoing clinical trials in this region. The list of documents applicable to clinical trials authorised under Regulation (EU) No 536/2014, are published at the Eudralex Volume 10 website [2]. The first document recommended for reading is the Questions and answers document – Regulation 536/2014 (Q&A –CTR) [3] in chapter V. Additional documents (guidelines, guidances, recommendation papers, Q&As) to be considered are given in chapter 6.

To find out if a particular clinical study is a clinical trial on a medicinal product or not, see decision tree in Annex I of the Q&A – CTR [3].

A clinical trial[1] may be conducted only if:

a. the rights, safety, dignity and well-being of participants are protected and prevail over all other interests; and
b. it is designed to generate reliable and robust data.

The design and conduct of the clinical trial should comply with the CTR and General Data Protection Regulation (EU) No 2016/679 (GDPR) [4] together with the complementary national legislation[2]. The following guidelines are also applicable:

- Investigational Medicinal Product (IMP) manufacture and distribution should comply with Good Manufacturing Practice (GMP) [5] and Good Distribution Practice (GDP) principles [6].
- The clinical trial should be conducted under the principles of good clinical practice (GCP) [7].

In case the provisions of CTR and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use **(**ICH) GCP guidelines differ, rules defined in the CTR prevail.

1.1 Some key principles of the CTR

The main principles of the CTR are as follows:

- A single EU application with a single Clinical Trial (CT) dossier (including a part I common for all Member States concerned (MSC) and a part II specific per MSC) is required.
- A prior national authorisation of the CT applications in a MSC is necessary before starting the clinical trial in that MSC.
- An EU coordinated assessment applies for the part I is led by one of the MSCs, named Reporting Member State (RMS). The CT dossier part I conclusion together with national aspects in part II is the basis for a single decision on each application by every MSC, irrespective of the number of bodies/institutions involved in the assessment. Common EU principles for the CT assessment are performed in most MSs by the national competent authority and by one MSC Ethic Committee.

[1] See definitions of 'clinical study', 'clinical trial' and 'low intervention clinical trial' in article 2 (1) to (3) of the CTR
[2] National legislations may be found in MS websites as mentioned in Annex III of the Q&A –CTR

- Increased transparency requirements with respect to the CT data and documents that should be made publicly available.
- A Clinical Trial Information System (CTIS)[3] facilitating the procedures to fulfil the requirements of the CTR
- Clear maximum timelines set in calendar days resulting in tacit decision (article 8.6, CTR) or application lapse if not adhered to.
- Relevant notifications to CTIS to document the status of the CT conduct and the safety surveillance activity by sponsor.
- Clinical trials with vulnerable subjects should comply with specific requirements[4].
- A damage compensation mechanism according to national legislations is necessary.
- Simplification is foreseen for a CT on authorised IMPs involving minimal additional risk and burden compared to normal clinical practice (low intervention CT)[1] [8].

1.2 Transition period of the Clinical Trials Regulation

The CTR is applicable in the EU/EEA since 31 January 2022 and has a three-year transition period.
This transition period is as follows:

- Until 30th January 2023 sponsors have the chance to submit new initial clinical trial applications (CTAs) under the CTR via CTIS or under national laws implementing the CT Directive 2001/20/EC (CTD) documented in EudraCT;
- From 31st January 2023 all new initial CTAs should be submitted under the CTR;
- As of 31st January 2025 all ongoing clinical trials with an active site in the EU/EEA should be conducted under the CTR.

For CTs authorised under the CTD and not transitioned to CTR, substantial amendments and other reporting obligations should take place according to CTD procedures until the end of the three-year transition period (i.e. 31 January 2025).
CTD trials can be transitioned to CTR during the transition period where the CTD decision will be respected. The procedure for transition is described in Guidance for the transition of clinical trials from the Clinical Trials Directive to the Clinical Trials Regulation [49]. The CTCG best practice for sponsor for the transition of multinational clinical trials [50] and template cover letter [50] is published at the CTCG website[5] at key document list.

2. Steps before the start of the clinical trial

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 organised.

In order to be prepared for submitting applications and notifications via CTIS, sponsors are advised to check the training modules for CTIS [9], the CTIS sponsor handbook [10] with details on how to use CTIS and the overview of structured data to be completed in CTIS [11].

[3] https://euclinicaltrials.eu/
[4] The CTR has specific rules for clinical trials with incapacitated subjects (CTR, article 31), minors (CTR, article 32), pregnant and breastfeeding women (CTR, article 33), additional national measures (CTR, article 34) and clinical trials involving participants in emergency situations (CTR, article 35).
[5] https://www.hma.eu/about-hma/working-groups/clinical-trials-coordination-group.html

A quick guide for getting started with CTIS is also available [12]. In the following chapters the main steps are described.

2.1 User, product and organisation registration

User registration

To access the CTIS sponsor workspace [13], a user will need to have a European Medicines Agency (EMA) account (i.e. username and password). Users already using other EMA applications (i.e. Eudralink, SPOR, IRIS, EudraVigilance, OMS) can use the same EMA account to access the CTIS sponsor workspace.

For individuals without an EMA account, it is necessary to create one by self-registration at the EMA account management page, i.e. Identity and Access Management site (IAM) [14]. The self-registration process is described in module 03 of the CTIS training material catalogue [9].

A multi-factor authentication (MFA) for CTIS users will be rolled out in 2023 (date to be decided). In preparation for the introduction of an MFA, it is recommended that each user is equipped with a mobile phone, or an office phone that can be used for second factor authentication.

Organisation-centric vs CT-centric approach

If one works for a sponsor that has a sponsor administrator user appointed in IAM (in CTIS called organisation-centric approach), roles with permissions must be given by the administrator(s) of this organisation before starting to work in CTIS.

For organisations that have no administrator users appointed in IAM (in CTIS called 'CT-centric approach'), no roles to sponsor users need to be assigned and the user can create a new CTA in CTIS directly. In that situation, this user will automatically receive a CT administrator role for the clinical trial(s). Access will be restricted to the trials created by the user, regardless of other CTAs created by another user from the same organisation. More information on user registration and management can be found in chapter 2 and 3 of the CTIS sponsor handbook [10].

Medicinal product registration

Before completing the clinical trial application in CTIS, 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 as well as products under development. More information on registration of investigational and auxiliary medicinal products (IMPs and AxMPs respectively)[6] can be found in chapter 6 of the CTIS sponsor handbook [10] and module 10 of the CTIS training material catalogue [9].

A placebo can be added manually without pre-registration in XEVMPD.

[6] Auxiliary medicinal product' means a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (CTR definition, article 2.2.8). For more information, see the recommendation paper on auxiliary medicinal products [17]

Organisation registration

CTIS retrieves organisational data (i.e sponsor, CT sites) from the Organisation Management Service (OMS) [15]. If the organisations to be recorded in CTIS are not registered in OMS yet (sponsor should check this first), it is necessary to register them via a change request in OMS. The registration process for a new organisation in OMS takes from five to ten working days. More information about how to check if an organisation is already registered and how to register an organisation can be found in chapter 2 of the CTIS sponsor handbook [10] and module 3 of the CTIS training material catalogue [9].

If registration in OMS is not feasible, an alternative is to record the organisation directly in CTIS, without the need to first register them in OMS. This is possible for a third party organisation (part I application dossier - sponsor section), trial sites (part II application dossier), site where a serious breach has occurred, inspection site (third country as well as EU/EEA Member States) [16].
For data quality and consistency reasons, prior registration in OMS is preferred. In case of any issues, contact the EMA service desk [18].

2.2 Clinical trial application content and submission via CTIS

Documents required will vary depending on the type of application or notification submitted. As an example, the content of the application for the initial authorisation of the clinical trial is outlined below.

CTIS has three sections which must be completed[7] before submitting an initial clinical trial application:

1. **Forms and MSC**
   - Forms, including placeholder for cover letter, proof of payment of fee, statement on compliance with GDPR and deferral setting, including justification for trial category (defining the transparency rules)
   - Overview of the MSCs including the proposed RMS by the sponsor
2. **Part I** consisting of trial details (including placeholders for upload of protocol and protocol-related documents and, if applicable, summary of scientific advice(s) and paediatric investigational plan), sponsor and product information (including placeholders for upload of the Investigator's Brochure (IB), Investigational Medicinal Product Dossier on Quality data (IMPD-Quality) and Investigational Medicinal Product Dossier on Safety and Efficacy data (IMPD-Safety and Efficacy), GMP documents and labels).
3. **Part II** consisting of clinical trial site details and placeholders for documents part II (recruitment arrangement, informed consent form, CV for principal investigator etc.).

In Annex 1 to this quick guide, the composition of the full clinical trial application is given including the name to be referenced in CTIS to easily identify the document according to the Clinical Trials Coordination Group (CTCG) naming convention [19]. Although part I is the same for all MSCs, there can be specific language requirements per MS. These language requirements are given in Annex II of the Q&A – CTR [3]. On Eudralex volume 10 [2] under

[7] Partial submission (only part I, without part II) is possible (see CTR, article 11). In that case, part II in CTIS can be submitted after conclusion on part I. It is important to know that a CT cannot be authorised until the conclusions of the assessments on both part I and part II are favorable to authorize the CT.

chapter I 'Application and application documents', some templates for part II documents are published, but it is up to each MS to decide on the use of these templates for their national documents. Annex III of the Q&A-CTR provides the link to the respective MS websites, where the requirements for part II documentation is provided. Therefore, it is advised to consult the respective MS website for the requirements on the use of templates and acceptable languages. A list of contact points for queries on part I and/or part II applications and the relevant website with information on MS specific requirements, can be found Annex III of the Q&A – CTR [3]. In addition, a list of national contacts points, one per MS represented in the Clinical Trials Coordination and Advisory Group (CTAG), is available under chapter V of the Eudralex volume 10 [2].

The sponsor is allowed to submit a full initial application (part I and part II at the same time to all MSCs) or a partial initial application (part I to all MSC and part II to none or some MSC). For more information, see also section 2 of Q&A CTR [3].

For a **partial initial application** (only part I) the following rules apply:
- A part II application cannot precede a part I application.
- A part II application can be submitted after the assessment part I has been concluded.
- A part II application must be submitted within two years after the part I conclusion. If this is not done, the application part I will lapse.
- The part II application shall be accompanied by a statement from the sponsor in which it is declared that the sponsor is not aware of any new substantial scientific information that would change the validity of any item submitted in the application on the aspects covered by Part I of the assessment report, in which the MSC participated.

Important for **partial initial applications** in a multinational clinical trial:
The sponsor can only submit a substantial modification or an additional MSC if all MSCs have issued a decision on the clinical trial, after having received both part I and part II. See also question 2.3 (additional MS) and 3.6 (substantial modification) of the Q&A – CTR [3].

2.2.1 Submission of IMPD-Q in CTIS if sponsor is not allowed access to IMPD-Q

In case the sponsor of a clinical trial is not the product owner (PO) of the IMP and should not have access to the IMPD-Q or associated considerations/RFI in order to protect commercially confidential information, there are several options for the sponsor and PO in CTIS as described in question 2.15 of the Q&A – CTR [3]. One of the options is the submission of the 'IMPD-Q only application' by the PO at the same time as the submission of the initial application of the clinical trial for which the IMP is intended by the sponsor. The conditions and procedure for this 'IMPD-Q only application' are also described in question 2.15 of the Q&A – CTR [3].

2.2.2 Complex clinical trials and submission in CTIS

In case of a complex clinical trial, a sponsor can submit the clinical trial as one single trial (master protocol plus all subprotocols under one EU CT number) or as separate clinical trials (master protocol with at least one IMP specific subprotocol with a specific EU CT number and several other subprotocols each with its own EU CT number with a cross reference to the EU CT numbers of the other subprotocol(s) and master protocol) in CTIS. CTCG has published a Q&A on the submission of complex clinical trials in CTIS (new or transition complex clinical

trials) which addresses the most important factors to be considered for a complex clinical trial application in CTIS [20].

2.3 Validation, assessment and decision by Member States Concerned

The sponsor proposes an MSC to be RMS for a multinational clinical trial. During the validation phase, the RMS will be selected by all MSCs on the basis of fair workshare and mutual agreement. For mononational clinical trials, the MSC who receives the clinical trial application is RMS by default. The RMS, in conjunction with MSCs, will validate if the clinical trial application is complete and within scope of the CTR. If the clinical trial application is valid, the assessment phase starts. The part I assessment is coordinated involving all MSCs and led by the RMS who prepares a draft assessment report, sends the request for information (RFI) with considerations, when applicable, (including also those from other MSCs, if applicable) to the sponsor and issues a conclusion for the part I assessment after reviewing the answers to the RFI.

The part II assessment is done by each MSC separately. Each MSC prepares an assessment report part II, sends an RFI with considerations, if necessary, to the sponsor and issues a conclusion of the part II assessment.

Within 5 days after part I and part II conclusions have been notified to the sponsor, each MSC notifies the sponsor whether the clinical trial application is authorised, authorised subject to conditions, or not authorised. The maximum timelines for each of these phases are provided in Annex 2 of this quick guide.

The Part I conclusion of the RMS is also valid for the MSC, unless that MSC disagrees with the conclusion of the RMS on the following grounds:

a. when it considers that participation in the clinical trial would lead to a subject receiving an inferior treatment than in normal clinical practice in the MSC;
b. infringement of its national law[8];
c. considerations regarding subject safety and data reliability and robustness were raised by an MSC during the assessment coordinated review phase.

A sponsor can appeal in each Member State to a refusal on these grounds. Another ground to appeal to a refusal is if the conclusion on part II is not acceptable. There could also be national legislation applicable with respect to an appeal, e.g. allowing appeal also on an authorisation with conditions.

Along the authorisation procedure, tacit approval or lapsed application principles apply:

- During the validation phase: a) if the RMS has not notified the sponsor within the applicable timelines, the application will be considered complete and valid and b) when the sponsor has not answered a request for information within the applicable timelines the application shall be deemed to have lapsed in all MSCs.
- During the assessment phase: in case the sponsor does not answer a request for information with respect to part I within the applicable timeline, the application shall be deemed to have lapsed in all MSCs. In case the sponsor does not answer a request for information with

[8] See CTR article 90, prohibiting or restricting the use of any specific type of human or animal cells, or the sale, supply or use of medicinal products containing, consisting of or derived from those cells, or of medicinal products used as abortifacients or of medicinal products containing narcotic substances within the meaning of the relevant international conventions in force such as the Single Convention on Narcotic Drugs of 1961 of the United Nations.

respect to part II within the applicable timeline, the application shall be deemed to have lapsed in that MSC.

– During the decision phase: Where the MSC has not notified the sponsor of its decision within the applicable timeline, the conclusion on Part I of the assessment report shall be deemed to be the decision of that MSC on the clinical trial application (tacit decision).

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 part I conclusion is notified to the sponsor (reporting date), the withdrawal will apply to the entire application in all MSCs. After the reporting date, but before the decision is taken by a particular MSC, the sponsor has the option to withdraw the application in that MSC. Once the decision regarding an application is taken in a MSC, a sponsor no longer has the possibility to withdraw the application in that MSC. After a withdrawal has taken place, resubmission of the application is possible.

If no subject has been included in the clinical trial in an MSC within two years from the notification date of the authorisation, the authorisation shall expire in that MSC unless an extension, on request of the sponsor by submission of a substantial modification application, has been authorised.

3. Steps while the clinical trial is being conducted

After a clinical trial has been authorised, the sponsor is required to monitor the CT conduct in order to ensure adherence to the protocol and submit applications for authorisation of a substantial modification or an additional MSC as well as fulfilling certain non-substantial modification notifications should they occur. There are also several mandatory notifications and obligations for the sponsor with respect to safety surveillance and the status of the clinical trial. The process for their submission via CTIS is shown in the sponsor's handbook [10].

3.1 Applications for substantial modifications, non-substantial modifications per article 81.9 and other non-substantial modifications on the authorised clinical trial

In annex IV of the Q&A – CTR [3] an overview is given of the different types of CT modifications requiring either authorisation or notification. See also section 3 of the Q&A – CTR [3]. At the time of their submission, there should be no other application in the MSC under assessment.

The article 81.9 changes to a clinical trial are those which are not substantial modifications (SMs) but are, nevertheless, relevant for the supervision of the clinical trials by the MSCs.

Before an SM can be applied, the SM application[9] needs to be assessed and authorised by the MSC, comparable to the procedure required for the initial application and according to the maximum timelines for an SM assessment[10].

[9] See substantial modification definition in article 2 (13) of the EU Regulation 536/2014. It also includes addition of a clinical trial site or the change of a principal investigator at a clinical trial site.
[10] See chapter 3 (articles 18-24) of the CTR for the applicable legal maximum timelines.

The sponsor or the investigator may take urgent safety measures without awaiting prior authorisation. If such measures constitute a temporary halt of the clinical trial due to safety reasons, the sponsor should submit an SM application before restarting the clinical trial. An application for the authorisation of a SM on part I is submitted to all MSCs, while an application for the authorisation on part II should be submitted to each MSC individually in CTIS. There is also the possibility to submit a combined SM part I/part II application.

Currently, substantial modifications on part I can only go to MSs that have authorised the CT. This requires that the sponsor submits part II in those MSC that only received a partial initial application (part I only), in order to be able to submit an SM involving part I.

The sponsor can also only submit an SM application if there is not an ongoing assessment of any other substantial modification (either part I only, part I and II or part II only). There is one exception: an SM part II can be submitted to an MSC with no other ongoing assessments while in another MSC has a part II assessment is ongoing. The procedure for substantial modifications in partial initial applications will be modified in the future, see also section 3.6 of the Q&A – CTR [3].

3.2 Addition of MSC

A procedure to add another MSC to an authorised clinical trial (article 14 CTR) can be applied for:

- after the clinical trials is authorised in all MSCs receiving a full (part I and Part II) initial application; and
- if there is no ongoing assessment of an SM part I or part I/II in any of the MSC.

Submission of an application for the extension of a clinical trial to another MSC is possible if there is an ongoing assessment of i) a substantial modification application part II only in any of the other MSCs or ii) another additional MSC. See also section 2 of the Q&A-CTR [3].

3.2.1 Addition of MSC and IMPD-Q for decentral point of care

In case the manufacturing of the IMP is done at a decentral point of care (PoC), e.g. at one of the clinical trial sites in the additional MS (eg. CAR-T cells production), there is no placeholder in CTIS to submit the IMPD-Q for this decentral PoC. This is due the fact that all slots part I to upload documents in CTIS, except the translation slots, are blocked in an additional MS procedure. To solve this issue, a work around is set up and included in the list of know issues and proposed workarounds [51]. The sponsor should indicate the cover letter for the additional MS application that the IMPD-Q of the decentral PoC is not part of the application because part I is blocked and will be uploaded after receiving a RFI from the RMS to upload the IMPD-Q. This will trigger the RMS to send an early RFI to the sponsor, during the validation step in CTIS, requesting to upload the IMPD-Q. The sponsor can upload the IMPD-Q in the slot “uploading a document linked to this consideration”. This slot has the label quality in order to prevent public disclosure of the IMPD-Q. At the next SM part I, the sponsor should complete the Part I application dossier in the part I – IMPD-Q section.

3.3 Safety surveillance[11]

The sponsor together with the investigators is responsible for the safety surveillance and minimisation of risks for the trial participants along the clinical trial duration, taking, if necessary, appropriate urgent safety measures to protect the subjects. The MSC will monitor the risks of investigational medicinal products (IMPs) considering the available information according to the procedures laid down in the implementing Regulation on rules and procedures for the cooperation of the Member States in safety assessment of clinical trials [21].

Safety reporting with regard to authorised AxMPs shall be made in accordance with the normal safety reporting requirements for authorised medicinal products[12].

For non-authorised AxMPs, the same requirements as those provided for the IMP in the CTR should be applied with regard to the obligations of the investigators and the sponsors for the collection, recording, management and reporting of adverse events. See also section 7 of the Q&A – CTR [3] and the overview of notifications given in this chapter.

Notifications required from sponsor or investigator in relation to safety of the CT subjects:

1. Reporting of adverse events and serious adverse events

The investigator shall record and document adverse events (AE) or laboratory abnormalities identified in the protocol as critical to the safety evaluation and report them to the sponsor in accordance with the reporting requirements and within the periods specified in the protocol. Any exception to the need to record and document all AEs should be included and justified in the protocol.

The investigator shall report a serious AE (SAE) to the sponsor not later than within 24 hours of obtaining knowledge of the events, except for the SAE for which the protocol indicates that no immediate reporting is required.

2. Reporting of suspected unexpected serious adverse reactions (SUSARs)

The sponsor of a CT shall report electronically to the EudraVigilance[13] database all relevant information about the following suspected unexpected serious adverse reactions (SUSARs):

- All SUSARs related to an IMP that occurred in any of the countries participating in the CT, even if the sponsor is aware of it only after the end of the CT.
- All SUSARs related to the same active substance that occurred in a CT conducted in third countries by the same sponsor or by another sponsor within the same parent company or who develops the medicinal product jointly.

The reporting period starts from the day the sponsor became aware of the reaction:

- in the case of fatal or life-threatening suspected unexpected serious adverse reactions, as soon as possible and not later than seven days.
- in the case of non-fatal or non-life-threatening suspected unexpected serious adverse reactions, not later than fifteen days.

[11] More information may be found at chapter VII and annex III of the CTR and section 7 of Q&A – CTR [3]
[12] Title IX of Directive 2001/83/EC.
[13] See https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance

To be able to report SUSARs in EudraVigilance, one must have an account. The EudraVigilance registration documents [22] describes in detail what is needed for registration with EudraVigilance, including the links to the different EMA systems. With an EMA account (see chapter 2.1 on user registration) a request for the role 'EV CS/NCS' can be submitted via the EMA Account Management Page [14]. Thereafter a ticket should be created for the EMA Service Desk [18] in which the requested documents should be attached. An overview of the documents that are needed, can be found on page 2 of the EudraVigilance registration documents [22]. One of the documents that should be attached to the ticket is a copy of the 'notification of successful completion of the EudraVigilance ICSR and XEVMPD knowledge evaluation' for the EudraVigilance user.
Non-commercial sponsors can complete an online training:
https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-training-support#eudravigilance-online-training-and-competency-assessment-for-non-commercial-sponsors-section
A more extensive (online) training (subject to fee) is being delivered by DIA. Information can be found at: https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/eudravigilance-training-support#virtual-live-hands-on-training-course-for-clinical-trial-sponsors-section

In case a sponsor, due to a lack of resources, does not have the possibility to report to EudraVigilance and the sponsor has the agreement of the MSC, it may instead report the SUSAR to the MSC. This MSC shall then report the SUSAR to EudraVigilance. This procedure is not feasible in all MSCs and should be verified first by contacting the MSC [23].

3. Other unexpected events relevant for the CT subject's safety

The sponsor shall notify the MSC through CTIS of all unexpected events that affect the benefit-risk balance of the CT that are not SUSARs. Reporting should be as soon as possible and no later than 15 days from the date the sponsor became aware of this event (e.g. the early end of another clinical trial with the same IMP due to safety reasons or results of a study showing genotoxicity for the IMP).

4. Annual safety report

The sponsor shall submit annually via CTIS a report on the safety of the investigational medicinal product used in a CT for which it is the sponsor. The format for an annual safety report (ASR) is according to the ICH guideline E2F on development safety update report [24]. This obligation starts with the authorisation of the first CT under CTR and ends with the end of the last CT conducted by the sponsor with this investigational medicinal product in any MS of the EU/EEA.
In case of a CT involving the use of more than one investigational medicinal product, the sponsor may, if provided for in the protocol, submit a single safety report on all investigational medicinal products used in that CT. A simplified report is acceptable for low intervention CTs and CTs with authorised IMPs.

5. Reporting of serious breaches

The sponsor shall notify the MSCs about serious breaches[14] of the CTR or of the version of the protocol applicable at the time of the breach through CTIS as soon as possible and not later than seven days after becoming aware of that breach. Notification should take specific guidance [25] into account.

6. Urgent safety measures

The sponsor shall notify the MSC, through CTIS, of an event likely to seriously affect the benefit-risk balance for the CT subjects and the measures taken. That notification shall be made without undue delay but no later than seven days from the date the measures have been taken. This is irrespective of the substantial modifications that could be necessary to update the CT dossier in relation to revert the potential risk.

7. Temporary halt of the CT[15] due to safety reasons

The sponsor shall notify the MSC of a temporary halt of a CT for reasons affecting the benefit-risk balance through CTIS. That notification shall be made without undue delay but not later than in 15 days of the date of the temporary halt. It shall include the reasons for such action and specify follow-up measures. The restart of the CT following a temporary halt will require an authorised SM application.

3.4 Other necessary notifications for the sponsor

- *Intermediate analysis of results*
  Where the clinical trial protocol provides for an intermediate data analysis date prior to the end of the clinical trial, and the respective results of the clinical trial are available, a summary of those results shall be submitted to CTIS within one year of the intermediate data analysis date[16].

- *A temporary halt of the CT not for safety reasons*
  The sponsor shall notify each MSC of a temporary halt of a CT for reasons **not** affecting the benefit-risk balance through CTIS. This notification should be performed within 15 days from the date of such temporary halt and shall include the reasons for such action. In this case, when the CT is resumed, the sponsor shall notify each MSC within 15 days through the CTIS. If the CT is not resumed within two years, the expiry date of this period or the date of the decision of the sponsor not to resume the CT, whichever is earlier, will be the date of the end of the CT.

- *The start of the CT, first visit of the first patient and end of recruitment dates* in every MSC, in all cases within the 15 subsequent days to such date through CTIS.

A full list of all notifications is given in Annex 3 of this quick guide.

[14] 'Serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.
[15] 'Temporary halt of a clinical trial' means an interruption not provided in the protocol of the conduct of a clinical trial by the sponsor with the intention of the sponsor to resume it. Depending on the reasons, it may affect all or part of the CT activities and may be implemented in all or in only certain CT sites.
[16] Article 37.8 CTR

4. Steps once the CT has ended

4.1 Notifications by the sponsor via CTIS

- *The end or early termination of the CT* in every MSC in EU/EEA as well as globally in case third countries participate. The date of the early termination of the CT is the same as the end of the CT. The end of trial or early end of trial in all cases must be notified within the 15 subsequent days to such date, providing also in the case of an early termination the reasons for the end of the CT and consequences for the CT subjects.

  In case of a complex CT with a master protocol and several sub-protocols, every sub-protocol should have an end of sub-protocol date, which is the date of the last visit for the last participant in the sub-protocol or, if justified, as defined otherwise in the sub-protocol. In addition, the CTR definition of early termination[17] of a clinical trial applies to any sub-protocol.

- *Summary of the CT results*
  Irrespective of the outcome of a clinical trial, and also in the case of an early termination of a CT (except when no subjects were recruited), within one year from the end of the clinical trial in all MSCs or within six months for clinical trials in paediatric populations, the sponsor shall submit to CTIS a summary of the results.

  Such summary should include the information set in Annex IV of the CTR. A summary understandable to laypersons according to Annex V of the CTR is also required.

  Where, for scientific reasons detailed in the protocol, it is not possible to submit a summary of the results within one year, for example when the clinical trial is still ongoing in third countries and data from that part of the trial are not available, i.e. the statistical analysis would be irrelevant, the summary of results shall be submitted as soon as it is available. In this case, the protocol shall specify when the results are going to be submitted, together with a justification.

- *Clinical study report*
  In cases where the clinical trial was intended to be used for obtaining a marketing authorisation for the investigational medicinal product, a clinical study report should be submitted to CTIS by the applicant for marketing authorisation within 30 days after the day the marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant for marketing authorisation has withdrawn the application.

[17] Early termination of a clinical trial' means the premature end of a clinical trial due to any reason before the conditions specified in the protocol are complied with. If the protocol mentions circumstances for early termination, and these circumstances are fulfilled, the notification on early termination should still be performed (See Section 10 of the Q&A-CTR [3])

4.2 Archiving

The sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial. The medical files of the subjects shall be archived in accordance with national law.

5. Transparency

The CTR brings unprecedented standards for transparency and publication of clinical trials data in the European Union[18] that are detailed in more specific guidance [26]. Access to clinical trials data supports clinical research as well as provides valuable information for researchers, health care professionals, patients and general public.

In order to promote trust in the society in relation to CTs and to support innovative and meaningful trials in European Union, while at the same time recognising the legitimate economic interests of sponsors, information on authorised and refused CTs has to be published in the CTIS public domain according to article 81.4 of the CTR [27].

The CTR also recognises that personal data, commercially confidential information (CCI), preparation of draft assessment reports and supervision measures from the Member States should be exempted from publication rules. To enable protection of personal data and/or CCI CTIS offers the users the possibility to upload redacted document versions 'for publication' and unredacted document versions 'not for publication'.

5.1 Protection of commercially confidential information

At the time of submission of an initial clinical trial application the sponsor has the option to define the deferral settings in accordance to the current transparency rules [26] to delay the publication of clinical trials data and documents. The deferral settings enable sponsors to protect commercially confidential information (CCI) without redaction in their documents. However, following the publication of the CTIS revised transparency rules [28] and until their implementation in the system, for initial clinical trials applications sponsors may already follow the principles of the revised rules, as described in section 4 of the ACT EU Q&A on the protection of Commercially Confidential Information and Personal Data while using CTIS [29]. A sponsor may therefore refrain from defining deferral settings and provide a version 'for publication' and 'not for publication' only for those documents in scope of the revised rules and detailed in Annex I of the revised CTIS transparency rules [28]. In the slot 'for publication' of those document types that will no longer be subject to publication, the sponsor can upload a page with the wording suggested in Annex I of the mentioned ACT EU Q&A [29]. Regarding the other applications that are not initial applications, but that are submitted on trials that are already present in CTIS, such as substantial modifications and the addition of a new MSC, sponsors should consider the preferred approach on protection of personal data and CCI, with the aim to decrease burden depending on the status of the trial, i.e. for example whether deferrals are already in place (see ACT EU Q&A[29]).

When submitting an initial clinical trial application, the sponsor will be able to choose whether the clinical trial falls into category 1, 2 or 3[19], in particular by taking into account the marketing authorisation status of the IMP. The category chosen allows to define the type of deferral that

[18] Article 81(4) of CTR on clinical trial database being public

[19] Category 1 CT includes: phase 0 and phase I CT, bioequivalence and bioavailability CT and similarity trials for biosimilar products or equivalence trials for combination or topical products where pharmacokinetic and or pharmacodynamics studies are not possible. Category 2 CT include phase II and phase III CT and Category 3 CT includes phase IV and low intervention CT [24].

can be requested under the current transparency rules [26], or the timing of publication of data and documents under the revised rules [28] (this is going to be appliable once the revised rules are implemented).The MSC will evaluate appropriateness of the category proposed by the sponsor.
Where a clinical trial protocol sets out a multiphase or adaptive study design that falls in both category 1 and 2, the trial will be treated in line with category 2.
Emergency situation CTs[20], where the informed consent is sought after the first trial-specific intervention, are always Category 2 or 3. CT protocols in situations of a declared public health emergency of international concern cannot be deferred, i.e. publication occurs at the time of decision on the CT application. It should be noted that for clinical trials, category 1, in paediatric populations and/or part of a paediatric investigational plan, it will not be possible to defer publication of main characteristics, notifications, summary of results and intermediate data analyses.

Under the current transparency rules [26], Member States Concerned are able to delay the publication of their documents (i.e. Assessment reports part I and part II) and requests for information part I and part II, in line with the sponsor's timelines for deferrals. However, until the technical implementation of the revised transparency rules [28] in CTIS, also the Member States may already follow the principles, as described before, and upload a page with the wording suggested in Annex I of the relevant ACT EU Q&A [29] in the slot ‘for publication’ of all documents that are no longer subject to publication in line with the revised rules, such as final assessment reports or decision letters.
Under the current transparency rules [26], once that the trial with a deferral has been authorised, the applicable data/documents subject to deferrals will not be published at the time of the decision. In case the CT with a deferral is rejected by all MSCs receiving the application, the clinical trial information will be published in CTIS public domain according to the same deferral rules as for authorised clinical trials and the date of decision of the last MSC receiving a full Part I and Part II application is taken as the date of the end of the clinical trial [26]. Under the revised transparency rules [28] the structured data fields for all trials’ categories of trials submitted before implementation of the rules will be published in line with the timelines and principles of the said rules; however, all documents contained in applications submitted to CTIS before the implementation of the technical changes will not be published. This is defined in the mentioned ACT EU Q&A [29] and it applies to all the so called ‘historical trials’ in the system, and regardless of the previous use of deferrals or publication status. Documents in scope of publication as per revised rules [28], that will be provided in applications, or submitted as results after the implementation of the technical changes, will be published in line with the timelines and principles of the revised rules.

5.2 Protection of personal data

Personal data included in documents uploaded in CTIS should be kept to the minimum and be provided when necessary to support the exchange of information between the parties[21]. If any personal data is needed, e.g. on pseudonymised subjects, this should be included in the document version ‘not for publication’ and anonymised in the document version ‘for publication’.

[20] Article 35 CTR
[21] Article 81(6) of CTR referring to 81(2) of CTR

More information on protection of personal data can be found in module 12 of the CTIS training material catalogue [8]. More detailed information on how to protect personal data and CCI when using CTIS can be found in the Guidance on publication of commercially confidential information and personal data and the associated ACT EU_Q&A on protection of commercially confidential information and personal data while using CTIS which includes recommendations from the members states and product owners on frequently asked questions [30, 29].

6. CT specific information

This chapter highlights specific legislation for CT on Advanced Therapy Medicinal Products and important guidance and recommendations to take into account for the clinical trials.

6.1 Clinical Trials on Advanced Therapy IMP

Advanced Therapy investigational Medicinal Products (ATiMP) have to comply not only with the general legislations for clinical trials [1] and ATiMP [31] but also with legislation from different frameworks, such as Directive 2004/23/EC [32] for the donation, procurement and testing of the starting materials to be converted into cell-based medicinal products or that for genetically modified organisms (GMO) Ref (Directives 2001/18/EC [33] and/or 2009/41/EC [34] when the product belongs to this category.

Due to the particularities of this IMP, clinical trials with ATiMPs have to comply with specific good clinical practice [34] and good manufacturing practice [36] rules that cover among other things the need for paying special attention to the selection criteria and to potential safety problems, even during long term follow up periods.

The use of each ATiMP has to be traceable and the sponsor is responsible of organising this. The individual product should be traceable from delivery to the clinical trial site up to the administration to the clinical trial subject and vice versa.

In addition, when the IMP is an ATiMP that contains cells or tissues of human origin, the traceability from the recipient of the product to the donor of the cells or tissues should be ensured. The traceability system should be bidirectional (from donor to subject and from subject to donor) and data should be kept for 30 years after the expiry date of the product, unless a longer time period is required in the clinical trial authorisation [35].

The guideline on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products [36] described that for some ATMP, in exceptional situations, the administration of out of specification (OOS) product may be necessary for the patient to avoid an immediate significant hazard to the patient. The treating physician should justify the administration of the OOS product taking into account the availability of alternative options for the patient and the benefit/risk for the patient of not receiving the cells/tissues contained in the product,
The protocol should describe the procedure for an OOS administration within a clinical trial. Also, the investigator needs to inform the trial participant about the possibility and chance on receiving an OOS product. This should also be described in the trial participant information letter.

The procedure on the use and notifications of OOS batches of authorised ATMPs is described in the questions and answers document from the EMA committee for Advanced Therapies (CAT) [36].

An OOS administration of a not authorised ATMPs is considered an unexpected event (CTR, article 53) as it may affect the benefit/risk balance of the clinical trial. The sponsor has to notify the Member States concerned via CTIS within maximum 15 days after the administration of an OOS product. For authorized products periodic reporting in CTIS is acceptable. The description of the event should start with: Out of Specification administration. In case reporting via CTIS may lead to unblinding of the trial, these notifications need to be done outside of CTIS via mail to all national contact points of the Member States concerned [23].

6.2 Specific requirements for CT on IMP being a GMO

The CTR does not specifically address environmental aspects. However, clinical trials with medicinal products that contain or consist of GMOs must comply with applicable requirements under the GMO framework and may require specific national authorisations related to this legislation [38]. In some MSs the applications for a CT and GMO can be submitted in parallel, for others the GMOs need to be approved prior to the CT.

In order, to facilitate the development of CT with medicinal products consisting or containing GMO, lack of harmonization between different GMO authorities across the EU has prompted the development of common voluntary procedures for some categories of products [39].

In spite of these requirements, in order to facilitate the development of new treatments for COVID-19, Regulation 2020/1043 [40] considers acceptable that all operations related to the conduct of clinical trials, including packaging and labelling, storage, transport, destruction, disposal, distribution, supply, administration or use of investigational medicinal products for human use containing or consisting of GMOs intended to treat or prevent COVID-19, with the exception of the manufacturing of the investigational medicinal products, shall not require a prior environmental risk assessment or consent in accordance with Directive 2001/18/EC [31] or Directive 2009/41/EC [34]. In these cases, sponsors shall implement measures to minimise foreseeable negative environmental impacts resulting from the intended or unintended release of the investigational medicinal product into the environment.

6.3 Other relevant guidances for CT

There are many other guidance documents, recommendation papers and Q&A for specific clinical trials. In addition to those in Eudralex –volume 10 [2], some relevant ones are highlighted with reference to useful web page:

- World Medical Association. Declaration of Helsinki [41]

- ICH E8 (R1) on general considerations for clinical studies [42]

- Recommendations and Questions and Answers related to CTs with complex design (e.g. umbrella, basket or platform trials) [43, 44]

- Recommendation paper on decentralised elements in clinical trials [45]

- Questions and Answers on the interface between CTR and Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR) [46]

- Human regulatory – EMA scientific guidances to different aspects of the development of a medicinal product (i.e multidisciplinary, about quality aspects of the IMP, about non-clinical studies or early phase clinical trials) [47]

- ICH guidelines [48]

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    https://euclinicaltrials.eu/website-outages-and-system-releases/

Annex 1. Composition of the clinical trial application in CTIS

Documents are shown following the order in Annex 1 CTR including naming convention [19] with clear self-explaining names for documents (including relevant identification) to be indicated in the CTIS field at the time a document is uploaded in order to ensure documents are easily found in the system.

Section Forms and MSC (*placeholders in CTIS)*
B1_Cover letter EU CT number
Proof of payment of fee[22]
Statement of compliance with Regulation (EU) 2016/679 (GDPR)[23]

Section Part I
D. Protocol *(placeholder protocol information in CTIS)*
D1_ Protocol EU CT number
D1_ Protocol synopsis[24]_ EU CT number (*include MS language code in title*)
D1_ Master protocol EU CT number and name and sub-protocol name and specific number/ID *(applicable for CCT)*
D2_ Protocol modification nr number EU CT number *(in case of SM as separate doc.*)
D3_ DSMB Charter EU CT number
D4_ Patient facing documents e.g. questionnaire or diary *(if applicable*)
E. Investigator's Brochure *(placeholder product information in CTIS)*
E1_ IB product name
E2_SmPC product name

F. Documents GMP compliance (if applicable) *(placeholder product information in CTIS)*
F1_ Marketing/importing authorisation MIA product name and abbreviated name manufacturer/importer
F2_ QP GMP declaration product name and abbreviated name manufacturer/importer
F3_ Other statements/licences *(e.g. import license*) product name and abbreviated name manufacturer/importer

G. Investigational Medicinal Product Dossier *(placeholder product information in CTIS)*
G1_ IMPD_Q product name
G1_ IMPD_E-S product name
G1_ Simplified IMPD_Q product name
G1_Simplified IMPD E-S product name

H. Auxiliary Medicinal Product Dossier *(placeholder product information in CTIS)*
H1_ AxMPD- product name

I. Scientific advice and pediatric investigational plan (PIP) *(same placeholder in CTIS)*
I1_ Scientific advice summary name organisation

[22] This could be proof of payment of fee or invoice details. See information from each MS in Annex III of Q&A - CTR
[23] Template for this statement is published on chapter I of Eudralex volume 10: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en
[24] See information on language requirements from each MS in Annex II of Q&A - CTR

I1_Scientific advice Quality name oganisation
I2_ PedCo opinion
I3_ EMA PIP decision name agency

J. Labelling *(placeholder product information in CTIS)*
J1_ Label IMP_MS product name (include MS language code in title)[20]
J2_ Label AxMP_MS product name (include MS language code in title)[20]

Section Part II – information per MSC[25]
K. Recruitment arrangement *(same placeholder in CTIS)*
K1_ Recruitment arrangements
K2_ Recruitment material description

L. Subject information sheet, informed consent form, other subject information material *(same placeholder in CTIS)*
L1_ SIS and ICF description (*e.g. SIS and ICF adults, SIS and ICF 12-16 yr)*
L2_ Other subject information material description (*e.g. information leaflet adults)*

M. Suitability investigator *(same placeholder in CTIS)*
M1_ CV Investigator name investigator and clinical trial site (*use abbreviations*)
M2_ DoI Investigator name investigator and clinical trial site (*use abbrevations*)

N. Suitability facilities *(same placeholder in CTIS)*
N1_ Site suitability form name clinical trial site

O. Proof of Insurance or indemnification *(same placeholder in CTIS)*
O1_ Trial participant insurance certificate
O2_ Proof of coverage sponsor or investigator name sponsor/trial site *(if not covered by O1*)

P. Financial and other arrangements *(same placeholder in CTIS)*
P1_ Compensation trial participants, investigator, funding and other arrangements

R. Compliance with national requirements on data protection *(same placeholder in CTIS)*
R1_ Compliance on the collection and use of personal data

S. Compliance with use of biological samples *(same placeholder in CTIS)*
S1_ Compliance on the collection, use and storage of biological samples

[25] See information on language requirements from each MS in Annex II and on websites with national requirements part II per MSC in annex III of Q&A CTR [2]

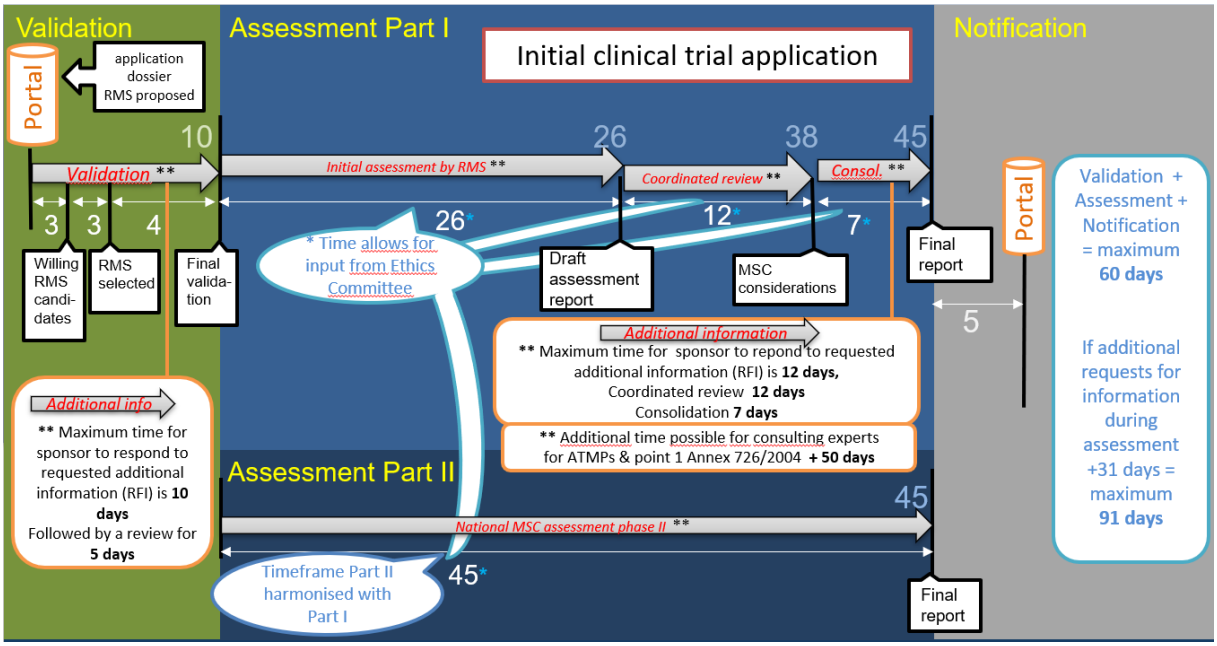
Annex 2. Calendar for the initial authorisation of a CT

The clock starts running the day after the application is submitted and follows the Central European Time (CET). Each phase - validation, assessment and decision - has its own maximum timelines for both MSCs and sponsors. The timelines are set in calendar days and are visible in CTIS, taking timelines ending on weekends and national holidays into consideration as provided for in Regulation (EEC, Euratom) No 1182/71 for the calculation of due dates in the system. If a sponsor exceeds the legal timelines when replying to a Request for information (RFI), the application will lapse.

The maximum calendar periods for the part I and part II assessment of the initial application for authorisation of a CT are 10 days for validation, extensible for up to 15 days, 45 for the assessment, extensible for up to 31 days and 5 days for every MSC to notify the decision to the sponsor. Substantial modifications have the same calendar, shortening the validation period to 6 days and the assessment to 38 days.

Diagram bellow represents the calendar for the initial application showing also the internal sub-periods for RMS exchange of information with the MSC on part I in case of a multinational CT.

The CTR foresees extending the assessment by a maximum further 50 days for clinical trials involving an advanced therapy investigational medicinal product or a medicinal product defined in point 1 of the Annex to Regulation (EC) No 726/2004, for the purpose of consulting with experts. The reporting Member State will communicate the sponsor any extension in the assessment period during the validation.



Annex 3. Overview notifications CTR

After the trial has been authorised, the sponsor must notify each MSC through the CTIS about the following information:

Notification	Definition	Timeline
Date, start clinical trial	First act of recruitment of a potential subject for a specific clinical trial, unless defined differently in the protocol	< 15 days of this date
Date, first visit of first subject		< 15 days of this date
Date, end of recruitment		< 15 days of this date
Restart of recruitment		< 15 days of this date
Date, end clinical trial in MSC	The last visit of the last subject, or at a later point in time as defined in the protocol	< 15 days of this date
Date, end clinical trial in all MSCs	The last visit of the last subject, or at a later point in time as defined in the protocol	< 15 days of this date
Date, end clinical trial in all MSCs and in all 3rd countries (global end)	The last visit of the last subject, or at a later point in time as defined in the protocol	< 15 days of this date
Temporary halt of clinical trial in all MSC for reasons not affecting benefit-risk balance	An interruption not provided in the protocol of the conduct of a clinical trial by the sponsor with the intention of the sponsor to resume it[26]	< 15 days (include reason)
Resume clinical trial after temporary halt (see row above)		< 15 days from the restart in all MSC
Early termination clinical trial for reasons not affecting benefit-risk balance	The premature end of a clinical trial due to any reason before the conditions specified in the protocol are complied with	< 15 days (include reason and when appropriate the follow-up measures for the subjects)
Temporary halt or early termination for reasons of safety	An interruption not provided in the protocol of the conduct of a clinical trial by the sponsor with the intention of the sponsor to resume it	< 15 days (include reason and specify follow-up measures)
Serious breaches	A breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.	Without undue delay but not later than 7 days of becoming aware of the breach

[26] In case the protocol foresee criteria for an early end of the CT, should these criteria occur, the sponsor has to notify the early termination of the CT. Early termination notifications related to CT with complex design also apply to sub-studies and are clarified in the Q&A on Complex CT in Eudralex volume 10 [41].

Unexpected events, not being SUSARs, which affect the benefit-risk balance		Without undue delay but not later than 7 days of becoming aware of the event
Urgent safety measures because of an unexpected event as referred to in previous row		Without undue delay but not later than 7 days from the date the measures have been taken
Summary of intermediate trial results (if foreseen in protocol)		Within one year of the intermediate data analysis date
Summary of results (Annex IV CTR)		Within one year from the end of a clinical trial
Summary of results understandable for laypersons (Annex V CTR)		Within one year from the end of a clinical trial
Clinical study report (only applicable for cases where the clinical trial was intended to be used for obtaining a marketing authorisation for the investigational medicinal product)		Within 30 days after the day the marketing authorisation has been granted, the procedure for granting the marketing authorisation has been completed, or the applicant for marketing authorisation has withdrawn the application.