Central assessment and local suitability in an efficient, accelerated process.

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Version: final February 23, 2023

Introduction

Cause

The EU Regulation *clinical trials of medicinal products for human use*[1] *536/2014* has been in effect since January 2022. This so-called *European Clinical Trial Regulation* (CTR) aims to simplify and accelerate clinical trials within the European Union, so more patients can benefit from the latest scientific developments at an earlier stage.

The speed and harmonization associated with the new legislation will allow Europe to take a stronger position in international competition.

The intention of the regulation is that the maximum lead time for the total review process of clinical trials is equal for all participating sites in EU countries. This applies to both investigator-initiated research and company-initiated research.

DCRF and CCMO consider the accelerated authorization process for clinical trials an opportunity to address the delays in all (medical) research subject to Medical Research Involving Human Subjects Act (WMO) in the Netherlands. Therefore, the aim is to implement the new process of site suitability for all (medical) research subject to Medical Research Involving Human Subjects Act (WMO) in the Netherlands.

What does the CTR (regulation) entail?

The central part of the regulation means that the medical-ethical review process for clinical trials is regulated at a European level. In case of multinational research, the participating member states collectively perform the review, in which one part of the dossier (Part 1) is reviewed at a European level. The other part (Part 2) is reviewed per Member State (further explanation under section "European Assessment"). Under the new law, sponsors will submit the application for the medical-ethical review of their clinical trial through a EU web portal, the Clinical Trial Information System (CTIS). The moment of submission marks the start of the central review process, which lasts up to three months.

[1] The VGO process will be used only in clinical trials with medicinal products. The CTR is applicable for all studies subject to the WMO.

The regulation also outlines that the reviewing committees[2] assess the suitability of the participating sites. Each participating Member State reviews the suitability of the site(s) in its own country. The site assessment takes place based on the declaration of suitability issued by the participating site(s) to the sponsor.

In the Netherlands, the participating sites issue the statement to the sponsor using the Site Suitability Declaration (Verklaring Geschiktheid Onderzoeksinstelling, VGO).

The Netherlands: an attractive country for research

To keep the Netherlands attractive for (international) sponsors (commercial and non-commercial) of clinical trials, it is necessary to accelerate the authorization process. This is regulated within the CTR and the Netherlands through:

- Assessing site suitability *before* submission in CTIS
  and
- Aligning the local suitability processes, completed with a signed CTA, in parallel with the assessment by the reviewing committee.
- The interest of making the Netherlands attractive for clinical research is broad: The knowledge level of doctors and healthcare professionals with regard to new and existing treatments;
- The possibility for patients to have access to new treatment methods in an early phase;
- The quality of care, due to experience with new treatment options;
- Employment opportunities in both companies and sites.

For sponsors it is of interest to ensure a timely and complete submission of documents necessary for local arrangements in the participating sites. Subsequently, a participating site needs at least 2 weeks to return a signed Suitability declaration (VGO form). The European CTIS submission date drives this process.

European Assessment

1. The submission process for medical-ethical review of clinical trials follows the EU CTR. This applies to both investigator-initiated and company-initiated trials.
2. The review of clinical trials in the European Member States takes place centrally, by review committees in the participating countries, of which one of the Member States acts as the reporter (the so-called reporting Member State (rMS)), whereas CTA Part 2 is reviewed by the individual Member States.
3. The standard clinical trial application (CTA) dossier submitted by the sponsors consists of two parts:
   - CTA Part 1 (rMS, 1 country is responsible for reviewing of the central part)
     - Final version of the research protocol
     - Expected therapeutic benefits for public health
     - Relevance of the clinical trial
     - Risks and inconveniences for the trial subjects
     - Reliability/robustness of the data

- Investigational Medicinal Product Dossier (IMPD): quality, production, safety, import IMPs/ AMPs
- Labelling
- Investigator's Brochure (IB)

- CTA Part 2 (individual Member State, every participating country is responsible for reviewing country-specific documents, the reviewing MREC is appointed by the National Clinical Trial Office (CCMO))
  - Subject Information Sheet (SIS) and Informed Consent Form (ICF) and informed consent procedure
  - Recruitment arrangements
  - Financial and other arrangements
  - Suitability of the investigator (Investigator Curriculum Vitae and Declaration of Interest) and Site Suitability (VGO)
  - Compliance with national requirements on data protection
  - Proof of Insurance cover or indemnification
  - Compliance with use of biological samples
  - Proof of payment fee

4. The submission of a CTA dossier takes place online via the CTIS portal of the European Medicines Agency (EMA). This also applies to trials that are conducted in the Netherlands only.
5. The sponsor determines the date of submission, with one date for all European countries, which will often be set outside of the Netherlands.
6. Review: In a multinational clinical trial, each Member State concerned receives Part 1 of the CTA dossier and provides their feedback to the reporting member state (rMS), who collects the feedback and responds to the sponsor. The review of CTA Part 2 is executed by each Member State concerned. In the Netherlands, the committee that reviews CTA Part 1 also assesses and reports on CTA Part 2.
7. Assignment of Part 2 of the CTA dossier to a review committee in the Netherlands is performed by the National Clinical Trial Office (CCMO).
8. The review procedure of Part 1 and Part 2 of the CTA dossier lasts a maximum of 3 months from the moment of submission.
9. The sponsor can only submit amendments after a review round has been completed. Adding a Member State and/or a participating site is considered as an amendment. Any subsequent review rounds also last a maximum of 3 months. It is the sponsor's decision whether to submit an amendment for the addition of a participating site.
10. The above applies to research to which CTR applies, i.e. clinical trials with medicinal products. In the Netherlands other research covered by the WMO will continue to be reviewed through a central Dutch MREC with parallel review through ToetsingOnline (CCMO). However, the timelines for submission of the CTA dossier and that of substantial amendments are deviate from the CTR.

As of 1 November 2021 the use of the VGO is mandatory for all clinical trials with medicinal products covered by the WMO. For all other studies subject to Medical Research Involving Human Subjects Act (WMO), the VGO will become mandatory at a time yet to be determined.

Procedure Local Suitability and local feasibility

The field organizations, united in the DCRF have prepared a procedure for Site Suitability, which describes the procedure for sponsors and investigators to quickly start up all research that is subject to Medical Research Involving Human Subjects Act (WMO). This means that the procedure will not only apply to clinical trials, but also to other research covered by the WMO and research that falls under the Medical Devices Regulation (MDR).

Aim

The aim of the procedure is to ensure that the moment of first patient in follows as soon as possible after the clinical trial has been authorized by the review committee. The review is done centrally, in parallel with a local process at the participating sites including (operational and financial) arrangements and documentation verification. With this approach, the start-up process of clinical trials in the Netherlands follows the requirements of the European legislation (CTR).

This process is secured by 3 formal legal documents

- VGO – Declaration of site suitability: *we can do it*
- CTA – Clinical Trial Agreement: *we are going to do it*
- EC – Central approval: *we are allowed to do it*

- The procedure will make sure that:Sites can start faster, so that investigators make full use of the inclusion period for all research subject to Medical Research Involving Human Subjects Act (WMO);
- Dutch sites are attractive for (international) sponsors of research subject to Medical Research Involving Human Subjects Act (WMO);
- The Netherlands has a good competitive position to other EU countries.
- There is an unambiguous parallel and harmonized procedure for all research subject to Medical Research Involving Human Subjects Act (WMO);
- Innovations are brought to patients at an earlier stage.

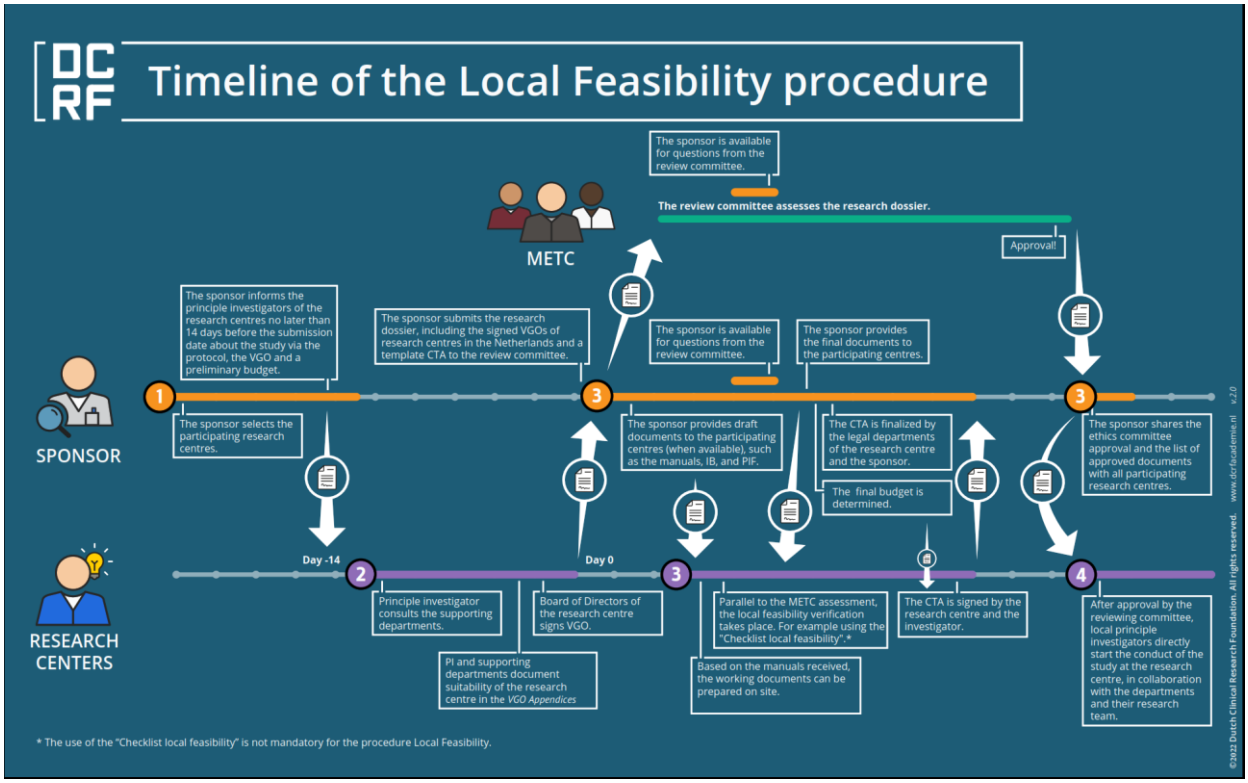
Setup

The procedures revolves around the time at which a complete CTA dossier will be submitted for review in the CTIS portal (for clinical trials) or at Toetsingonline (for all other trials subject to Medical Research Involving Human Subjects Act (WMO)).

The procedure describes:

- The activities that ought to take place during the pre-submission period;
- The activities that ought to take place during the review period.

The procedure is divided into three roles (METC, Sponsor and participating investigator/ site) and four steps; two steps during the pre-submission period and two steps after the moment of submission in the CTIS/Toetsingonline. The steps are explained in more detail below and then further elaborated with the activities per role.



More information about the local suitability procedure and the use of the VGO and the developed instruction training can be found at the DCRF academy: https://dcrfacademie.nl/trainingen/vgo

Local suitability and feasibility in 4 steps:

Step 1: Inventory of sites/ site selection

Step 1 is the period in which the sponsor requires to identify sites. After site selection, the sponsor submits the following documents to the local principal investigator: the protocol, the minimum global budget and the pre-filled VGO. The VGO translates the protocol into instructions for the supporting departments; what is required from the involved supporters/departments to execute the protocol at the site?

Step 2: Arranging local suitability at the site

During Step 2, the local principal investigator within the site discusses with the relevant supporting departments the feasibility of the study procedures. The investigator arranges, if necessary, with the help of a research coordinator and/or the research office of their own site, that the outcome of this consultation is recorded in the Site Suitability Declaration Form (Verklaring Geschiktheid Onderzoeksinstelling, VGO). The VGO is the document that provides the suitability of the study facilities. The VGO is used by the review committee when reviewing Part 2 of the CTA dossier (see section 'Situation after 31 January, 2022').

The appendices of the VGO outline what is expected of the supporting departments.

The VGO is signed by the Board of Directors (Raad van Bestuur, RvB) or mandated person to confirm the suitability of the site. This associated with a conditional clause in the Clinical Trial Agreement (CTA) that links the VGO to the Clinical Trial Agreement and the approval of the

reviewing committee. All three documents constitute the legal basis for the start of a clinical trial at a site.

During step 1, a minimal global budget is specified and this budget is further negotiated after the VGO has been signed. In principle, this minimum budget will only be reduced if procedures are deleted. This means that a site is never obliged to conduct the research for too low a fee.

A site can always choose to withdraw after signing the VGO.

Step 3: Review of research by Reviewing Committee assessment of local feasibility

Step 3 represents the period of time required by the Member States to review the clinical trial. During this period, the sponsor answers questions from the reviewing committee of the reporting Member State (rMS).

.Immediately after submission, the sponsor will share relevant documents from the CTA dossier with the participating sites for the local files (Investigator Site File). With these documents, the local principal investigator can work with the supporting departments involved during Step 3 on outlining the various working documents (manuals etc.), and various operational and financial agreements can also be further elaborated upon.

The sponsor will share the (final) documents, as mentioned in the Checklist Local feasibility as soon as possible after the question round of the review committee. The checklist contains the documents required by the site from the sponsor and investigator. Based on this documentation, the local suitability procedure can be completed and the final budget can be determined with the sponsor. As soon as this process is completed, the clinical trial agreement (CTA) will be signed, in principle before the approval of the reviewing committee is issued.

In case after the medical-ethical review documents are changed, the sponsor shares the final versions, together with the review outcome with the participating sites.

Step 4: Initiation-visit and start inclusion trial subjects
Step 4 is the period after reviewing MREC approval. This includes: startup of the study at the site and including the trial subjects.

Step by step activities of the sponsor and investigator

The steps mentioned above are further elaborated below.

Step 1: Inventory of participating sites

Essential documents:

- ***Protocol***
  In the protocol, the sponsor indicates in sufficient detail which procedures are required to execute the research. If available, this information can be supported with various (draft) manuals.

- ***Site Suitability Declaration (Verklaring Geschiktheid Onderzoeksinstelling, VGO form)***
  The VGO exist of the VGO and appendices.
  The sponsor provides a pre-filled, site-specific VGO..

  The appendices contain general information about the study, such as sponsor's details, study title, study medication used, etc. In addition, there is an appendix for all supporting departments, listing the necessary procedures during the study. The appendices are pre-filled by the sponsor, so the requirements are clear to the supporting departments. The Investigator, together with the supporting departments, can use this information to determine whether the study can be conducted at site.

  The latest version of the VGO can be downloaded from the CCMO website.

  By signing the VGO, the (mandated representative of the) Board of Directors/Management declares that its site is suitable to conduct the intended research. The signed version of the VGO becomes part of Part 2 of the CTA dossier.

- ***Estimated Budget and concept Clinical Trial Agreement (CTA)***
  The sponsor provides in the VGO an estimation of the minimal global per trial subject budget. Establishing the final budget is part of Step 2, in which local operational and financial preparation, including document management, is completed.

  On the CCMO website the template CTAs and template Informed Consent Form (ICF) are available. established for the Netherlands

  The sponsor, the site and the investigator record the arrangements in the CTA. This standard contract contains a paragraph stating that when the contract is signed by the Board of Directors, *before* the review committee has authorized the study, the Board of Directors (or mandated person) provides permission to the investigator, subject to conditions precedent, to execute the research at its site. The conditions precedent are:

    - approval for study execution by the reviewing committee;
    - adjustment of the agreements in the contract, including financial agreements, if is necessary according to the assessment report of the reviewing committee.

  In this legally secured parallel process, the CTA must be signed before the reviewing committee's approval is issued.

Timelines

The submission date for the central review is the deadline for the VGO. For clinical trials under CTR, this is the planned European submission in the CTIS portal. This date is determined by the sponsor (or the CRO concerned) and communicated in the VGO.

On the VGO, the sponsor states a date on which, at the latest, the Investigator is obliged to submit the VGO, signed by the Board of Directors (or its mandated party) to the sponsor. The Investigator needs at least 2 weeks to collect the information from the supporting departments and to collect the signature from the Board of Directors, or its authorized representative. Following this, the sponsor needs a maximum of one week to process the supplied VGOs in the CTIS portal.

Step 2: Delivery of signed VGO

1. Establishment of site suitability in VGO:
    a. Upon receipt of all relevant information (see Step 1) and prior to the submission of Part 2 of the CTA dossier, the local principal investigator possibly together with the research office (Wetenschapsbureau) and/or the research coordinator at the participating site, discusses the site's suitability with all relevant supporting departments.
    b. During this consultation, the local principal investigator coordinates with all involved supporting departments, such as the pharmacy, the laboratory, the radiology department, etc. whether they would be able to participate in the research within planning and the globally available budget, based on the protocol and the site- and study-specific VGO.
    c. During or after the suitability meeting, the local principal investigator/research coordinator/employee of the research office (Wetenschapsbureau) will record the outcome of the consultation based of the VGO: *we can do it*
2. Informing the Board of Directors:
    a. The local principal investigator confirms the agreements made based on the information in the appendices of the VGO.
    b. The information from the appendices is sent to the (representative of the) Board of Directors for information. If the latter agrees to conduct the research at their site, they will ensure signing the VGO.
3. Providing information about the suitability of the sites for the purpose of review:
    a. The local principal investigator sends the VGO, signed by the Board of Directors or its mandated authority, to the sponsor to submit for the review of Part 2 of the CTA dossier.
    b. The local principal investigator sends the remaining required information to the sponsor for the CTA dossier:
        i. Resumes (CV's)
        ii. The contact details of the participating site for the ICF, in addition to the details of the data controller and the data protection officer of the site.
4. The sponsor submits the CTA in the CTIS/ToetsingOnline for the medical-ethical review.

Step 3: Review of research by reviewing committee and completion of trial preparation

1. Determination of the Final budget
   After the VGO has been signed, the final budget is determined during step 3 based on discussions with and offers from the supporting departments. This is performed parallel to the central review.
2. Verification of local suitability
   In parallel to the MREC review the verification of local suitability occurs conform the local feasibility checklist. The latest version of the local feasibility checklist can be downloaded from the DCRF website. Immediately after the question round, the sponsor shares the final, submitted documents and also the documents submitted after the EC query round with the participating sites, so there is sufficient insight into the final form of the study so the institutions can prepare for the actual local implementation. This involves checking within the site whether:
   - the ICF contains the local information,
   - the principal investigator is suitable according to local requirements,
   - operational and financial agreements have been finalized,
   - working documents have been developed.
3. Signing of the standard clinical trial agreement (CTA)
   The signing can take place when the local suitability has been verified only after the sponsor has answered the questions of the reviewing committee, and before the approval of the reviewing MREC. Based on the, by sponsor provided, documents to the participating sites the local suitability verification should be completed in a timely manner.
   Upon signing the CTA, in which the 'conditions precedent' are described, the Board of Directors gives conditional approval for the trial to be conducted. The study can only be conducted if these suspending conditions are met.
4. Work processes
   In order to enable a quick initiation of the inclusion of trial subjects, the sponsor, in agreement with the participating sites, ensures the following to take place during the review procedure:
   a. all working documents for the supporting departments (pharmacy, lab, etc.) are made and shared with all participating sites before the start of the inclusion period;
   b. all involved parties are trained, if necessary, to be authorized to execute the study (GCP-WMO, BROK, study-specific training, etc.);
   c. the (pre-)initiation visits are carried out in the sites.

Step 4: Start inclusion trial subjects

When the study has been approved by the review committee and the research contract (CTA) has been signed in full, the conditional approval of the Executive Board changes into definitive approval. This means that the execution of the study at the site can start on short term.