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

Title: From mutual acceptance to a signed local declaration of suitability

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Introduction

Cause

The EU Regulation concerning *clinical trials of medicinal products for human use*[1] *536/2014* will apply from January 2022 onwards. 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 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 denotes 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 "Situation *after* January 2022"). 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.

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).

[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.
[2] The CTR uses the term reviewing committee and not MREC.

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 possible through:

- Assessing the site suitability *before* submission to the reviewing committee, rather than afterwards,
  and
- Aligning the local feasibility assessment with the assessment by the reviewing committee.

The implementation of this procedure will contribute to keeping Dutch study sites attractive. After all, there will be competition from other participating Member States in multinational research. It is important to continue to participate in clinical trial as this contributes to:

- The knowledge level of doctors 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 a lack of knowledge of, and experience with new treatment options;
- Employment opportunities in both companies and sites.

For sponsors It is of importance to ensure a timely and complete submission of documents necessary for local agreements in the participating sites. For that, a participating site requires a minimum of 2 weeks. The sponsor should take this into consideration when determining the date of submission.

The sites must organize their processes in such a way that the VGO can be supplied to the sponsor in time, i.e. *before* the application for the central medical-ethical review has been submitted.

Situation *after* 31 January 2022

1. The submission process for medical-ethical review of clinical trials will change as a result of new EU legislation. This applies to both investigator-initiated and company-initiated trials.
2. The review of clinical trials in 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 Part 2 is reviewed by the individual Member States.
3. The standard research file submitted by the sponsors consists of two parts:
   - 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)

- 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 review file 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.
6. Review: In a multinational clinical trial, each Member State concerned receives Part 1 of the submission dossier and provides their feedback to the reporting member state (rMS), who collects the feedback and responds to the sponsor. The review of Part 2 is executed by each Member State concerned. In the Netherlands, the committee that reviews Part 1 also assesses and reports on Part 2.
7. Assignment of Part 2 of the research file 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 research file 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). For these studies, the VGO will be used as an explanation of the site suitability for the reviewing committee. However, the timelines for submission of the review file and that of substantial amendments are unchanged under the current situation.

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 (expected by mid-2022).

Procedure Local Suitability and local feasibility

The members of the DCRF's Local Feasibility Task Force have made a proposal for a Site Suitability procedure, 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. With this approach, the start-up process of clinical trials in the Netherlands follows the requirements of the new European legislation (CTR). Following the procedure enables 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.

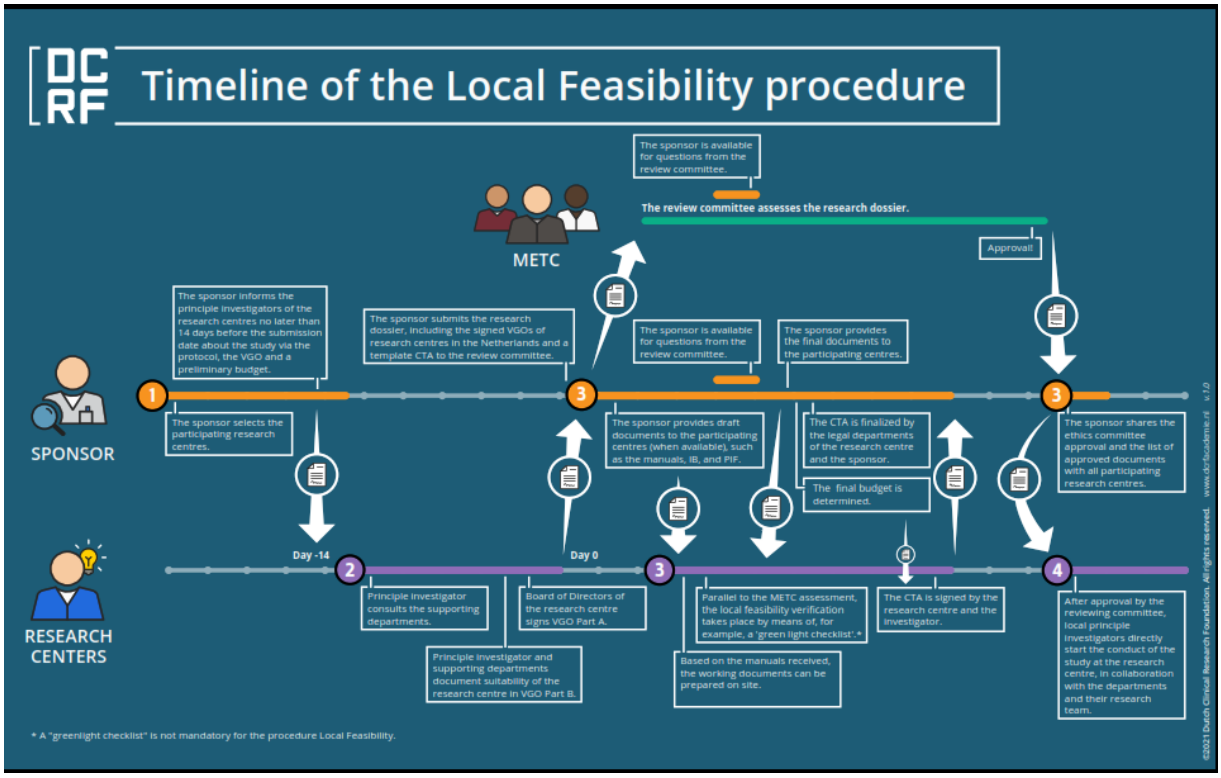
Setup

The core of the procedure is the time at which a complete research file is 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, up to and including the inclusion of the first subject.

The procedure is divided into 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 for the sponsor and investigator.



More information about the local feasibility 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

Step 1 is the period that the sponsor recruits trial sites. After a site has been selected, 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 hospital departments to execute the protocol at the trial site?

Step 2: Arranging local suitability at the trial site

During Step 2, the local principal investigator within the trial site discusses with the relevant supporting departments the feasibility of the 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 confirms the suitability of the study facilities. Part A of the VGO is used by the review committee when reviewing Part 2 of the research file (see section 'Situation after 31 January, 2022').

Part B and the appendices of the VGO outline what is expected of participating sites.

Part A is signed by the Board of Directors (Raad van Bestuur, RvB) or delegate to confirm the suitability of the site. This includes a conditionality clause that links the VGO to the Clinical Trial

Agreement (CTA) and the approval of the reviewing committee. All three together constitute the legal basis for the start of a clinical trial.

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) as well as the questions from the Member State concerned (MSc).

In parallel, the preparation of the research is completed. This includes sharing relevant documents from the research file with the participating sites for the local files (Investigator Site File). With these documents, the local principal investigator can work with the departments involved during Step 3 on outlining the various working documents (manuals etc.). 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 feasibility 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 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 MREC approval. This includes: startup of the study and including the trial subjects.

Activities of the sponsor and investigator per step

The steps mentioned above are further elaborated below.

Step 1: Inventory of participating trial 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)***
  The sponsor provides a pre-filled, site-specific VGO, in which the Investigator can record the

results of the suitability meeting. The latest version of the VGO can be downloaded from the CCMO website.
The VGO consists of Part A and Part B. By signing Part A, the Board of Directors/ management declares that its site is suitable for conducting the intended study. The signed version of Part A becomes part of Part 2 of the clinical trial application.
Part B of the VGO contains general information about the study, such as the sponsor's details, the title of the study, the study medication used, etc. This part also contains an appendix for all supporting departments involved, 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.

- ***Estimated Budget and concept Clinical Trial Agreement (CTA)***

  The sponsor provides an estimation of the minimal globally available budget.

  The sponsor is advised to use one of the template CTAs that have been established for the Netherlands, and also to use the template Informed Consent Form (ICF).

  The sponsor supplies the standard clinical trial agreement to record the arrangements. 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 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 step 1 a concept Clinical Trial Agreement will be provided. The attachments including the details of the contract are completed during Steps 2 and 3, after which the contract can be signed.

  The latest version of the standard research contract (CTA) can be downloaded from the CCMO website.

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).

On the VGO, the sponsor states a date on which, at the latest, the Investigator is obliged to submit Part A of 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 involved 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 Part A of the 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 research file, the local principal investigator possibly together with the research office (Wetenschapsbureau) and/or the research coordinator at the participating site discusses the study with all relevant supporting departments to determine local suitability.
    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 on Part B of the VGO.
2. Informing the Board of Directors:
    a. The local principal investigator confirms the agreements made based on the information in Part B and the appendices of the VGO.
    b. The information from part B of the VGO 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 of Part A of the VGO.
3. Providing information about the suitability of the sites for the purpose of review:
    a. The local principal investigator sends the Part A of 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 research file.
    b. The local principal investigator sends the remaining required information to the sponsor for the research file:
        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 file 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 feasibility
   in parallel to the MREC review The verification of local feasibility occurs by means of 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 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 feasibility has been verified only after the sponsor has answered the questions of the reviewing committee, and before the approval of the MREC. If the sponsor shares the final, submitted documents with the participating sites immediately after the question round, the local feasibility verification can be completed based on sufficient insight into the final form of the study.
   Upon signing the standard contract, 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 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 involved 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.