

# **Clinical Research with medicinal products in the Netherlands**

## **Instruction Manual**

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**Ministry of Health, Welfare and Sport**

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## Preface

The requirements as described in the EU Clinical Trial Directive 2001/20/EC have been transposed into the revision of the Medical Research in Human Subjects Act<sup>1</sup> and the Medicine Law<sup>2</sup>. The implementation into the daily practice of clinical research has been prepared by a Ministerial Working Group representing all parties involved in clinical research with medicines in the Netherlands.

In a multidisciplinary clinical research team the investigator is the most important player. This manual has been drafted primarily for the investigator. It has become a comprehensive document and guidance on how to conduct clinical research with medicines in the Netherlands in compliance with the regulatory requirements.

**Chapter 1 Overview of changes and general requirements** describes the main changes for the conduct of clinical Research with medicines in the Netherlands.

**Chapter 2 Prior to the start of the clinical trial** concentrates on the preparation and initiation of a clinical trial in the Netherlands in general and a clinical trial with medicines in particular. The tasks and obligations for the investigators, their staff and the sponsor, the accredited ethics committee (aEC) and the competent authority (CA) have been described.

**Chapter 3 During the conduct of the clinical trial** describes the tasks and obligations for investigators and sponsors during the experimental part of the clinical trial and in particular all reporting requirements.

### Chapter 4 Appendices:

List of members of the Working Party for implementation of Directive 2001/20/EC  
List of relevant organisations with contact information  
List of abbreviations and relevant definitions

The Working party for implementation of Directive 2001/20/EC  
*Adam Cohen, chairman*

<sup>1</sup> Also known by its Dutch abbreviation 'WMO'.  
<sup>2</sup> Also known by its Dutch abbreviation 'WOG'.



## Acknowledgements

The membership of the working party was a broad reflection of virtually all parties involved in research with medicinal products . Representatives from government, national institutes, industry, and academia all provided their time and enthusiasm to this project. In addition to the persons mentioned in this acknowledgement many others also provided input and it is impossible to mention all by name.

Herman Pieterse was instrumental in the production of this manual and edited and produced it for a large part. The working party is extremely grateful for his help.

The GCP flow chart in paragraph 2 has been kindly supplied by Profess Medical Consultancy B.V.



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# Chapter 1

## Overview of changes and general requirements

In this chapter the most important changes in the WMO are described. Although a few alterations concern all research with human subjects, the most important only involve research with medicinal products.

### 1.1 Approval of the protocol by two bodies

The review of the dossier for clinical research is primarily conducted by the accredited Ethics Committee (aEC) or the CCMO. In addition, the Competent Authority (CA) should decide whether there are "grounds for non-acceptance" concerning the study. In the Netherlands the CA will only perform a limited check on completeness of records and will check the EudraVigilance database (Clinical Trial Module) for serious adverse reactions which form an unacceptable risk for the subject of the study. Also a check of relevant inspection reports by the Health Inspectorate will be made in the EudraCT database. In most cases (dossiers for which the medical-ethical review will be conducted by an accredited Ethics Committee) the CCMO has been appointed as the Competent Authority. For the protocols for which the CCMO conducts the medical-ethical review (see [www.ccmo.nl](http://www.ccmo.nl) for recent information) the Minister of Health, Welfare and Sport is the Competent Authority. The assessment by the Ethics Committee and by the Competent Authority may be conducted in parallel or sequentially, to be decided by the sponsor.

### 1.2 Timelines

The timelines within which the accredited Ethics Committee (60 days) and the Competent Authority (14 days) have to reach their decision are limited.

### 1.3 EudraCT database

The European database has been built to provide European regulatory authorities with an overview of clinical trials being conducted in the community. It will facilitate communication between the authorities and will enable them to have a better overview of ongoing clinical trials and investigational medicinal product development. This will ensure enhanced protection of clinical trial subjects. It is foreseen that the EudraCT database with information on the clinical trial is linked to the EudraVigilance Clinical Trial Module for the reporting of Suspected Unexpected Serious Adverse Reactions (SUSAR). The EudraCT database and the EudraVigilance Clinical Trial Module share common key fields including the clinical trial identification (EudraCT number and sponsor protocol code number), the product identification and the sponsor identification.

#### 1.4 Expertise of Ethics Committees

To evaluate the information concerning the investigational medicinal product(s), accredited Ethics Committees that review protocols for research with medicinal products need to appoint a qualified hospital pharmacist and a clinical pharmacologist. When the pharmacist is also qualified as clinical pharmacologist or vice versa only one person is sufficient. If the assessment of the product requires special expertise that is beyond the expertise of the pharmacist or pharmacologist, the Ethics Committee can via the CCMO consult an established network of experts (consisting of both institutions and individuals).

#### 1.5 Other changes affecting the review of clinical research by the accredited Ethics Committee

- a The accredited Ethics Committee will, in addition to the aspects that were already mentioned in the WMO before revision, have to pay attention to the payments to investigators and study sites (already included in the current ABR-form).
- b In case a competent subject is physically not able to write, consent may be given orally, in the presence of at least one witness (art. 6).
- c Gene therapy trials may not be carried out which result in modifications of the subject's germ line genetic identity (art. 13c).
- d An accredited Ethics Committee reviewing a protocol for a trial with subjects under the age of 18 should have paediatric expertise or should obtain advice in clinical, ethical and psychosocial aspects in the field of paediatrics (art. 13e sub d).
- e An accredited Ethics Committee reviewing a protocol for a trial with incapacitated adult subjects unable to give consent should have expertise in the relevant disease and the patient population concerned or should obtain advice in clinical, ethical and psychosocial aspects in the field of the disease and the population concerned (art. 13f sub c).
- f The statutes of an accredited Ethics Committee should contain the provision that a member that is personally involved in the protocol will not take part in the discussion and decision concerning that protocol (art. 14 sub 9).

#### 1.6 No appeal anymore with the CCMO

Under the old legislation, parties could file an appeal with the CCMO against an Ethics Committee decision. This will no longer be possible for research with medicinal products, since the CCMO is already involved in the review process as the Competent Authority. The first level of appeal is the accredited Ethics Committee that reviewed the dossier. Under the new legislation, the second level of appeal is with a court of

law. However, since the review process of the Competent Authority is now largely an administrative check, some advocate to restore the appeal at the CCMO. This would require an adjustment of the WMO. After the implementation this issue will be discussed with all parties involved.

#### 1.7 Notification of adverse events and end of trial

Serious adverse events and suspected unexpected serious adverse reactions have to be notified. Annual reports of suspected serious adverse reactions have to be submitted (articles 13 l, o, p, and q).

#### 1.8 A trial with a medicinal product?

In the Clinical Trial Directive, non-interventional studies with medicinal products are defined as studies in which the medicinal product is investigated in normal medical practice, and in which subjects are not subjected to treatment or required to change their behaviour. This means that the tests and procedures involved do not deviate from normal medical practice, i.e. the frequency of the tests and the extent of the tests are not changed with the aim to answer a scientific question. Moreover, the patient must not be allocated to one of several treatments by randomisation and the patient may not be specifically recruited for the study under a set of in- and exclusion criteria. If all these conditions are met the study is non-interventional and the Directive does not apply.

Trials that fall under this section of the law involve the administration of classical small molecule medicines, but also gene therapy vectors, allogenic cell therapy, xenotransplantation and proteins. Endogenous substances – even administered in physiological dosage – also fall under the directive. Background medication, diagnostic agents or substances used to evoke certain biological responses for research purposes (challenge medication) may fall under the directive if the substance is object of investigation in the trial or if the product is not authorized in the Netherlands for the indication (This item is still under discussion). It needs to be stressed up front that the supplied information to the ethics committee must always be tailored to the purpose of the trial and the intended use of the substance.

#### 1.9 Definition of a sponsor

Institutions initiating a clinical study with a medicinal product and requesting independent research grants from third parties will be regarded in the Netherlands as the sponsor (in Dutch: "verrichter") of the study. The sponsor is clearly defined in the Dutch law and as such indicated on the application form (ABR-form). The sponsor or a

legal representative of the sponsor should be established as a legal entity in the European Union (EU) (art. 13d sub).

The parties involved in the organisation of the clinical study can agree which party will have the role of the sponsor and hence the sponsor responsibilities according to GCP. It is often self-evident that a pharmaceutical industry performing a multicentre trial, or an academic research group conducting a study with a medicinal product without any assistance from another organisation, is the sponsor of the study. If it is unclear who the sponsor of the study is, the parties should reach agreement about the fulfilment of the various roles. This can also be the case if the envisaged sponsor has no legal EU representative (see paragraph 1.10). The nomination of the sponsor is one of the obligations. A simple contract can solve these issues.

There is no legal objection against a university medical centre or a hospital acting as the sponsor of a study performed with a pharmaceutical company provided that centre will take the responsibility that all required functions and tasks will be fulfilled according to Good Clinical Practice. This does not necessarily mean that the sponsor has to physically perform all these obligations - assurance that they are fulfilled is sufficient (for instance by a contract with a list of tasks).

### 1.10 Sponsor's legal representative

The sponsor should have a legal representative in the European Union. The legal representative is responsible for the proper conduct of the clinical trial. The tasks and responsibilities of the legal representative should be described in full detail in a contract.

A legal representative is a natural person or a legal entity that can act on behalf of the sponsor with regard to the performance of the trial in question. It is recognised that many sponsoring organisations and companies have no legal representative in the EU and this should not be an impediment for performing trials in the Netherlands. The simplest solution is to arrange that the organisation that performs the trial in the Netherlands is nominated as the sponsor and that the different obligations are laid down in a contract. However, other arrangements are acceptable, provided that obligations with regard to subject safety and integrity of the results are fulfilled.

### 1.11 Study medication and devices free of charge

Investigational medicinal products and the devices used for their administration should be made available to the subjects by the sponsor free of charge. In the law an exception is made for registered medicines, even if they are administered in a trial for another indication. (art. 13d sub b). The reason for this exception is that the obligation to dispose the medicinal products free of charge was a great hindrance to non-

commercial studies. The funding of the investigational medicinal products will remain similar to the situation before the change of the WMO (art. 13d sub b).

### 1.12 Inspections by the Health Care Inspectorate of the Ministry of Health, Welfare and Sport

Section 15 of the Directive 2001/20/EC clearly explains: *"whereas the verification of compliance with the standards of Good Clinical Practice and the need to subject data, information and documents to an inspection in order to confirm that they have been properly generated, recorded and reported, are essential in order to justify the involvement of human subjects in clinical trials"*.

Such GCP inspections can take place before, during or after the conduct of clinical trials, and/or as part of the verification of applications for marketing authorizations (or follow-up to these). Systems for the conduct of GCP inspections have been established in The Netherlands. The changes in legislation will not result in major changes in the practical conduct of these inspections. The inspection reports will be made available to the sponsor of a study while safeguarding the confidential aspects and privacy of the subjects. The inspection reports will also be made available to the other EU Member States, to the accredited Ethics Committee and the Agency (EMA) at their reasoned request. All inspections will be recorded in the EudraCT database. The results of the inspections shall be recognised by all the other EU Member States (mutual recognition). The effect of this increase in formal communication will further enhance the protection of the subjects and the quality of the data of the clinical trials.

### 1.13 Transition period

Applications submitted before the implementation date of the new trial law in the Netherlands, will be reviewed according to the old regulations. This means that only a positive decision of the accredited Ethics Committee is required, and no EudraCT number or IMPD has to be submitted before that date.

For trials submitted before the implementation date but extending beyond this date, SUSARs have to be notified according to the new regulations. An IMPD or EudraCT number will not have to be submitted. However this information should be provided in those cases where additional product information is necessary to evaluate the SUSAR.

For studies started under the old regulations, the notification of an amendment and of the end of the trial may be done according to the old regime. However (e.g. in international trials), notification according to the new rules is also allowed. Annual safety reports also have to be submitted for those trials. The reporting time frame starts with the date of approval of the trial by the accredited Ethics Committee, if there is no international starting date.



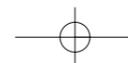
## Chapter 2

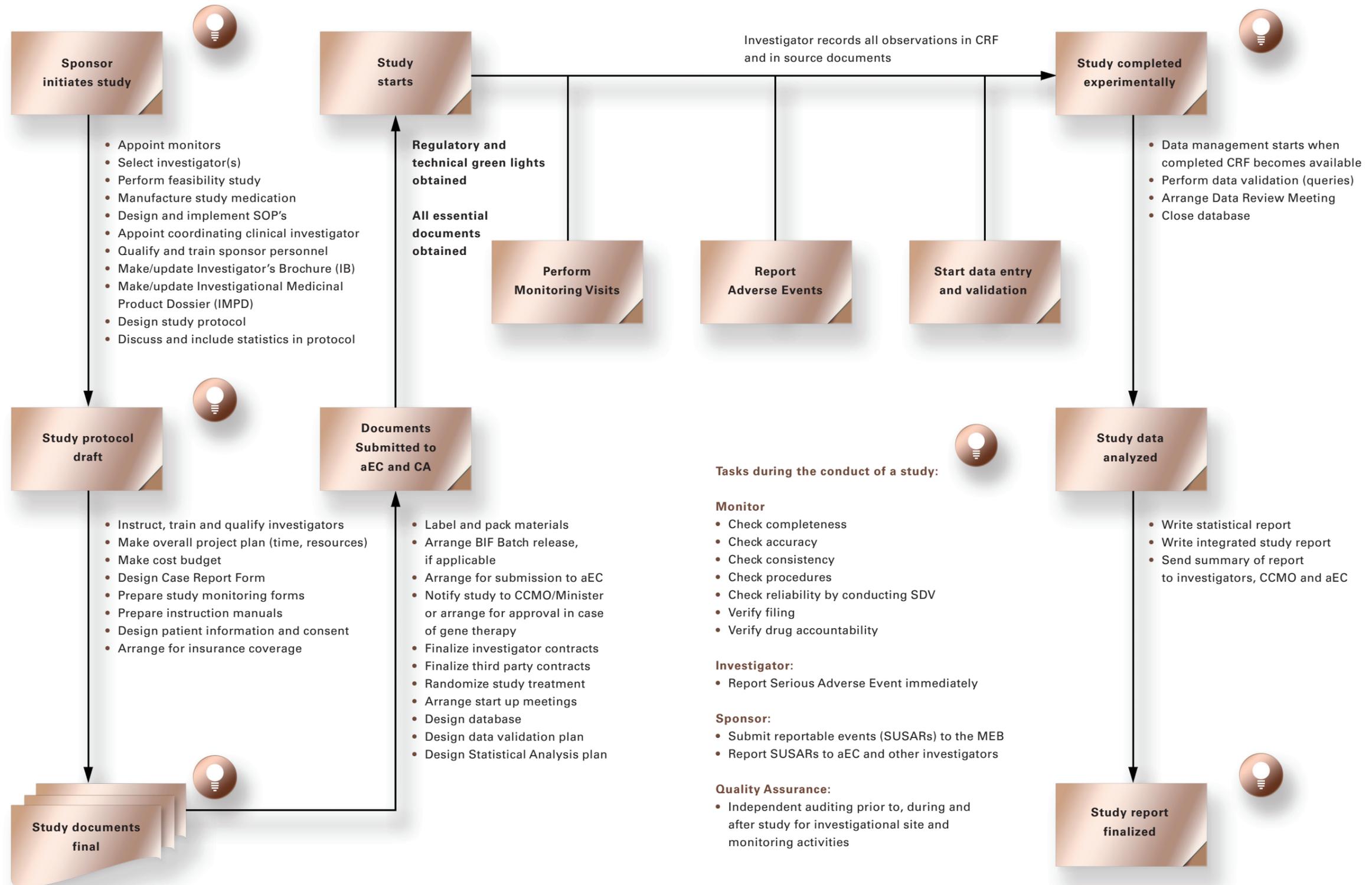
### Prior to the start of the study

A general listing of the tasks and responsibilities of the sponsor, monitor and investigator is given in the ICH GCP guideline for clinical trials with medicinal products (CPMP/135/95).

Compliance with this guideline ensures the safety, welfare and personal integrity of the subject who is participating in a clinical trial. Moreover, when the tasks are conducted in compliance with the guideline then the responsible person can guarantee that the data that are collected are reliable.

An overview of the tasks and responsibilities has been given in the GCP Flow Chart on the next page.







**Other sponsor responsibilities:**

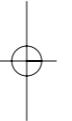
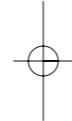
- Sign approved study protocol
- Ensure that all deviations from protocol are reported and accounted for
- Ensure that all AEs are reported as required
- Inform all investigators about all SAEs
- Inform investigator when study is terminated prematurely or suspended
- Inform investigators on development status drug
- Review and approve deviations from study protocol
- Collect, store, keep secured and ensure completion of essential documents

**Other monitor responsibilities:**

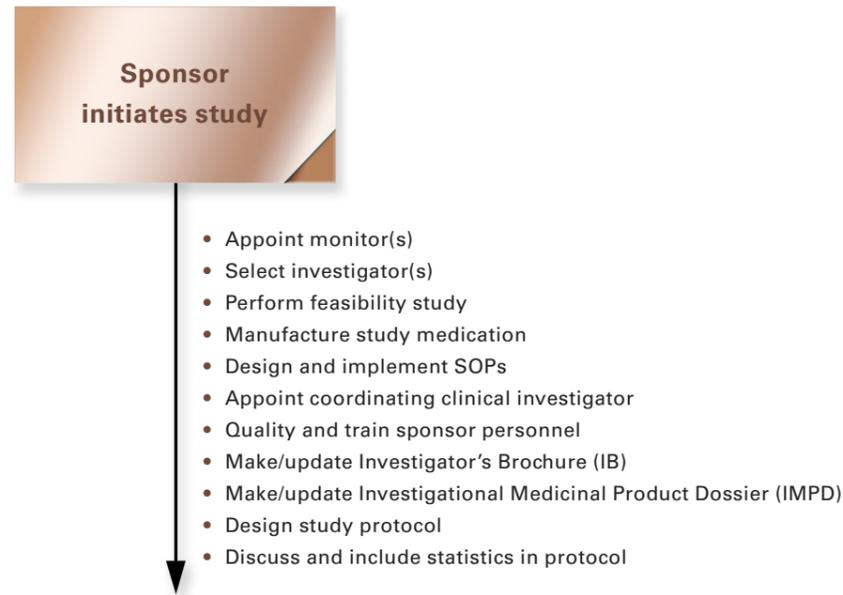
- Verify if compliance with protocol is maintained
- Verify if drug is used according to plan
- Verify qualification of investigational staff
- Verify if investigator has access to adequate number of subjects
- Verify if informed consents are properly signed and dated
- Verify if AEs have been recorded and reported adequately
- Verify drug accountability and traceability
- Verify maintenance and calibration equipment
- Verify recording subject withdrawal, non-compliance
- Report monitoring visits

**Other investigator responsibilities:**

- Have resources to conduct study
- Has adequate facilities and competent staff
- Instructs staff on study protocol
- Has no conflict of interest
- Knows the drug and its properties
- Knows the study protocol
- Supports the monitor and auditor
- Communicates deviations from the protocol
- Ensures compliance with the protocol for all staff
- Protects health and welfare of subjects
- Communicates with the aEC on SAEs and submission of amendments
- Endeavors to ensure adequate recruitment
- Ensures that informed consent is obtained and documented
- Reports any deviation due to emergency
- Ensures drug accountability



According to the ICH GCP Guideline (135/95/CPMP) the sponsor of a clinical study with a medicinal products should initiate the tasks and activities as indicated in the figure below.



For the design of a study protocol the CCMO has made an extensive protocol template that can be downloaded from the website [www.ccmo.nl](http://www.ccmo.nl)

For the design of the product documentation like the Investigator Brochure chapter 7 of the ICH GCP guideline gives a comprehensive Table of Contents and guidance on how to prepare an IB.

The contents and structure of an IMPD has been published on the CCMO website [http://www.ccmo.nl/English/legal\\_framework/implementation\\_EU\\_directive\\_2001/20/EU/example\\_IMPD](http://www.ccmo.nl/English/legal_framework/implementation_EU_directive_2001/20/EU/example_IMPD) (implementation EU Directive 2001/20/EU). This template will be updated regularly by the CCMO.

## 2.1. EudraCT number

The new EudraCT database will give an overview of all clinical research with medicinal products being conducted in the EU and will facilitate planning of inspections for compliance with Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) standards. The database is confidential and accessible only to the Competent Authorities of the Member States, the EMEA and the European Commission. Sponsors do not have access to the database.

Each clinical study gets a unique number (EudraCT number) that will be generated automatically. The printed form displaying the EudraCT number must be included in the submission of the request for the trial to the competent authorities and ethics committees, and the EudraCT number must be used in any amendments or the end of trial report. The EudraCT number will also be used for SUSAR reporting.

The EudraCT application will also provide access to standard forms for the Clinical Trial Authorisation application, the Ethics Committee Application, the notification of substantial amendments and the notification at the end of the trial. The EudraCT system is designed to meet the minimum requirements of the Directive. Sponsors can access the standard forms and other functionalities via a public site only. The sponsor does not yet file the data in a central database, but data needs to be filed locally on the sponsor's computer system.

Surf to <http://eudract.emea.eu.int> to obtain a EudraCT number.

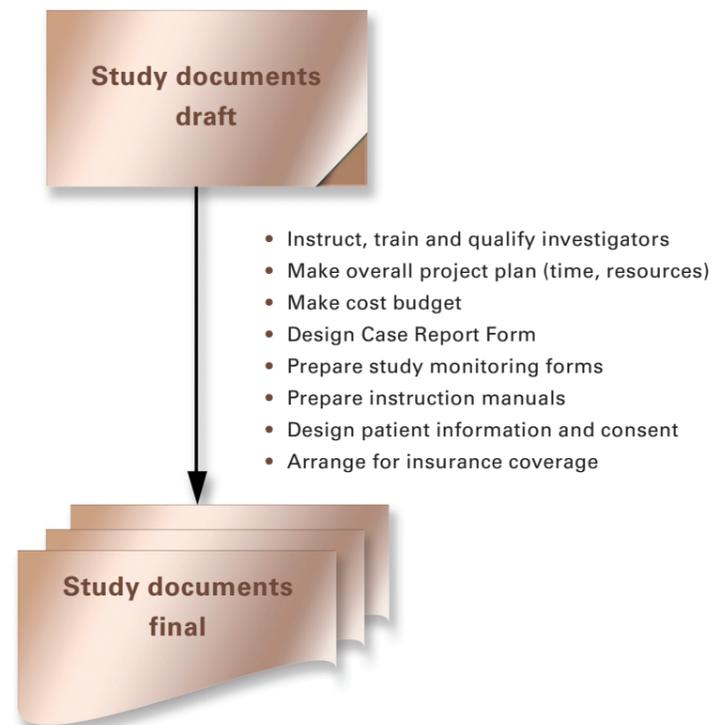
Details can be found in the guidance document:

[http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/april/cp\\_and\\_guidance\\_eudract\\_april\\_04.pdf](http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/april/cp_and_guidance_eudract_april_04.pdf)

In order to facilitate the implementation of the database and to enable search and reporting functions, data should be entered in English wherever possible. Where feasible dropdown menus/pick lists are provided in other languages. It is recognised that not all dictionaries will be available in all official EU languages and may initially exist only in English.

**What should be done next?**

At the completion of the design phase of a clinical study a final study protocol should be available. In case of a multicentre study, a number of investigators should have been selected. After the design phase of a clinical study internal preparatory activities will start as indicated in the figure below.



- The SOP-Z quality system is a tool for the design of a project plan, a Case Report Form, and all other study forms and manuals ([www.profess.nl](http://www.profess.nl)).
- For the design of the patient information and consent forms details can be found in Chapter 4.8.10 of the ICH GCP Guideline or the CCMO website; go to one of the appendices of the Quality Handbook for Accredited Ethics Committees [http://www.ipfier2.nl/hipe/uploads/downloads/Toetsingshandleiding-2002\\_ENG\(1\).pdf](http://www.ipfier2.nl/hipe/uploads/downloads/Toetsingshandleiding-2002_ENG(1).pdf)
- Insurance should be arranged according to the WMO. Details can be found on the CCMO website: [http://www.ccmo.nl/English/legal\\_framework/insurance](http://www.ccmo.nl/English/legal_framework/insurance)

**2.2 Design and maintenance of Investigator's Brochure (IB) and IMPD****2.2.1 How to design an Investigator's Brochure?**

The Investigator's Brochure (IB) is a compilation of the clinical and non-clinical data on the investigational product(s) that are relevant to the study in human subjects. It will provide the investigators and others with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the study, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures. The IB should also support the clinical management of the study subjects during the course of the clinical trial.

The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

The guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. In a study with a marketed product that will be investigated for a new use (i.e., a new indication), then an IB specific to that new use should be prepared.

- The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the accredited ethics committees (aECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible aECs. In the case of an investigator-sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer.

 If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, background information in the trial protocol that contains the minimum current information described in this guideline. Such an approach may also be applicable to diagnostic agents or substances used in physiological experiments (challenge agents).

For detailed information on the general contents of the IB Chapter 7 of the ICH GCP guideline should be consulted.

### 2.2.2 How to design an Investigational Medicinal Product Dossier

The Investigational Medicinal Product Dossier (IMPD) is part of the information that has to be supplied to the accredited ethics committee and the competent authority in the Netherlands. The general contents for this document are described in the relevant guidelines: 'Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use' (as required by Article 8 of Dir. 2001/20/EC) [http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/april/cp\\_and\\_guidance\\_CA\\_rev\\_28\\_Apr\\_04\\_Final.pdf](http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/april/cp_and_guidance_CA_rev_28_Apr_04_Final.pdf)

In the Netherlands all product documents will be reviewed by the accredited ethics committee. The guidance is directed towards both non-commercial and commercial sponsors as well as to the Ethics Committees to provide a minimum standard of documentation required.

For the purpose of this section the accredited ethics committee and the Competent Authority are taken as one (indicated as aEC/CA) because the documents that will be supplied to both bodies are identical.

 The contents of the IB and the IMPD are given in the relevant guidelines. However it needs to be stressed that the purpose of this information is not the registration of the medicinal product for general use, but rather a particular clinical trial about which the aEC/CA will give an opinion. It is not efficient to supply a large amount of irrelevant information as this will take an inordinate amount of time of the authorities. An example of an IMPD is available for downloading at [www.cmo.nl](http://www.cmo.nl)

**The IB/IMPD must contain sufficient information about the treatments used in the trial for the aEC/CA to reach a decision on the safety of the subjects in the proposed study and the validity of the scientific objectives. This information cannot be seen in isolation from the study protocol that will be used by the aEC/CA to reach its final decision.**

This indicates that the amount of information about a certain chemical or biological entity depends on the nature of the entity and the nature of the intended trial. A relatively well-known entity in a simple intervention trial will require a small amount of information. For a gene therapy vector the information is likely to be extensive. The final decision about which level of detail is provided is left to the sponsor. After submission the aEC/CA decides if the information is sufficient and the aEC/CA always has the right to request more information.

If the IB is set up as a self-contained document this can be supplied to investigators and study centres in a multicentre study without the IMPD which only has to be submitted to the ethics committee and the competent authority.

### 2.2.3 How to avoid duplication of non-clinical and clinical information as needed in the IMPD and also described in the IB?

The IMPD should contain in addition to the IB, the available chemical, biological and pharmaceutical data.

The IB and IMPD may be combined into one document, at the sponsor's discretion and depending on the development status of the investigational product, which, for instance, depends on the availability of a registered Summary of Product Characteristics (SPC).

The preclinical and clinical information can be supplied in the IB but also in the IMPD. It is left to the sponsor how to split the information between the IB and the IMPD. This also holds for the physical presentation: separate documents for the IB and the IMPD, the IB with the IMPD as an appendix, or one integrated document are all equally acceptable. It is advised to have as little overlap between the two documents as possible. This can be done by cross referencing between the two documents. The most efficient approach may be to supply the relevant chemical-pharmaceutical data in the IMPD. The relevant preclinical and clinical data and a short summary of the pharmaceutical information can then be taken up in the IB.

### 2.2.4 When to update the IB or the IMPD and how?

The IB should be evaluated at least once a year and revised when appropriate according to the guidelines of the sponsor. Revision should include the SUSARs, as mentioned above. This means that an IB/IMPD with an issue date of less than 12 months can be submitted to an Ethics Committee, which will assume that no

additional information has become available since the issue date. It needs to be stressed that the sponsor is responsible for the supply of the most recent information and withholding such information will be considered a breach of the law .

Information supplied to the aEC/CA must be up to date. It should be stated in the application that no extra information relevant to the submission is available. Any relevant information that becomes available during the evaluation by the aEC/CA must be supplied immediately. The information is considered relevant if it conforms to the definition of a substantial amendment (see paragraph 3.1.1).

Information on the Investigational Medicinal Product (IMP) to be included in the IB/IMPD, according to the status of the product.

Table 1 Reduced information requirements for IMPs known to the concerned competent authority.

| Types of Previous Assessment   | Quality Data | Non-Clinical Data    | Clinical Data        |
|--|--------------|----------------------|----------------------|
| The IMP has a MA in any EU Member State and is used in the trial:  |              |                      |                      |
| • Within the conditions of the SPC   | SPC          | SPC                  | SPC                  |
| • Outside the conditions of the SPC  | SPC          | Yes (if appropriate) | Yes (if appropriate) |
| • After it has been blinded  | P+A          | SPC                  | SPC                  |
| Another pharmaceutical form or strength of the IMP has a MA in any EU Member State and:                                    |              |                      |                      |
| • the IMP is supplied by the MAH   | P+A          | Yes                  | Yes                  |
| The IMP has no MA in any EU Member State but drug substance is part of product with a marketing authorisation in a MS and: |              |                      |                      |
| • is supplied from the same manufacturer   | P+A          | Yes                  | Yes                  |
| • is supplied from another manufacturer  | S+P+A        | Yes                  | Yes                  |
| The IMP has a previous CTA in the Member State(s) concerned <sup>3</sup> :   |              |                      |                      |
| • no new data available since CTA  | No           | No                   | No                   |
| • new data available since CTA   | New Data     | New Data             | New Data             |
| The IMP is a placebo   | P+A          | No                   | No                   |

S Drug substance data P Drug product data A appendices of the IMPD SPC summary of product characteristics

3 This may require a letter of authorisation to cross-refer to the data submitted by another applicant.

**2.2.5 How to cope with safety updates during the study?**

Safety updates concern suspected unexpected serious adverse reactions (SUSARs; serious adverse events that are likely related or definitely related to the investigational product and have not been documented in the IB or SPC).

Safety updates are in general communicated in the form of a so-called 'Dear doctor letter' or 'Dear investigator letter', along with the corresponding CIOMS report.

Safety updates should be considered as a supplement to the IB until the updated version becomes available.

Safety updates should be incorporated in the updated version of the IB (refer to When to update the IB and how?).

**2.3 Manufacture, import, and release of study medication**

**Manufacture of IMPs in The Netherlands**

For manufacturing of study medication in The Netherlands, a manufacturing license for IMPs is required. Manufacturing includes production, packaging and labelling of the medicinal products. A manufacturing license for IMPs is also required for hospital pharmacies. An application for a manufacturing license can be obtained from the unit Farmatec ([www.farmatec.nl](http://www.farmatec.nl)), a department of the Ministry of Health, Welfare and Sport. Each batch of study medication has to be released by a Qualified Person (QP) of the manufacturing license holder. When a hospital pharmacy is only involved in preparation for use a manufacturer's licence is not necessary. Preparation for use is also relabelling study medication according to a prepared randomisation list. For instance, when a pharmacy receives batches of placebo and active drug that need to be extemporaneously prepared for an individual subject (for instance according to body weight) and blinded (and supplied with a coded label) this is not manufacturing. If the pharmacy prepares batches of placebo and active drug this is considered manufacturing. There is no difference for the above considerations for iv-preparations or aseptic preparation. When it is just preparation for use a manufacturer's license is unnecessary. Also the labelling for extension of the expiry date can be carried out by a hospital pharmacist or a responsible person without a manufacturer's license (see article 33 of Annex 13 of the EU GMP). The relabelling procedure should be conducted according to a written standard operating procedure including quality control by a second competent person.



Further Information on licenses can be obtained on [www.farmatec.nl](http://www.farmatec.nl)

#### Import of IMPs manufactured in a non-EU Member State into The Netherlands

For the import of study medication from a non-EU Member State an import license for IMPs is required. An application for an import license can be obtained from the unit Farmatec ([www.farmatec.nl](http://www.farmatec.nl)). All batches of study medication imported from a non EU Member State must be released by the QP of the import license holder. It has to be verified that the batch has been manufactured and checked in accordance with standards of GMP, that the batch is in accordance with the product specification file and that each batch has been checked with the information in the IMPD. Re-analysis after import from a non-EU Member State is not obliged for IMPs. It is the responsibility of the QP to establish the GMP status of the manufacturer (see also Annex 16 of the EU GMP).

For import of comparator medicinal products that have a marketing authorization in The Netherlands, re-testing is required if a certificate that the batch has been produced according to GMP principles, is not available.

The former notification procedure (notification of import of unregistered products to the Chief Inspector of Health Care) is not applicable after the changes in the Decree on the Manufacture and Supply of Medicines for clinical trials (Besluit Bereiding en Aflevering van Geneesmiddelen, BBA) enter into force, both for IMPs imported from a EU Member State and for IMPs imported from a non-EU Member State.

#### Import of IMPs from a EU Member State

Batches of study medication manufactured in another EU Member State or imported from a non-EU Member State and released in another EU Member State can be distributed either directly to a site in the Netherlands where the study will take place (hospital) pharmacy or to a wholesale license holder in The Netherlands. The IMP does not have to undergo further checks if the batch is imported together with a release certificate signed by the QP of the manufacturer or the importer. The manufacturer or importer should have a license in that Member State.

#### Batch release of immunologically active products

In conformance with the Immunological Medicinal Products Decree, Article 5.e, (the so-called Besluit immunologische farmaceutische producten (Bif)) certain unregistered immunologically active products can only be supplied when production batches are released by the Chief Inspector of Pharmacy and Medical Technology from the Dutch Health Care Inspectorate. On behalf of the Inspectorate, the National Institute for Public Health and the Environment (RIVM) is responsible for administration and execution of the procedure. For further information on the subject, please refer to the website of the RIVM: <http://rivm.nl/en/pubhealth> under the chapter "Batch release unregistered immunological pharmaceutical products" (or for the Dutch version of this information:

[www.rivm.nl/preventie/geneesmiddelen/vrijgifte\\_klinisch\\_proefmateriaal.jsp](http://www.rivm.nl/preventie/geneesmiddelen/vrijgifte_klinisch_proefmateriaal.jsp).

Immunologically active products are defined as substances whose effect is based upon an immunological reaction (i.e. an antigen-antibody interaction or a T-cell mediated immune response). This will include vaccines, gene therapy vectors with an immunological action and antibodies. Although small molecules with an effect on the immune system could also be considered as immunologically active products in this sense, this is not the intention of the regulations and they do not require batch release.

In accordance to current regulations the dossier for the clinical study is assessed by an accredited ethics committee (aEC) or the Central Committee on Research Involving Human Subjects (CCMO). Subject to approval of the applicant, the RIVM/Inspectorate may contact the aEC or CCMO to confer on their opinion and decision. This could prevent any overlap of the decisions of the aEC and/or the CCMO and the batch release by the Chief Inspector for Pharmacy and Medical Technology. In this case the applicant should consider the differences in time frames in order to gear the procedures to one another.

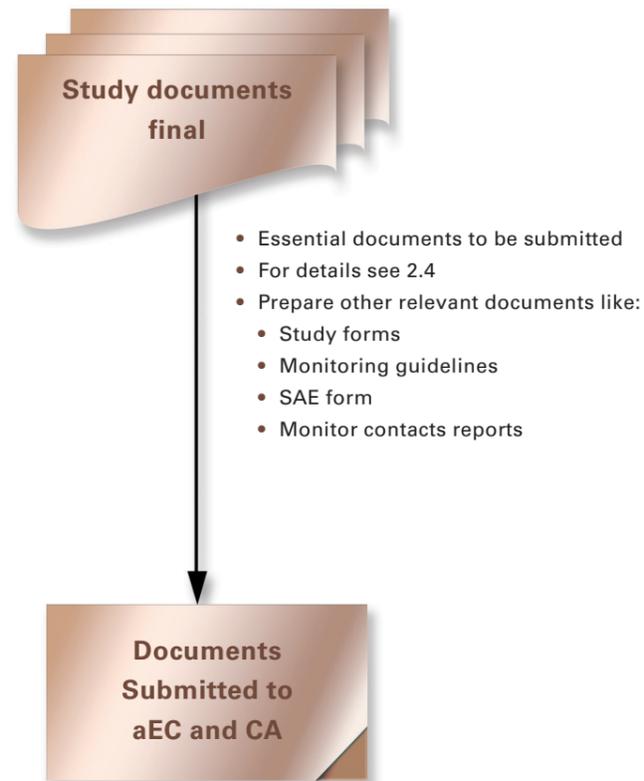


For any questions please contact: [bif-info@rivm.nl](mailto:bif-info@rivm.nl)

#### Required licenses

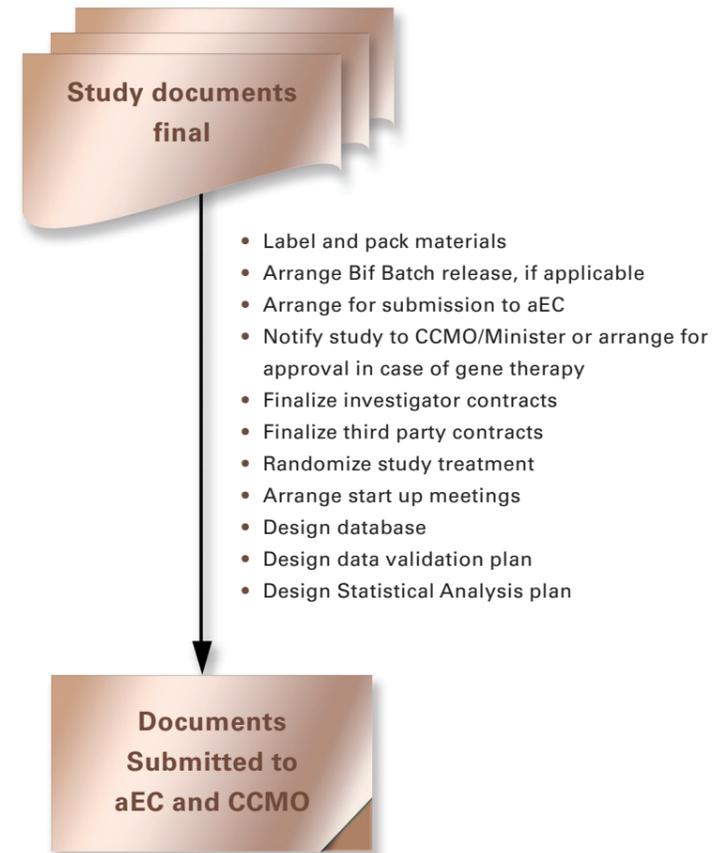
Only pharmacists and wholesale license holders are allowed to store clinical trial material. If a CRO temporarily stores study medication other than for immediate use, a wholesale license is required. Medication cannot be delivered from a license holder to an investigator or patient directly, but can only be delivered to a (hospital) pharmacist. The pharmacist is responsible for distribution to the investigator or the patient.

Next step is to prepare for submission of the trial dossier to the authorities:



## 2.4 Essential documents to be submitted

When all study documents have been completed the required documentation package will be submitted to the aEC and the CCMO/Minister.



Go to the CCMO website to download the latest version of the ABR form and to the EudraCT website to download the European application form. Collect all documents as described in paragraph 2.4. Submit the documentation package. The CCMO is in the final stages of the introduction of the clinical trial portal. This electronic submission site will be introduced in stages, starting in the 4th quarter of 2005 and

will eventually be the single submission site for clinical trial dossiers and other documents in an electronic form. Please refer to the website of the CCMO for updates about these developments.

### Contents of dossier for submission to the accredited Ethics Committee and the Competent Authority

The main parts of the dossier can be divided by tabs numbering with A, B, etc. The subparts should be numbered with A1, A2, etc. It is strongly recommended to follow this table of contents in the order indicated as this will expedite review and filing by the EC and CA.

|          |  |
|----------|--|
| <b>A</b> | <b>Letters</b>   |
| A1       | Cover letter to the aEC (or CA)  |
| A2       | Letter of authorisation from the sponsor if the applicant is not the sponsor                               |
| A3       | Confirmation of receipt of EudraCT-number (e-mail)   |
| <b>B</b> | <b>Forms</b>   |
| B1       | ABR-form and summary (on paper and diskette/ CD-Rom)   |
| B2       | Local addendum to ABR-form, if applicable  |
| B3       | Gene therapy/GGO-form, if applicable   |
| B4       | EudraCT application form (on paper and in XML format on diskette/CD-Rom)                                   |
| <b>C</b> | <b>Protocol and amendments, if applicable</b>  |
| C1       | Study protocol   |
| C2       | Amendments in chronological order  |
| <b>D</b> | <b>Product information</b>   |
| D1       | Investigator's Brochure  |
| D2       | In gene therapy studies: nucleotide sequence of the vector on diskette, in ASCII format                    |
| D3       | IMPD (or SPC, if applicable), including list of relevant trials with the investigational medicinal product |
| D4       | Relevant statements/licenses   |
| D5       | Examples of labels in Dutch  |
| <b>E</b> | <b>Information for the subjects</b>  |
| E1       | Information(s) for subjects and their representatives  |
| E2       | Consent form(s)  |
| E3       | Advertising materials or other means for the recruitment of subjects                                       |

|          |   |
|----------|---|
| <b>F</b> | <b>Questionnaires for the subjects to be used in the study</b>  |
| <b>G</b> | <b>Insurance certificate</b>  |
| G1       | WMO insurance for subjects  |
| G2       | Liability insurance for the investigator and the sponsor  |
| <b>H</b> | <b>CVs</b>  |
| H1       | CV of the independent physician(s)  |
| H2       | CV of the coordinating investigator (for multicentre studies)   |
| <b>I</b> | <b>Information of participating sites in the Netherlands</b>  |
| I1       | List of participating sites with their respective principal investigator  |
| I2       | Declaration of local feasibility from the Hospital Board/ Management per centre (in case of external review, multicentre studies) |
| I3       | CV of the principal investigator per centre.  |
| <b>J</b> | <b>Extra information on financial compensation</b>  |
| J1       | To subjects   |
| J2       | To investigators and sites  |
| <b>K</b> | <b>Other documents if available:</b>  |
| K1       | Copy of assessments by other bodies (peer review) like grant-giving body  |
| K2       | Copy of review by scientific review boards and/or international aECs/CAs  |
| K3       | Other documents (e.g. letter to the general practitioner/ treating physician)   |

### Gene Therapy

Apart from a positive decision from the CCMO and no objections from the Competent Authority (the Minister of Health, Welfare and Sport), a GMO-license from the Ministry of Spatial Planning, Housing and the Environment (VROM) is compulsory if genetically modified organisms are used. In case of immunologically active products, according to the Immunological Medicinal Product Decree release of the batches of the product by the Health Inspectorate is also required (see chapter 2.3).

Before submitting a gene therapy protocol, researchers are given the opportunity to ask for a pre-submission meeting with the CCMO (and representatives of the Ministry of Spatial Planning, Housing and the Environment and of the Health Inspectorate, if applicable) to discuss the study and other relevant items informally.

To facilitate submissions a single counter for gene therapy has been instituted. All enquiries regarding gene therapy protocols should be directed there:

**RIVM / SEC / Bureau GGO**  
(coordination counter gentherapy)

Postbus 1                                    **t** +31 30 274 27 93  
3720 BA Bilthoven                        **f** +31 30 274 44 01  
Antonie van Leeuwenhoeklaan 9    **e** [bggo@rivm.nl](mailto:bggo@rivm.nl)  
3721 MA Bilthoven

*Contact person*  
Harm Hermsen

The submission and approval process remains complicated but the staff at the coordination counter will do their utmost to help with the dissemination of submissions to the relevant authorities and they will also arrange informal consultations. Although the simplification of the rules and reducing the number of governmental bodies involved are under discussion, the situation is unlikely to change in the near future. The CCMO website will have the latest news.

-  If specific arrangements (e.g. on recruitment procedures) are made for e.g. vulnerable subjects it should be considered to document these arrangements. The accredited ethics committee can assess these arrangements and approve them.
-  In the Netherlands the CVs of the principal investigators per site have to be submitted to the aEC/CA (see above). The CVs of all sub-investigators will be collected in the Trial Master File. They will not be subject to assessment by the accredited ethics committee nor the CCMO.
-  A list of the relevant running and completed clinical trials with the IMP should be submitted to the accredited Ethics Committee. The applicant can refer to the IMPD and the IB for the current overview of all clinical trials.

## 2.5 Authorisation by the Competent Authority

### 2.5.1 Competent authority

The CCMO has been appointed the Competent Authority task for the authorisation of most clinical trials with medicinal products in the Netherlands. For those protocols for which the CCMO conducts the medical-ethical review (see [www.ccmo.nl](http://www.ccmo.nl) for recent information) the Minister of Health, Welfare and Sport is the Competent Authority. The Competent Authority's evaluation of the dossier will be limited to a check of completeness of the records, and a check of the EudraCT and clinical trial module of the EudraVigilance databases for indications that may affect the conduct of the trial, because of serious adverse reactions or because of findings from earlier inspections.

The dossier that should be submitted to the Competent Authority is the same as that required by the accredited Ethics Committee. The list has been described in paragraph 2.4. The latest version of the documents can be found on the CCMO website.

### 2.5.2 Assessment of the documentation package

The Competent Authority will upon receipt of the dossier check immediately whether the dossier is complete (valid). If it is, a confirmation of receipt will be sent, and the time period for review starts on the date of receipt of the package. If the dossier is not complete, the Competent Authority will notify the applicant as soon as is practically possible. In that case, the time period for review starts when the complete information is received by the authority.

### 2.5.3 Timelines

Since the authorisation by the Competent Authority has been limited to the aspects described above, timelines for this authorisation can be short. In the revised WMO the Competent Authority is bound to review the dossier within 14 days for all trials. Where possible the CCMO/Minister of Health, Welfare and Sport will react within shorter timelines, giving a written notification to the sponsor and the Ethics Committee as soon as possible. There is no possibility for suspension of the review period. If no notification has been received within the time period mentioned, the trial may start once the accredited Ethics Committee has reached a positive decision (tacit approval). For trials involving medicinal products for gene therapy, somatic cell therapy and all medicinal products containing genetically modified organisms, it is allowed to extend the timeline for the review by the competent authority with a maximum of 30 days extra to the 14 days review.

If the Competent Authority notifies the sponsor of grounds for non-acceptance, the sponsor may thereafter amend the application only once.

## 2.6 Approval by an accredited ethics committee

In order to obtain approval to conduct a clinical study with medicinal products in the Netherlands a request for assessment should be submitted to an accredited ethics committee in the Netherlands. For multicentre studies the assessment of one accredited ethics committee is required from a regulatory point of view.

For certain protocols (see [www.ccmo.nl](http://www.ccmo.nl)) the application for an ethical and scientific review should be submitted to the CCMO in its role as accredited Ethics Committee. In this case the Minister of Health, Welfare and Sport will act as the Competent Authority.

### 2.6.1 What is a valid request?

The documentation that should be attached to the application is exactly the same as the information needed to obtain approval from the Competent Authority. The list has been described in chapter 2.4. The latest version of the documents can be found on the CCMO website. It is strongly recommended to follow the file contents as described in this manual to facilitate and expedite review.

### 2.6.2 Assessment of the documentation package

The accredited Ethics Committee will upon receipt of the dossier check immediately whether the dossier is complete (valid). If it is, a confirmation of receipt will be sent, and the time period for review starts on the date of receipt of the package. If the dossier is not complete, the Ethics Committee will notify the applicant instantly. In that case, the time period for review starts when the complete information is received by the aEC.

### 2.6.3 Timelines

The maximum term for the assessment is 60 days. Within that period the accredited Ethics Committee can ask for more information only once. When this is the case the clock stops until the new information has been submitted and has been found adequate to answer the queries.

In case of trials involving medicinal products for gene therapy, somatic cell therapy and all medicinal products containing genetically modified organisms, a further extension of the timeline with a maximum of 30 days is allowed. In the case of xenogenic cell therapy there is no time limit for the accredited Ethics Committee.

### 2.6.4 Multicentre and external review

On May 1, 2004 the new CCMO External Review Directive has come into force. This directive applies to the review of multicentre research and the external review of monocentre research. For multicentre studies with a number of investigational sites

in the Netherlands, and for trials reviewed by an external Ethics Committee (i.e. a committee that is not linked to any institution at which some or all of the research is to be performed), the application for a request to assess the clinical study by the accredited Ethics Committee should be accompanied by a Statement of the Hospital Board of Directors (or management of the site) of the respective investigational sites regarding the feasibility and applicability of the study in that study centre. An example of such a feasibility statement (in Dutch) can be downloaded from the CCMO website: <http://www.ccmo.nl/Nederlands/wet-en-regelgeving/multicenteronderzoek/RET-verklaring>



The reviewing accredited Ethics Committee may start the review process and come to a decision concerning the protocol if at least one declaration on feasibility has been submitted. Other sites may later be added, during the review process (after consulting the reviewing Ethics Committee) or in the form of amendments.

Submission of the declaration on feasibility during the review process is not regarded as an amendment to the study protocol.

The Hospital Board of Directors can decide to provide the declaration directly, or first ask advice from the institutional ethics committee or another body before signing the declaration. This declaration on local feasibility should be delivered as soon as possible and should be based on the following criteria:

- a the expertise, competence and experience of the local researchers must be sufficient;
- b all personnel contributing professionally to the research must be properly informed about the study protocol;
- c the local facilities must be suitable, given the requirements of the proposed research;
- d the research must be consistent with the institution's policies on research and patient care, and no other research that might compromise a successful conduct of the trial must be simultaneously in progress.

The Hospital Board of Directors may decide to combine the declaration on local feasibility with a provisional approval for conducting the study (provided that the study is approved by the Competent Authority and accredited Ethics Committee) in a single document. In any case, each investigational site should have official approval from their Hospital Board of Directors.

If hospitals (or other institutions) want to participate in research, it is important that the hospital board establishes an efficient procedure for issuing a declaration on local feasibility and approval of the study.



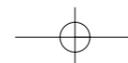
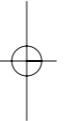
### **2.6.5 Confidentiality**

All accredited Ethics Committees and the Competent Authority are governmental agencies in the Netherlands and as such all members fall under the confidentiality requirements of Governmental bodies. In addition all members of accredited Ethics Committees have signed personal non-disclosure agreements and statements regarding absence of any conflict of interest. All aEC members will have to submit this document to the CCMO once. Further updating of these statements (and CVs) will be the responsibility of the accredited Ethics Committees.

For advice regarding the review of the IMPD the accredited Ethics Committees can make use of an expert network facilitated by the CCMO. The CCMO will see to it that members of this network sign a confidentiality statement.

Accredited Ethics Committees can also arrange advice from an external expert. In that case this external expert should sign a confidentiality statement. An example of such a confidentiality statement can be found on the CCMO website..

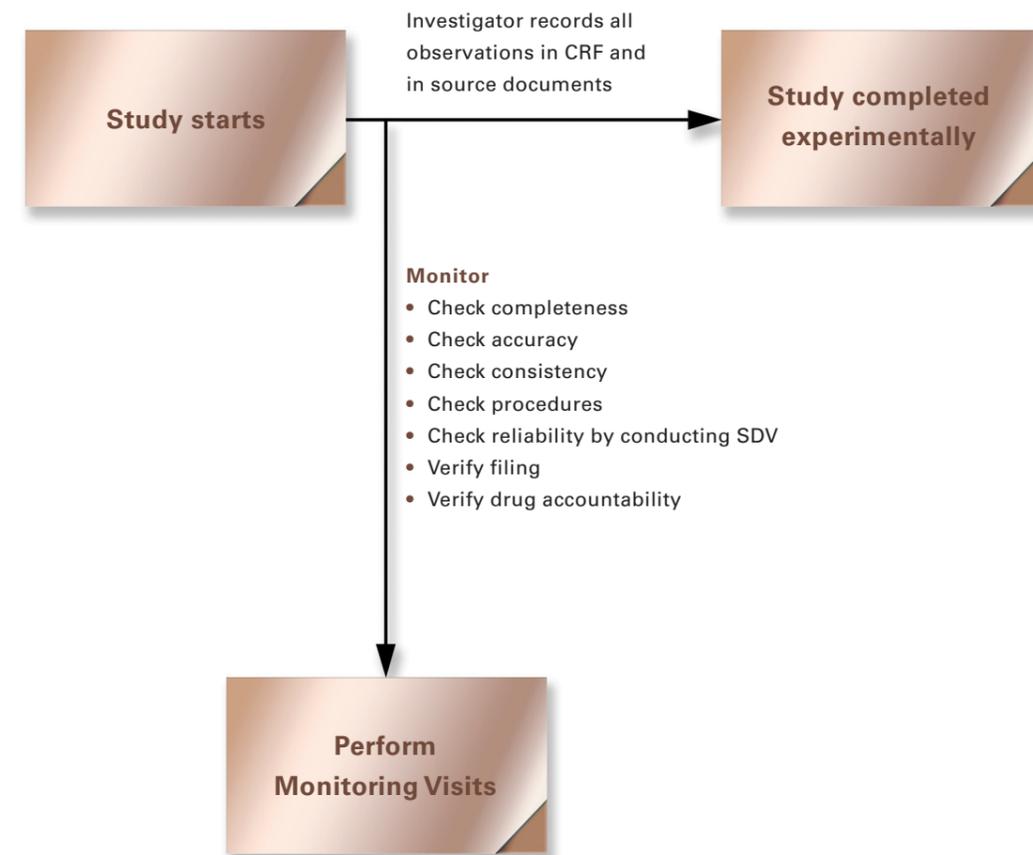
There is no requirement for accredited Ethics Committees to inform the sponsor if the aEC contacts an external adviser. If the sponsor wants to be informed he should ask the aEC to do so. Ethics committees are required to arrange proper secrecy and absence of conflict of interest statements from their advisors.



## Chapter 3

### During the conduct of the study

Once the clinical study has been initiated the investigator will recruit the patients and will record all observations required by the protocol. The qualified monitor will function as the controller of the quality and liaison between the sponsor and the investigator. For academic studies where the investigator is also the sponsor of the study, the investigator should arrange, in cooperation with the hospital management board that monitors will be trained and educated. Several academic medical centers start with a trial bureau and arrange that a pool of qualified monitors will become available. If this is not feasible, then the investigator should request his colleague to perform the quality control of his work. It is advised to document how the quality control will be executed (what to be checked for 100 %, what to be checked in a sample). The Case Report Forms have to be verified for completeness, accuracy, consistency and reliability. This reliability will be verified by means of a check with the available source documents.



### 3.1 Amendments to the protocol

#### 3.1.1 Substantial amendments

During the trial, the sponsor may amend the protocol. The sponsor will decide if an amendment is substantial or not. If the amendment is substantial, it must be submitted to the accredited Ethics Committee. The amendment may only be implemented after a positive decision of the aEC. The competent authority (CCMO/Minister of Health, Welfare and Sport) will receive a notification that consists of the completed amendment form and the adjusted original XML file containing the application form, if applicable. All amendments will be primarily assessed by the aEC. The competent authority will confirm the receipt of the amendment notification, which without further information can be interpreted as no grounds for non-acceptance.

Substantial amendments to the trial have a significant impact on:

- The safety or physical or mental integrity of the subjects;
- The scientific value of the trial;
- The conduct or management of the trial; or
- The quality or safety of any investigational medicinal product used in the trial.

The list of potential substantial amendments presented below should function as guidance and should explicitly not be seen as fixed. For instance a planned design or dosage change in a study with an adaptable design (if approved a priori in this way by the accredited Ethics Committee) are not substantial amendments, as these were foreseen and approved by the ethics committee. It is strongly recommended to use this procedure to limit the number of amendments that have to be evaluated by the aEC.

- 1 Purpose of the trial
- 2 Design of the trial
- 3 Informed consent
- 4 Recruitment procedure
- 5 Measures of efficacy
- 6 Schedule of samples
- 7 Addition or deletion of tests or measures
- 8 Number of participants
- 9 Age range of participants
- 10 Inclusion criteria
- 11 Exclusion criteria
- 12 Safety monitoring

- 13 Duration of exposure to the IMP
- 14 Change of posology (dosage scheme) of the IMP
- 15 Change of comparator
- 16 Statistical analysis

- 17 Change of the principal investigator or addition of new one
- 18 Change of the co-ordinating investigator
- 19 Change of the trial site or addition of new sites
- 20 Change of the sponsor or legal representative
- 21 Change of the CRO assigned significant tasks
- 22 Change of the definition of the end of the trial

- 23 Changes of name or code of IMPs
- 24 Immediate packaging material
- 25 Manufacturer(s) of active substance
- 26 Manufacturing process of the active substance
- 27 Specifications of active substance
- 28 Manufacture of the medicinal product
- 29 Specification of the medicinal product
- 30 Specification of excipients where these may affect product performance
- 31 Shelf-life including after first opening and reconstitution

- 32 Storage conditions
- 33 Test procedures of active substance
- 34 Test procedures of the medicinal product
- 35 Test procedures of non-pharmacopoeial excipients

- 36 Results of new pharmacology tests
- 37 New interpretation of existing pharmacology tests
- 38 Result of new toxicity tests
- 39 New interpretation of existing toxicity tests
- 40 Results of new interaction studies

- 41 Safety related to a clinical trial or human experience with the investigational medicinal product
- 42 Results of new clinical pharmacology tests
- 43 New interpretation of existing clinical pharmacology tests

- 44 Results of new clinical trials
- 45 New interpretation of existing clinical trial data
- 46 New data from human experience with the investigational medicinal product
- 47 New interpretation of existing data from human experience with the investigational medicinal product

One amendment could refer to several changes in the protocol or scientific supporting documents.

The documentation that will be included in the submission should cover the following information:

- 1 Covering letter, including the reasons for the amendment in one or two sentences, a brief description of the changes that are included in the amendment, the names of the documents that are modified, and the reason for qualification as substantial.
- 2 The amendment application form, containing the identification of the clinical trial, the sponsor and the amendment (sponsor's amendment number, date and/or version) and a description of the amendment and the reason. This Clinical Trial Amendment form is available on the EudraCT website.
- 3 An extract of the modified documents, where applicable, showing both the previous and new wording, where applicable. If a substantial amendment changes data in the original EudraCT Application Form a new corrected version of the XML-file must be submitted on diskette/CD-Rom. The paperwork needs to include a printout of the revised application form with the changes highlighted.
- 4 The new version of the modified documents, where applicable, identified with updated number of version and date.

Any supporting documentation could include:

- Summaries of data, if applicable;
- An updated overall risk benefit assessment, where applicable;
- Possible consequences for subjects already included in the trial;
- Possible consequences for the evaluation of the results.

A substantial amendment will be assessed by the accredited Ethics Committee within a period of 35 days. The aEC can decide to assess certain substantial amendments more efficiently, i.e. through a subcommittee on an expedited basis.

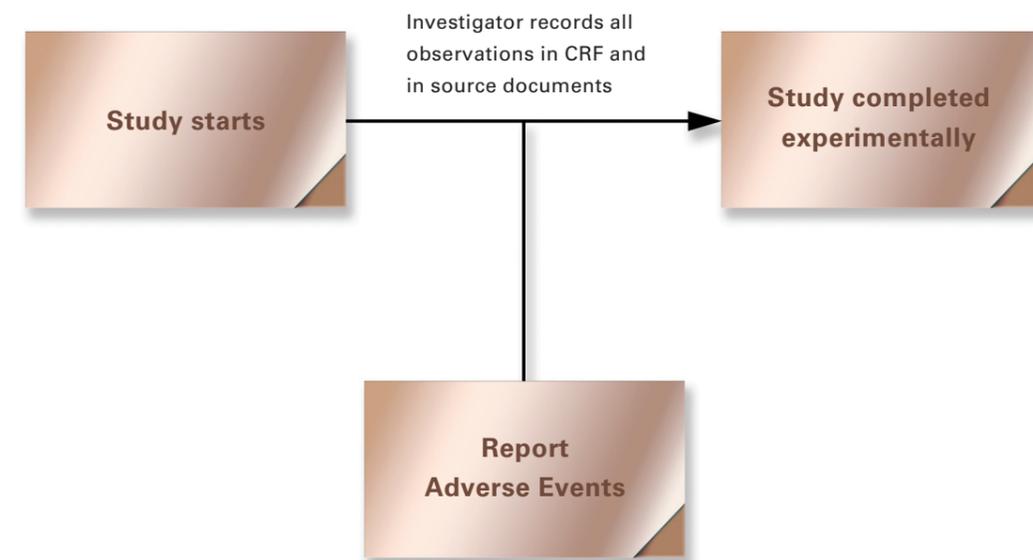
### 3.1.2 Non-substantial amendments

Non-substantial amendments should be recorded and filed by the sponsor and should be available on request for inspection at the trial site and/or the sponsor's premises as appropriate.

Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.

Non-substantial amendments are also those amendments assumed to be non-substantial as assessed by the sponsor. Also amendments as mentioned on the above list could be non-substantial as justified by the sponsor.

## 3.2 Reporting requirements for Serious Adverse Events and Suspected Unexpected Serious Adverse Reactions



#### Investigator:

- Report Serious Adverse Event immediately

#### Sponsor:

- Submit reportable events (SUSARs) to the CBG (MEB)
- Report SUSARs to the aEC and other investigators

See also EU Commission document 'Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, revision 1, ENTR/CT3, April 2004':

[http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/april/cp\\_and\\_guidance\\_SUSARs\\_23\\_04\\_04.pdf](http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/april/cp_and_guidance_SUSARs_23_04_04.pdf)

### 3.2.1 Definitions

#### 3.2.1.1 Adverse Event (AE):

any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product but which does not necessarily have a causal relationship with this treatment.

#### 3.2.1.2 Adverse Reaction (AR):

all untoward and unintended responses to an IMP related to any dose administered.

All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an IMP qualify as adverse reaction. The causality assessment given by the investigator should not be downgraded by the sponsor.

#### 3.2.1.3 Unexpected Adverse Reaction:

an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

#### 3.2.1.4 Serious AE or Serious AR:

any untoward medical occurrence or effect that at any dose:

- Results in death,
- Is life-threatening (at the time of the event),
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect;
- Is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, post study event, etc.

### 3.2.2 Adverse Event reporting

The investigator shall report all Serious Adverse Events (SAEs) immediately to the sponsor except for those that the protocol or Investigator's Brochure identifies as not requiring immediate reporting.

### 3.2.3 Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting

The sponsor is responsible for the expedited reporting of SUSARs to the Medicines Evaluation Board, CCMO or Minister if applicable), aEC and competent authorities in other Member States where the IMP is subject of a clinical trial run by the same sponsor.

Expedited reporting means not later than 15 days after the sponsor obtained first knowledge of the adverse reactions. For fatal or life threatening cases the maximal term is 7 days for a preliminary report with another 8 days for completion of the report. In case of a multinational trial with an authorised medicinal product with different SPCs in the different Member States the sponsor must select one of the SPCs as reference document in order to be able to judge the expectedness. The reference document to be used should be a part of the investigator's brochure; it should be attached in the Clinical Trial Application and mentioned in the covering letter. Also SUSARs which occur in another trial with the same IMP conducted by the same sponsor, within or outside the European Economic Area (EEA; the European Union, Norway, Iceland and Liechtenstein) should be reported as well as SUSARs related to comparators (including placebo).

#### 3.2.3.1 Managing SUSARs in blinded trials

Codes should be broken prior to reporting only for that specific patient. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for data-analysis and interpretation of results at the study's conclusion. Especially in trials in high morbidity and/or mortality disease state it is recommended that an independent Data and Safety Monitoring Board (DSMB) be in charge of the decision to unblind of single SUSAR cases. It may be appropriate to reach agreement with the aEC in advance concerning serious adverse events that would be treated as disease-related (for instance tumour progression in oncology trials and organ failure in sepsis trials) which could be exempt from to systematic unblinding and expedited reporting.

#### 3.2.3.2 Informing the accredited Ethics Committee

SUSAR-reporting to the aEC will be done on the basis of the protocol irrespective where the SUSAR occurs (i.e. domestic and non-domestic SUSARs) in an expedited manner. This means within 7/15 days. SUSARs which occur in another trial with the same IMP conducted by the same sponsor either in the European Community or in a third country will be reported in a 6-monthly line listing accompanied by a brief report by the sponsor highlighting the main points for concern. However, if the latter SUSARs have profound consequences for the safety of the research subjects in the study reviewed by the aEC, these SUSARs should also be reported in an expedited manner with a clear description why this SUSAR has consequences for the safety of the research subjects in the study reviewed by the aEC.

**3.2.3.3 Electronic Reporting of SUSARs**

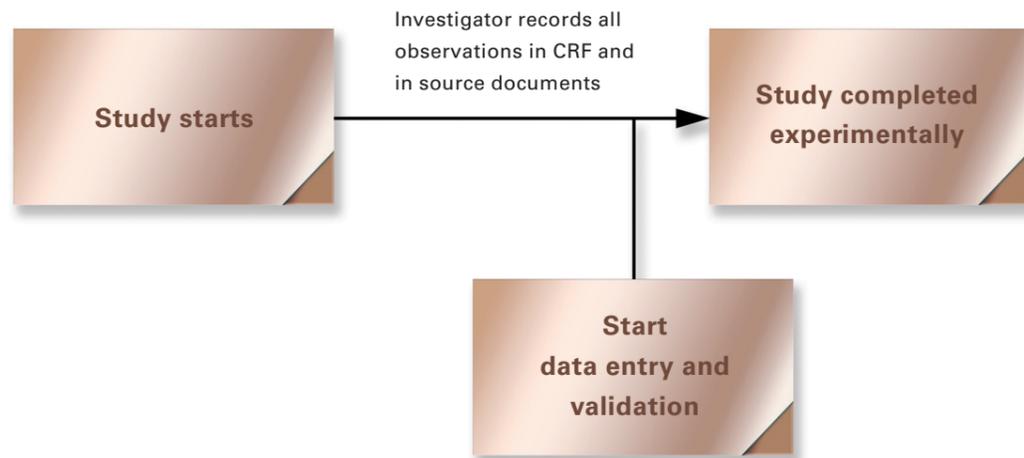
Sponsors should send their SUSARs to the EudraVigilance Clinical Trial module (EV CT) at the EMEA, the MEB, the aEC and the CCMO. For the latter two an electronic SUSAR-reporting form (i.e, eSUSAR-form) will be made accessible through the CCMO portal.

For reporting SUSARs occurring in non-industry sponsored trials it will be possible to report SUSARs to the EudraVigilance Clinical Trial module using the eSUSAR-form. After completion of the form the MEB/Lareb will transform the report to an E2B compatible file which will be transmitted to EudraVigilance CT thereafter.

A SUSAR-working party has been established with the aim to develop the above described eSUSAR-form. This working party will also work on procedures to facilitate the electronic submission of SUSARs and the review of SUSARs by the aEC. Based on the advice of the SUSAR-working party, the CCMO will develop further regulations on this issue that will also clarify which SUSARs will require expedited reporting and which SUSARs will be included in periodical SUSAR line listings for review by the aEC. See also paragraph 2.4 and the CCMO-website for the latest news on the SUSAR-working party and the electronic SUSAR-reporting form.

See also EU Commission documents 'Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance - Clinical trial Module)' and 'Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use'. These and other documents can be found on the EU-website:

<http://pharmacos.eudra.org/F2/pharmacos/dir200120ec.htm>



**3.3 Annual reporting requirements for the progress and safety**

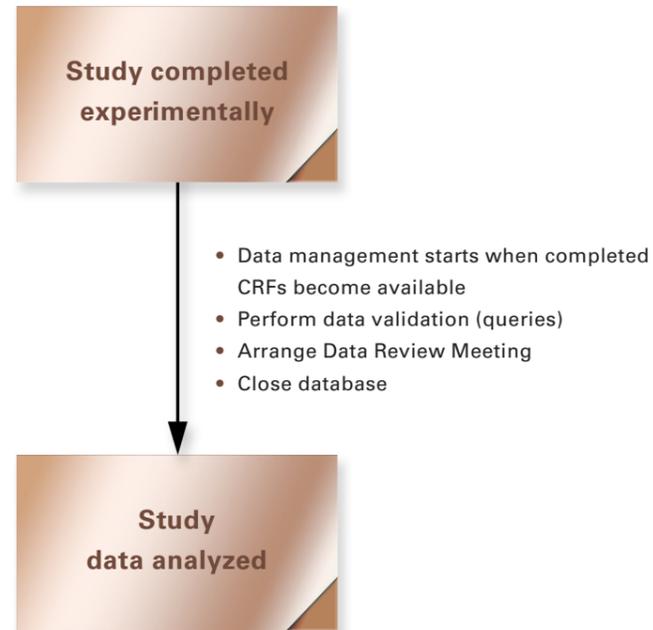
According to the ICH-GCP guideline the investigator should at least once a year submit a summary of the progress of the trial to the accredited Ethics Committee. In practice the sponsor will draft the annual progress report. Information that should be provided in the annual progress report concerns the date of inclusion of the first subject, the numbers of subjects that have been included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

Time point zero is the first approval in the first country in the EEA (European Union, Norway, Iceland and Liechtenstein). The report should be submitted within 60 days after data lock point. For trials with a shorter duration the annual reporting may coincide with the reporting of the declaration of the end of the trial, i.e. within 90 days after the completion of the trial. For a trial with a registered medicinal product for which the applicant is the marketing authorization holder, time point zero is the international birth date of the medicinal product.

Sponsors should also submit, once a year throughout the clinical trial or on request, a safety report to the relevant aEC, the CCMO (Minister) and competent authorities of the concerned Member States. The annual safety report should discuss all suspected serious adverse reactions occurred in the concerned trial.

For detailed instructions see EU Commission document "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, revision 1, ENTR/CT3, April 2004, section 6.3.2.

[http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/april/cp\\_and\\_guidance SUSARs 23 04 04.pdf](http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/april/cp_and_guidance_SUSARs_23_04_04.pdf)



When the study is terminated prematurely, this declaration of the end of the study should be submitted to the accredited Ethics Committee and the Competent Authority within 15 days, with the reasons for the premature termination.

Within one year after the end of the experimental phase of the clinical study in all countries the sponsor and/or the coordinating investigator should submit a summary report with the results of the clinical study to the accredited Ethics Committee and the Competent Authority.

The summary of the results of the study should comply as much as possible with Annex 1 of the ICH E3 guideline on the contents and structure of clinical study reports (CPMP/137/95) which can be found in <http://www.ich.org>

### 3.4 Reporting requirements for the declaration of the end of the trial

The sponsor is required to notify the competent authority and the accredited Ethics Committee of the end of the trial, or of its early termination. This should be done within a period of 90 days. This is done through the Notification of End of Trial form available on the EudraCT public website. The Competent Authority will use this form to update the EudraCT database.

When the last patient has visited the investigator for the last visit, then the experimental phase of the clinical study has been completed. The sponsor of the study will notify both the accredited Ethics Committee and the Competent Authority of the end of the trial.

 The end of the trial is defined as the last patient's last visit. However, if the sponsor wishes to define the end of the trial otherwise, e.g. the date of database closure, then the sponsor can do so. The sponsor should describe in the study protocol what will be regarded as the end of the trial.

## Chapter 4

### Appendices

#### 4.1 List of members of the Working party for implementation of Directive 2001/20/EC

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    [www.nefarma.nl](http://www.nefarma.nl)

**4.2 List of relevant organisations with contact information**

Competent Authority for studies with medicinal products where the review is performed by an accredited Ethics Committee:

**CCMO**

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 2500 BH The Hague  
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Competent Authority for studies with medicinal products where the review is performed by the CCMO:

**Ministry of Health, Welfare and Sport****GMT**

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The documentation for the Minister of Health, Welfare and Sport can also be sent in through the CCMO as an extra copy marked for the CA. The CCMO will in that case arrange transfer to the person responsible.

Competent authority for the EudraCT database and SUSAR reporting to the EudraCT Pharmacovigilance module:

**Medicines Evaluation Board**

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CIOMS forms (paper copy) should be sent to:

**CBG-MEB**  
P.O. Box 16229  
2500 BE The Hague  
The Netherlands

The CBG (MEB) is also ready to receive CIOMS forms as an e-mail attachment (PDF format). A special CBG (MEB) e-mailbox will be made available: [susarct@cbg-meb.nl](mailto:susarct@cbg-meb.nl)  
It will also be possible to transmit the PDF files through a secured system called EudraLink. Sponsors interested to make use of EudraLink are advised to make this known to: [re.sloot@cbg-meb.nl](mailto:re.sloot@cbg-meb.nl)

In stead of the CIOMS form an electronic SUSAR-reporting form (i.e. eSUSAR-form) will be made available through the CCMO-portal for submission of SUSARs to the aEC and the CCMO. In addition it can be used by non-industry sponsors for submission of SUSARs to the EudraVigilance database (via MEB/Lareb). See paragraph 3.2.3.3 for the details.

Competent authority for the inspection of clinical trials:

**Health Care Inspectorate of the Ministry of Health, Welfare and Sport**

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### 4.3 List of abbreviations and relevant definitions

|         |  |
|---------|--|
| ABR     | ABR form (General Assessment and Registration form) is the application form that is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie) |
| aEC     | accredited Ethics Committee  |
| ADE     | Adverse Device Effect  |
| AE      | Adverse Event  |
| AMvB    | Governmental regulation other than a law and a Decree (Algemene Maatregel van Bestuur)   |
| AR      | Adverse Reaction   |
| AWB     | General Administrative Law Act   |
| BBA     | Dutch abbreviation for the Decree on the Manufacture and Supply of Medicines (Besluit Bereiding en Aflevering (van geneesmiddelen)   |
| Bif     | Immunological Medicinal Products Decree (Besluit Immunologische Producten)   |
| CA      | Competent Authority  |
| CBG     | Medicines Evaluation Board (MEB) (College ter Beoordeling van Geneesmiddelen)  |
| CCMO    | Central Committee on Research Involving Human Subjects   |
| CIOMS   | Council for International Organizations for Medical Sciences   |
| CPMP    | Committee for Proprietary Medicinal Products   |
| CRA     | Clinical Research Associate  |
| CRF     | Case Report Form   |
| CRO     | Contract Research Organisation   |
| CTA     | Clinical Trial Authorisation   |
| CTM     | Clinical Trial Medication  |
| CTMS    | Clinical Trial Management System   |
| CV      | Curriculum Vitae   |
| DSMB    | Data Safety Monitoring Board   |
| EC      | Ethics Committee   |
| EMA     | European Medicines Evaluation Agency   |
| EudraCT | European drug regulatory affairs Clinical Trials   |
| EU GMP  | European Good Manufacturing Practice Guideline   |
| EV CT   | EudraVigilance Clinical Trial module of the EudraCT database   |
| FDA     | Food and Drug Administration   |
| GCP     | Good Clinical Practice   |
| FMWV    | Federatie van Medisch Wetenschappelijke Verenigingen   |
| GMO     | Genetically Modified Organism  |
| GMP     | Good Manufacturing Practice  |
| IB      | Investigator's Brochure  |

|       |  |
|-------|--|
| IC    | Informed Consent   |
| ICH   | International Conference on the Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use    |
| IGZ   | Health Inspectorate (Inspectie voor de Gezondheidszorg)  |
| IMP   | Investigational Medicinal Product  |
| IMPD  | Investigational Medicinal Product Dossier  |
| IND   | Investigational New Drug (USA)   |
| IRB   | Institutional Review Board   |
| ISF   | Investigator Site File   |
| KWZ   | Health Institution Quality Law (Kwaliteitswet Zorginstellingen)  |
| MA    | Marketing Authorisation  |
| MEB   | Medicines Evaluation Board (synonym CBG)   |
| METC  | Dutch word: Medisch-Ethische Toetsingscommissie (synonym for IEC/IRB/EC)   |
| MoH   | Ministry of Health, Welfare and Sport  |
| NOMET | Abbreviation for National Trainingtraject for Medical Ethical Assessment (Nationaal Opleidingstraject Medisch-Ethische Toetsing) |
| PCS   | Plain Common Sense (which is needed to translate rules into daily practice for clinical research)                                |
| QA    | Quality Assurance  |
| QC    | Quality Control  |
| RIVM  | National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieuhygiëne)                  |
| (S)AE | (Serious) Adverse Event  |
| SDV   | Source Documents Verification  |
| SOP   | Standard Operating Procedure   |
| SPC   | Summary of Product Characteristics   |
| SUSAR | Suspected Unexpected Serious Adverse Reaction  |
| TSE   | Transmissible Spongiform Encephalitis  |
| UAE   | Unexpected Adverse Event   |
| WBIG  | Health Profession Law (Wet Beroepen in de Gezondheidszorg)   |
| WGBO  | Law on Medical Treatment Agreement (Wet Geneeskundige Behandelingsovereenkomst)  |
| WMO   | Medical Research in Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen)                                       |
| WOG   | Medicines law (Wet op de Geneesmiddelenvoorziening)  |