The EFGCP Report on
The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe
(Update: April 2012)

The Netherlands

**Question 1**: What laws or regulations apply to an application for conducting a clinical trial in The Netherlands?

Research involving human subjects has been legally regulated since 1999 via the Medical Research Involving Human Subjects Act (WMO).

A revised version of the WMO, which gives effect to the Directive 2001/20/EC, came into operation on 1 March 2006.

**Question 2**: Which government, legal or authoritative body or bodies is or are responsible for the establishment and/or accreditation of (research) ethics committees for IMPs, and for their supervision and quality? Are there different (research) ethics committees reviewing other projects?

The WMO stipulates two types of committee involved in the assessment of research protocols involving humans - the accredited Medical Research Ethics Committees (METCs) and the Central Committee on Research Involving Human Subjects (CCMO).

All research involving human subjects that fall under the WMO must be assessed in advance by a committee. This is usually undertaken by an accredited METC or occasionally by the CCMO, depending on the type of research. Drugs trials, medical devices, genetic research are all covered by the above mentioned Act. METCs consider all clinical trials on investigational medicinal products as well as non-therapeutic observational studies, and the CCMO considers medical research in the field of gene therapy, iRNA, anti-sense oligonucleotides, (stem) cell therapy, xenotransplantation, vaccines, and non-therapeutic interventional studies with minors and incapacitated subjects.

Research with spare embryos and IVF technology (e.g., embryonic stem cell research) is covered by the Embryos Act and are reviewed by the CCMO.
Both the accredited METCs and the CCMO are independent governmental bodies with a legal status that reach a legally binding decision on research protocols, and thus are not advisory boards.

**Question 3:** What is the process for achieving clinical trial authorisation from the competent authority in The Netherlands?

A research protocol concerning a study with medicinal products is submitted to the Central Committee on Research Involving Human Subjects (CCMO). The website for CCMO is at [http://ccmo-online.nl](http://ccmo-online.nl). It is this body that acts as the competent authority for research with medicinal products involving human subjects in The Netherlands. The licensing authority is not involved until it evaluates the outcome of submitted research for a request for marketing authorisation.

The Dutch licensing authority is College ter Beoordeling van Geneesmiddelen (CBG). The website for CBG is at [http://www.cbg-meb.nl](http://www.cbg-meb.nl).

**Question 4:** What is the process for obtaining ethical review of a clinical trial protocol by a competent (research) ethics committee in The Netherlands?

Only accredited research ethics committees (METCs or the CCMO) can review biomedical research with human subjects. The criteria for accreditation are laid down in the WMO. In short a research ethics committee has to fulfil the minimal composition, has to have standing orders and SOPs in which their operations are described and has to review on average 10 research protocols per year or more. The Central Committee (CCMO) is responsible for the accreditation and oversight of the accredited research ethics committees. If an METC no longer fulfils the criteria, the accreditation can be withdrawn by the Central Committee.

**Question 5:** Is there a single organisation to which to apply for ethical review of a clinical trial for an investigational medicinal product, regardless of whether this is for a single site or multiple sites?

Only one decision of one accredited METC is required for research projects in the Netherlands including multicentre research.

**Question 6:** What is the website for the organisation that issues guidelines on the ethical review of a clinical trial for an investigational medicinal product?

The standard application form to be used for all applications to an METC will be included within the revised guidance.


**Question 7:** Is there a procedural interaction between the national or local competent authority and the (research) ethics committee during the approval process?

Yes, the competent authority informs the accredited METC that reviews the research protocol with medicinal products the outcome of their review within 14 days.

**Question 8:** Does the application to the REC and to the competent authority have to be submitted in parallel, or, if not, in which order?

Can be in parallel.

**Question 9:** How many (research) ethics committees are there in The Netherlands?

Twenty-seven accredited METCs and the CCMO.

**Question 10:** How are RECs funded in The Netherlands? Do they charge fees? If yes, what is their scale of fees?

Research ethics committees are funded by fees and, in case of research committees in an institute or hospital, also by the parent body. Section 20 of the WMO allows an METC to cover the costs of its protocol review activities by charging fees to the parties submitting protocols for review. The fees charged may not exceed the reasonable cost for conducting the review. The fees can be found on the CCMO-website: [http://www.ccmo-online.nl/main.asp?home=1&pid=14&sid=16&ssid=33&def=22](http://www.ccmo-online.nl/main.asp?home=1&pid=14&sid=16&ssid=33&def=22).

**Question 11:** Who is responsible for submitting the request for ethical review to the competent (research) ethics committee for single-site and for multi-site clinical trials?

The sponsor.
**Question 12:** How is a “single opinion” achieved for multi-site studies?

In general the accredited METC to which the chief investigator relates is designated the Reviewing METC. But sponsors can in principle choose any accredited METC that meets the requirements. The sponsor is responsible for obtaining the local feasibility declarations from the participating institutes. The directors of the participating centres (and thus not the METC’s in the institutes) are responsible for the local feasibility declaration. It is to the discretion of the hospital director whether he/she asks advice from his METC before signing the local feasibility declaration.

**Question 13:** How many members serve on a REC?

This varies between the different committees, but there must be at least 5, from the disciplines specified in the WMO (see 18. below), and 7 in case the METC reviews research protocols on medicinal products. For all accredited METCs the CCMO publishes the composition (names, role and background of all members) on the web. See the CCMO website [http://www.ccmo.nl](http://www.ccmo.nl) for details.

**Question 14:** How many members constitute a quorum?

All disciplines that are specified in the WMO (see Question 18 below) have to be present for a committee meeting.

**Question 15:** How are REC members appointed?

All members of a METC have to be approved by the Central Committee (CCMO).

**Question 16:** How is the independence of members ensured?

Upon the approval by the CCMO, METC members have to fill in their other activities to see whether there is a conflict of interest, and a confidentiality agreement. Furthermore, in their standing orders each METC describes how it will handle any instance of a conflict of interest. In general a committee member that is involved in the research under review will have to leave the meeting room and thus will not participate in the discussion and decision making process.

**Question 17:** How are conflicts of interest of REC members avoided?

See Question 16 above.

**Question 18:** What backgrounds and/or qualifications of members are actively sought?

The disciplines that are mandatory for METCs are:

- Physician.
- Lawyer.
- Ethicist.
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- Methodologist.
- ‘Lay person’ (member that assess the research from the perspective of the human subject).
- Hospital pharmacist (in case of drug trials).
- Clinical pharmacologist (in case of drug trials).

**Question 19: How do RECs obtain specialist expertise?**

If an METC needs additional expertise, it can ask advice from an expert. The CCMO is establishing a network of experts and it is via the CCMO that the METC can seek advice from one of the experts participating in this network.

**Question 20: What are the training requirements for members of RECs?**

Training is not compulsory.

**Question 21: What training programmes are available for REC members in The Netherlands?**

Some University Hospitals (i.e., the VUmc Amsterdam) are organising training courses for committee members and their staff. The CCMO supports these initiatives by providing speakers and cases for workshops in which a research file is being discussed.

**Question 22: What are the timelines for the assessment of single- and multi-site studies?**

The ethical review of research with medicinal products, whether single- or multi-site, must be completed within 60 days of receipt of a valid application. For specific studies (e.g., gene therapy) the timeline is 90 days. The clock may stop once to request further information or clarification from the applicant.

**Question 23: How are substantial amendments submitted during the review process dealt with?**

These require a new decision from the METC, but the chairman may be mandated to review the amendment without the involvement of the full committee.

**Question 24: How does a REC assess the suitability of investigators and of sites?**

For most accredited METCs that are associated with an institute or hospital where the research is being done, this is not an issue. The members of the committee are in general well informed on the local situation and a CV from the local investigator will in general be sufficient.
In the case of multi-site trials the director of each participating centre has to sign a local feasibility declaration which together with the research protocol is sent by the sponsor to the accredited METC for review.

**Question 25:** How are the requirements for (research) ethics committees to review the contractual or financial arrangements in clinical trials for both investigators and hospitals handled?

The most important issues on contracts and financial arrangements are addressed by the national application form (ABR-form). When this raises questions, the research ethics committee can ask for additional information for review. Since 1 January 2009 the review of the Clinical trial agreement is part of the review process. This has been arranged in the CCMO Directive on the Assessment of Clinical Trial Agreements. The review concentrates on two issues:

(i) The criteria for premature termination of the trial.
(ii) Restrictions on the public disclosure of research results.

**Question 26:** How are the requirements for (research) ethics committees to review the compensation arrangements for study subjects handled?

Compensation for study subjects is reviewed by the METC. A guideline on this issue has been published on the CCMO website.

**Question 27:** Is there an ongoing quality assurance process (e.g. audits, inspections, internal SOP) for (research) ethics committees in The Netherlands?

All accredited METCs committee participate in the “secretaries’ working group”. The purpose of the group is to work on professional support by the secretariats. Together the secretaries work on SOPs in which the SOP-system of the secretariat of the Central Committee (CCMO) is being used as a template.

In 2009 the CCMO developed a new method for continuous oversight of the activities of the accredited METCs. Currently the CCMO is testing the new methodology in which the review of research protocols by METC is being evaluated by the CCMO.

**Question 28:** Is there an appeal mechanism?

Yes, the CCMO operates also as an appeal body.

**Question 29:** How do RECs deal with SUSAR reports and Annual Safety Reports?

SUSARs and SAEs are now submitted electronically to the MRECs and Competent Authority using the webportal ReviewOnline (ToetsingOnline). From 1 January 2010 onwards, the use electronic submissions on SAEs and SUSARs using the web portal
Question 30: How are ‘substantial amendments’ defined?

Substantial amendments are defined as changes in the research protocol that have a significant impact on:

- the safety or physical or mental integrity of the research subjects,
- the conduct or management of the trial, or
- the quality or safety of any investigational product used in the trial.

See the fore mentioned Instruction Manual, paragraph 3.1.

Question 31: What are the indemnity insurance requirements for research projects?

By official decree there has to be a “subject’s”-insurance for all research subjects participating in biomedical research. However, if there is no risk for the research subjects, this insurance requirement can be waived. This is up to the METC to decide.

Question 32: What are the indemnity insurance requirements for (research) ethics committee members themselves?

For METCs that are housed within a research institute or hospital, liability for the trial within that institute is covered by the liability insurance of the parent body. There is however no coverage for research that is performed outside that institute or hospital. So for multi-site trials there may not be complete liability insurance.

For METCs that are not based on an institute or hospital there is now liability insurance.

Question 33: How is informed consent obtained from vulnerable subjects who are potentially to be involved in a clinical trial?

In the case of children, both parents have to sign the informed consent form. If the child is 12 or older, he/she should sign as well. In the case of incapacitated subjects (e.g., Alzheimer patients) their partner, children (> 18 years old) or their legal representatives should sign.

Question 34: How do RECs assess the progress and outcome of research projects that they have approved?

All METCs require an annual progress report. The CCMO has made a simple report form for this. Currently the first part of an internet portal ToetsingOnline (ReviewOnline) for the submission, review, registrations and public disclosure of medical research is operational. In future the annual progress reports will be submitted
electronically (via the internet portal) to the METCs. Via the internet webportal the applicant can follow the review process of his/her submission by the CCMO and accredited METC.

**Question 35:** How does the REC ensure reception of the Annual Safety Report and the Summary of the Final Report of a research project that it has approved?

The internet portal **ToetsingOnline** (*ReviewOnline*) described briefly (see Question 34 above) will automatically generate e-mail alerts for investigators/sponsors and METCs. One of the alerts concerns a message to the investigator/sponsor that they are requested to submit their annual safety reports. Upon receipt, the investigator/sponsor will receive a message that the annual report has arrived.

**Question 36:** Do national regulations in The Netherlands allow research on healthy volunteer children (subjects under 16)?

Yes, but there are special requirements in the Dutch law on non-therapeutic research with minors.

**Question 37:** Do national regulations in The Netherlands allow payment, (other than expenses), to children taking part in research?

Yes. It is up to the reviewing Ethics Committee to evaluate this.

**Question 38:** Do RECs invite or allow a) applicants or b) observers to attend committee meetings?

The CCMO meetings are attended by an observer form the Ministry of Health. Quite a few Dutch accredited METCs invite the applicant to present his/her study for the whole committee and respond to questions of the committee members. However (s)he should leave the meeting room when the committee starts it's discussion. This procedure should be described in detail in the Standard Operating Procedures.

**Question 39:** Are the minutes of (research) ethics committee meetings made public?

The minutes of the meetings and decisions are not made public actively. The CCMO, however, receives a copy of all decisions of the accredited METCs.

**Question 40:** Is there any scope for Chairman’s actions in between meetings?

METCs do allow the chairperson (sometimes together with vice-chairperson) together with staff members to review the response of an applicant on the questions that were sent after the committee meeting. However this should have been described in detail in Standard Operating Procedures (SOP's). Furthermore, if the chairperson feels that
more expertise is required to decide on the reply letter (s)he can decide to discuss it in the committee meeting.

**Question 41:** Do (research) ethics committees ever appoint subcommittees for any specific purpose?

METCs do allow the chairperson (sometimes together with vice-chairperson) together with staff members to review amendments. However this should have been described in detail in Standard Operating Procedures (SOP's). Furthermore, the chairperson is responsible for the decision not to review an amendment in the whole committee. If (s)he feels that more expertise is required, the amendment is normally discussed in a committee meeting.

**Question 42:** Is there a national policy on the registration of clinical trials before they start?

Yes. For all studies with human subjects core data of the national application form (e.g. the ABR-form) is imported into the public CCMO-trial registry (see www.ccmo.nl and go to register) after the review of the METC is completed. Sponsors can request the CCMO not to publish the core data in the public trial register. In the written request it should be clearly described why the core data of a specific trial should not be incorporated in the public register.

**Question 43:** If the answer to Question 42 is ‘yes’, do (research) ethics committees have any role to play in reviewing such registration?

See Question 42. The core data of the national application form of each study is imported in public registry after the review has been completed.

**Question 44:** If the answer to Question 42 is ‘yes’, is this register of clinical trials made available to the public?

Yes, the trial register is made available to the public.

**Question 45:** With regard to Clinical Trial Insurance, do research ethics committees in The Netherlands work to a set template of requirements?

The METC also assess the policy of the insurance for the research subjects according to the requirements that have been stipulated in the Dutch law.

**Question 46:** If the answer to Q45 is ‘yes’, how are these requirements

a) Decided upon?

b) Cross referenced to statutory requirements?
c) Updated?

See answer to Q45.