



The EFGCP Report on The Procedure for the Ethical Review of Protocols for Clinical Research Projects in Europe (Update: March 2008)

The Netherlands

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.

2. Which government, legal or authoritative body or bodies is or are responsible for the establishment and/or accreditation of (research) ethics committees for reviewing clinical trials for investigational medicinal products, 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 an legally binding decision on research protocols, and thus are not advisory boards.

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>. 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>

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.

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

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 CCMO issued a Manual on the Review of Medical Research Involving Human Subjects (the 2002 version is about to be updated). The 2002 version is available at [http://www.ipfier2.nl/hipe/uploads/downloads/Toetsingshandleiding-2002_ENG\(1\).pdf](http://www.ipfier2.nl/hipe/uploads/downloads/Toetsingshandleiding-2002_ENG(1).pdf)

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

Recently a Instruction Manual on research with medicinal products has been produced with guidelines for investigators and sponsors. The Instruction Manual can be found on the CCMO website http://www.ccmo-online.nl/hipe/uploads/downloads_cati/Instruction%20manual%20versie%202.pdf

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.

8. Does the application to the EC and to the competent authority have to be submitted in parallel, or, if not, in which order?

Can be in parallel.

9. How many (research) ethics committees are there in the Netherlands?

31 accredited METCs and the CCMO.

10. How are ECs 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>

11. Who is responsible for submitting the request for ethical review to the competent ethics committee for single-site and for multi-site clinical trials?

The sponsor.

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.

13. How many members serve on an EC?

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> for the details.

14. How many members constitute a quorum?

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

15. How are EC members appointed?

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

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.

17. How are conflicts of interest of EC members avoided?

See 16. above.

18. What backgrounds and/or qualifications of members are actively sought?

The disciplines that are mandatory for METCs are:

- physician
- lawyer
- ethicist
- 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)

19. How do ECs 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.

20. What are the training requirements for members of ECs?

Training is not compulsory.

21. What training programmes are available for EC members in the Netherlands?

There is a national training programme (NOMET) for members of METCs established by the University of Maastricht, and in addition an extra training course is being organised for hospital pharmacists and clinical pharmacologists. The latter course will be modified and held in English and will also be open for international participants.

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 time line is 90 days. The clock may stop once to request further information or clarification from the applicant.

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.

24. How does an EC 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.

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 (e.g., a copy of the contract) for review.

26. How are the requirements for ethics committees to review the compensation arrangements for study subjects handled?

Compensation for study subjects is reviewed by the METC. Currently a guideline on this issue is under discussion.

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

Most 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.

Additionally, the Dutch Society on Research Ethics Committees (NVMETC) has established a visitation system. Each accredited METC is reviewed every approximately 5 years. The website of the NVMETC can be found at <http://www.ceg.nl/cgi-bin/orga.pl?id=58>

28. Is there an appeal mechanism?

Yes, the CCMO operates also as an appeal body.

29. How do ECs deal with SUSAR reports and Annual Safety Reports?

In spring 2005 a SUSAR-working group was formed to establish an electronic SUSAR-report form and a submission and review procedure for investigators, sponsors, research ethics committees (METCs) and the Competent Authority (the CCMO in this context). A WORD version of the SUSAR-form is available from the CCMO website. The electronic SUSAR-form will be built into the webportal ReviewOnline (ToetsingOnline) which is currently operational for submissions to the CCMO and accredited METCs. For the webportal see <https://toetsingonline.ccmo.nl/>

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.

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.

32. What are the indemnity insurance requirements for 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 as yet, no liability insurance. Currently the CCMO is exploring the possibilities for a liability insurance for all accredited research ethics committees for all the research (i.e., mono-site and multi-site) that they review.

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.

34. How do ECs assess the progress and outcome of research projects that they have approved?

Most 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.

35. How does the EC 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 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.

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