The Dutch System of Research Ethical Assessment and Weportal ReviewOnline

EFGCP workshop: Streamlining application to the regulatory & ethical review processes

Kingston-Upon-Thames, 2 March 2011

Marcel Kenter, executive director
Central Committee on Research Involving Human Subjects
Presentation

• Dutch review system

• Implementation EU clinical trial directive

• Webportal ToetsingOnline

• Summary
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Legislation on review of medical research

• **April 1999**: installation of the Central Committee on Research Involving Human Subjects (CCMO)

• **December 1999**: Medical Research Involving Human Subjects Act (WMO) into force

• **September 2001**: Embryos Act

• **March 2006**: EU Clinical Trial Directive into force (implementation in WMO)
Tasks of the CCMO (1/2)

- Competent authority of drug trials in NL
- review specific categories of medical research
- appeals body
- collect data of all research in national registry
Tasks of the CCMO (2/2)

• accreditation of local MRECs ⇒ governmental bodies
• supervision of accredited MRECs
• improving the quality and harmonisation of the MREC’s review
• make legally binding directives for aMRECs
CCMO

Office  Committee

Ethics Committee  Competent Authority  Appeal body  EC Oversight  Annual Report  New Developments
CCMO

Office

Committee

Ethics Committee

Competent Authority

Appeal body

EC Oversight

Annual Report

New Developments

Embryo research

Gene therapy

Nucleotide research

Cell therapy

Non-therap. research with incap. subjects

Research with gametocytes

Research with GMOs

Xenotransplantation

Vaccin trials

Heroin trials
Accreditation is given to MREC when:

- minimal requirements for the MREC-composition are fulfilled
  - one physician
  - one ethical expert
  - one lawyer
  - one research methodologist
  - one research subject member
  - one clinical pharmacologist
  - one pharmacist

- MREC has proper regulations
- a minimum number of research dossiers is reviewed
- MREC has a quality assurance system (e.g. SOPs)

- For all disciplines criteria have been established
- All members have to be approved by the CCMO
Average number of decisions/ MREC/ year; over the years: 2001 - 2002 - 2003
Accredited MREC's in 1999 - 2006

The graph illustrates the number of accredited MREC's and withdrawals from 1999 to 2006. The non-official transition period is indicated by a dotted line, followed by the professionalisation period of MREC's.

- **Number Accredited MREC's**
- **Number Withdrawals**

The data points are marked with blue circles for accredited MREC's and red diamonds for withdrawals.
Accredited MRECs September 2004

- University medical centres
- Hospitals
- Others

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Who's afraid of the European Clinical Trials Directive?

Wouldn’t it be nice if the approval and monitoring of clinical research done in the many, varied, and ever-increasing number of European countries could be simplified and streamlined? This deceptively simple idea was first mooted well over a decade ago and by 1995 the European Commission had published a concept paper for a European Directive on Implementing Good Clinical Practice. Several complex rounds of negotiation between the various European legislative bodies followed and the result, Directive 2001/20/EC, was officially adopted on April 4, 2001. The race is now on for Europe’s member states to incorporate the Directive into domestic legislation, since compliance will be mandatory as of May, 2004. Most European countries published draft legislation earlier this year. Somewhat belatedly, some of Europe’s academic aspects of a trial but no one person or organisation is required to take overall responsibility. The inscription of this requirement into law will expose the single sponsor to the risk of litigation, a risk that charities, universities, and other publicly funded research bodies are unsurprisingly unwilling to take. It will be the sponsor’s role to apply for trial authorisation and ethics-committee approval, activities currently the responsibility of the principal investigator.

Ethics committees will be obliged to give an opinion within 60 days of receipt of a standard trial application. The Directive provides the first European description and enforcement of the responsibilities of ethics committees, which include not only trial authorisation but also long-term monitoring. Serious concerns have been raised as to whether the ethics committees of Europe are sufficiently equipped and
Research file

protocol & pat. info + IB & IMPD

Accredited EC
Competition Authority CCMO

Medical scientific and ethical review
Marginal review

60 days
14 days

EudraVig db

Review system in the Netherlands
Central versus decentral assessment

Central review
- hudge workload
- review by civil servants
- review limited to part of the research file
- responsibility CA & EC unclear
- no interdisciplinary discussion
- harmonisation easy
- scientific/safety review independent of ECs
- no support for ECs required

Decentral review
- modest workload
- review by peers in institute
- review of the complete research file
- responsibility CA & EC clear
- interdisciplinary discussion in committee meeting
- harmonisation difficult
- scientific/safety review by ECs
- support ECs is essential
The impact of clinical trials legislation on clinical pharmacology: problems and solutions

Morris J. Brown


Clinical Pharmacology Unit, University of Cambridge, Addenbrookes Hospital, Cambridge, UK

Figure 1

Annual decline in UK submissions for ethical approval since the implementation of the EU directive. Data redrawn from http://www.nres.npsa.nhs.uk/news-and-publications/news/nres-year-in-review/ (year’s run April-to-March; 2008 projected from data until October)
UK research trials are on verge of extinction

Sir, clinical research, including trials of new and old drugs, is one of the outstanding achievements in the UK academic sector and current Government Enterprise initiatives are directed at capitalising on this success and expertise. It is, therefore, disturbing that British biotech companies — until recently the strongest in the world after the United States — are on the verge of extinction, and that a key reason is the crippling self-inflicted extra costs of clinical trials in the UK that have forced the industry to use overseas trials units.

European directives introduced to "harmonise" clinical research have led, in the UK, to an explosion of agencies that add months or even years to the simplest and safest phases of clinical research, and millions of pounds to the cost — for those few investors with the patience to persist. The pharmaceutical industry now recruits only one third the number of patients to clinical trials in the UK compared with the period before the EU clinical trials directive; the number of studies seeking ethical approval has fallen by 30 per cent; and the Government's regulatory agency has logged a 99 per cent reduction in non-commercial trial authorisations.

Over the same period, since 2004, other European agencies have logged a stable or increased number of trials. For smaller biotech companies, transferring activity abroad is less feasible than for pharma. For academic researchers on fixed-term grants, the financial and logistic consequences of delay are often insuperable. People of all ages benefit from ethical pharmaceutical and clinical advances used to treat disease. The waste of taxpayers' and charitable money on red tape has managed to reduce productivity but not enhance safety — as reflected by the Northwick Park debacle of 2006.

For decades before 2004, the UK led on an effective simple process ensuring ethical approval of trials with patients giving written informed consent using intelligible consent documents. It is, of course, essential that brand-new drugs face scrutiny. However, the current system does not distinguish at an early stage between projects on a risk basis, ensuring that even the simplest projects take a huge amount of time to gain approval. A chief investigator can now spend months of full-time work before administering the first dose of a drug that he or she prescribes every day in the clinic.

The majority of the regulatory burden may have little basis in law and is unique to the UK. Clinical research should be regulated by those who care for patients, who realise that academic research is essential to patients — and development of new drugs. We must not need multiple bodies to share responsibility for reviewing research but a simplified system, such as the Dutch model, employing a single form to harmonise the process.

Professor George C. Giffen
Chair, Association of Clinical Professors
Professor Morris Brown
Chair of Clinical Pharmacology, University of Cambridge
Professor Ian Gilmore
President: Royal College of Physicians
Professor Sir Nicholas Winton
Warden of Barts and the London School of Medicine and Dentistry
Professor Sir Neil Douglas
President, Royal College of Physicians of Edinburgh
Plus 105 members of the Association of Clinical Professors of Medicine

To see the full list of signatories it timesonline.co.uk/letters

Jeremy Swain
Chief Executive, Thames Reach
We do not need multiple bodies to share responsibility for reviewing research but a simplified system, such as the Dutch model, employing a single form to harmonise the process.
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Webportal ToetsingOnline (ReviewOnline)

- ABR-form (research file)
- Amendment
- Annual rep.
- SUSAR/SAE
- End of trial report
- Correspond.
- Review Online
- Decision
Central Committee on Research Inv. Human Subjects (CCMO)

About the CCMO | For investigators | For research committees | Legal framework | Register

PO Box 15302
2500 BH The Hague, the Netherlands
Parnasusplein 5
2511 VX The Hague, the Netherlands

Fast track to:
- The review system in the Netherlands:
  Research covered by the Medical Research Involving Human Subjects Act and/or the Embryos Act must be submitted to an accredited Medical Review Ethics Committee (eMREC) for approval before it is carried out. In some cases, the CCMO acts as the Review Committee.
- Review step plan RC:
  Follow the step plan for research committees (RC) to find out whether your study has to be reviewed, by which committee, and what will be examined during (and after) the review itself.
- Review step plan CA:
  Follow the step plan competent authority (CA) to find out whether your study is with medicinal products and if so, which (extra) committee must give the decision whether there are ‘grounds of non-acceptance’ concerning the study, and what procedure must be followed before and even after the review CA.
- Forms:
  This page contains all the forms that may be relevant during or after the medical ethics review.
- Web portal TesturingOnline:
  Internet portal for submission and review of medical ethics research with human subjects in the Netherlands.

CCMO website: www.cccmo.nl
In December of 2008, the CCMO took into use a trial version (beta version) of the public trial register with core data on research involving human subjects. Publication took place on a voluntary basis, but is standard as of November 2009. A username or password is not necessary to consult the public register.

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. The request should also include a copy of the concerning research protocol. De CCMO evaluates these requests on the individual (study) basis. Requests can be submitted for all types of clinical research.

**Which data are made public?**

The core data which are made public are marked with a globe symbol in the general assessment and registration form (ABR form).

The core data from the ABR form are only entered into the public CCMO register after the accredited medical research ethics committee (cmREC) has assessed the research file (including the signed ABR form), and has sent their decision (within 7 working days) to the CCMO.

**WHO accreditation**

The CCMO will apply for accreditation of her public register at the WHO. After accreditation by the WHO, the filling in of the ABR form and assessment by an cmREC is sufficient to meet the requirements laid down by the editors of biomedical journals united in the International Committee of Medical Journal Editors (ICMJE) (NEJM 2005, 352:2436-2438). A second registration in a trial register is then no longer necessary.

However, it will take some time before the CCMO register is recognised by the WHO. Therefore, registration in a WHO accredited trial register (for instance www.trialregister.nl) is, as yet, still required.

**Suggestions**

Suggestions on how to improve the trial version are welcome and can be sent to admin@ccmo.nl.
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[Trialregister](#)
CCMO Register

Language / Taal
- Dutch / Nederlands
- English / Engels

Method
- Keyword
- Dossier number ToetsingOnline
- EudraCT number
- Advanced

Dossier number ToetsingOnline

EudraCT number

Reviewing committee

Date decision

Decision

Is the protocol (also) registered in another public trial register?
- yes
- no
- clear

Name applicant or contact person for the reviewing committee
- Kind of organisation or company
- Organisation or company
- Name of organisation or company
- Surname applicant or contact person

Sponsor of the research
- Kind of company or institute
- Company/institute
- Name of company or institute

Full title of the research

Short title of the research/acronym

Keywords

Clear Fields

New search

Search
CCMO Register

Language / Taal
- Dutch / Nederlands
- English / Engels

Method
- Keyword
- Dossier number ToetsingOnline
- EudraCT number
- Advanced

Keyword
- diabetes

Query
- diabetes

574 documents found
- NL3990.041.09: Is the Level of Skin Autofluorescence (SAF) Related to Complications in Pregnant Patients with Diabetes Mellitus?
- NL22506.042.08: Integrated psychological treatment in patients with diabetes burnout
- NL12894.029.06: Susceptibility to type 2 diabetes: perceptions and family communication regarding inheritance and primary prevention
- NL33491.028.10: Blood pressure regulation during spinal anesthesia in patients with diabetes mellitus type 2
- NL12406.026.09: Contribution of a defective adipose tissue and skeletal muscle lipolysis to diacylglycerol-mediated insulin resistance in obesity and type 2
CCMO Register

Language / Tool
- Dutch / Nederlands
- English / Engels

Method
- Keyword
- Dossier number
- TestingOnline
- ExtraCT number
- Advanced

Keyword
- diabetes

Query

Show selected documents
- Diabetes

De Centrale Commissie Mensgebonden Onderzoek

574 documents found

NL3827-058-96 The Anti-interleukin-1 in Diabetes Action trial
NL22247-019-96 Aspirin sensitivity in diabetes mellitus: the role of glycaemic control and dosing
Background of the study:
The aim of the Anti-Interleukin-1 in Diabetes Action trial (AIDA) study is to test the feasibility, safety/tolerability and potential efficacy of anti-IL-1 therapy in maintaining or enhancing beta-cell function in people with new-onset Type 1 diabetes.

The hypothesis is that anti-IL-1 treatment as add-on therapy to conventional insulin therapy will preserve or enhance beta-cell function assessed as the 2 h-area under the curve (AUC) for C-peptide in response to standard mixed meal.

For 20 years it has been recognized that the pro-inflammatory cytokine interleukin-1 is selectively cytotoxic to rodent and human beta-cells in vitro and anti-IL-1 therapies reduce diabetes incidence in animal prevention models. The following observations can be highlighted: 1) IL-1 alone or in combination with other inflammatory cytokines causes beta-cell destruction in rodent and human islets and in perfused pancreas via the MAPK and NFkB signalling pathways, 2) IL-1 given i.p. to non-diabetes prone animals causes transient insulinopenic diabetes 3) IL-1 is expressed early in NOD islets 4) anti-IL-1 intervention prevents diabetes development in models of Type 1 diabetes and islet graft destruction and 5) transgenic mice with knock-out of the IL-1 receptor reduces diabetes incidence by 30%. We recently reported that 13 w of IL-1 receptor antagonist therapy improved glycaemia and beta-cell function in Type 2 diabetes, a disorder in which glucose-induced beta-cell apoptosis may be IL-1 dependent and the intervention is safe.

Objective of the study:
The aim of the Anti-Interleukin-1 in Diabetes Action trial (AIDA) study is to test the feasibility, safety/tolerability and potential efficacy of anti-IL-1 therapy in maintaining or enhancing beta-cell function in people with new-onset Type 1 diabetes.

Study design:
A randomized, placebo-controlled, double-masked, parallel-group, multi-centre trial of IL-1 antagonism in subjects with newly-diagnosed Type 1 diabetes. Patients are instructed to inject 100 mg human recombinant interleukin-1 receptor antagonist (anakinra, Kineret®, Amgen, CA) or placebo s.c. once daily for 2 years. Endpoints will be evaluated every three months, with an interim analysis after 6 months.
CCMO public trial register with core data on different types of research

(Febuary 2006 - April 2010)
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Decentral controlled & integrated peer review system

- **Decentral:** review by 27 accredited MRECs
- **Controlled:** oversight by the CCMO
- **Integrated:** all documents in one review
- **Peer review:** review by experts in accredited MRECs
- **Limited central review:** by CCMO (i.e., gene therapy, embryo research, xenotransplantation)
Contact:
ccmo@ccmo.nl

More information:
www.ccmo.nl
Disclaimer

Aan deze presentatie kunnen geen rechten worden ontleend. Hoewel de CCMO grote zorg heeft besteed aan de in deze presentatie opgenomen informatie, kan zij niet instaan voor de juistheid daarvan.

In deze presentatie opgenomen opvattingen of meningen zijn uitsluitend die van de auteur en zijn daarmee niet per definitie een weergave van die van de CCMO. De CCMO aanvaardt geen aansprakelijkheid voor de gevolgen van het gebruik van deze presentatie of de daarin opgenomen informatie.

Hergebruik van informatie opgenomen in de presentatie is toegestaan onder voorwaarde van bronvermelding.