

WMO 2005

Changes in Dutch Medical Research Involving Human Subjects Act (WMO)

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acknowledgment

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1999: Medical Research Involving Human Subjects Act (WMO)

- Research in humans judged by either:
 - Institutional Medical Ethics Review Board
 - Central Committee on Research Involving Human Subjects (CCMO):
 - Serves as MERB for certain types of research (*eg* legally incompetent subjects, gene therapy)
 - Administrative body dealing with appeals and objections
- Accreditation of MERBs by CCMO
 - Limited numbers
 - Formal governmental bodies
- Adverse Events:
 - Registered products: Medicines Evaluation Board (CBG)
 - Unregistered products: Health Inspectorate (IGZ)
- Law supervised by Health Inspectorate (IGZ)
- No-fault insurance policy for all research participants
- No specific licence needed for preparation of research medication

Changes needed according to 2001/20 EC.....

- All drug research, except studies without interventions
- Administrative harmonisation
- One MERB-review per study per country
- Judgment by two independent bodies
- Competent authority
- European registration of all research (EUDRACT) and adverse events (EUDRAvigilance)
- Preparation of research drugs according to GMP

EU Directive in Practice?

review procedure (1)

- Dual judgment:
 - **One local MERB**
 - Review of protocol AND study drug
 - Multicentre trials: 'feasibility statement' by boards of participating hospitals
 - **CCMO**
 - Competent Authority
 - Check of protocol and study drug in European databases

EU Directive in Practice?

review procedure (2)

- Dual judgment (c'td):
 - Concomitant procedures
 - Local MERB: within 60 dagen
 - CCMO: within 49 days
(21 days for phase I)
 - Appeal to MERB-judgment no longer by CCMO but in court of law

EU Directive in Practice?

review procedure (3)

- Local MERBs: review of study medication
 - Quality of research medication
 - Production data
 - Pharmacological and toxicological data
- Increased demands to pharmaceutical and clinical pharmacological expertise
- Clinical pharmacologist / hospital pharmacist
- Training courses and backup by National Institute for Public Health and Environment (RIVM)

EU Directive in Practice? production of study drugs

- Study drug import and preparation:
 - GMP conditions
 - Manufacturing authorisation required
 - Needed for all pharmaceutical procedures
- Permits granted to all applying hospital pharmacies
 - Ongoing improvements production facilities and procedures
 - Inspections planned later

EU Directive in Practice?

European databases (1)

European databases:

- EudraCT-database for all drug research within EU
 - Eudract-TrialNumber
- Eudravigilance-module
 - 'suspected unexpected serious adverse reactions' (SUSARs)
 - unknown (not in IB or product information sheet)
 - probable or certain relationship to trial medication
 - serious (life-threatening, hospital admission, birth defect etc)
 - immediate reporting to authorities and MERB; sponsor responsible
 - other 'serious adverse events/reactions'
 - (bi)annual safety report to Medicines Evaluation Board

● Reports no longer to Health Inspectorate (IGZ),
but to Medicines Evaluation Board (CBG)

EU Directive in Practice?

European databases (2)

- Medicines Evaluation Board (CBG) responsible for data entry and queries
- Databases accessible to:
 - Medicines Evaluation Board (CBG)
 - CCMO/Health Minister
 - Health Inspectorate (IGZ)
 - Competent authorities of other member states
 - EMEA
 - European Committee
- Not accessible to MERBs, sponsors or investigators

EU Directive in Practice?

Old vs New (1)

Review by single organ

- Institutional MERB

Study medication not reviewed extensively

No central registration

Review by two organs

- Accredited MERB (governmental bodies)
- CCMO

Explicit review by MERB experts

- clinical pharmacologist
- training courses

European database check by CCMO

European databases

- all clinical trials
- serious adverse events

EU Directive in Practice?

Old *vs* New (1)

Report (serious) adverse reactions

- to Health Inspectorate (IGZ) for unregistered drugs
- to Medicines Evaluation Board (CBG) to registered drugs

No GMP-conditions or special permits needed for pharmaceutical procedures

Report all (serious) adverse events/reactions to CBG

Drug import and production according to GMP, with specific permits

State of affairs

- Revised Medical Research Involving Human Subjects Act (WMO) unanimously accepted by 2nd Chamber of Parliament (~ 'House of Commons')
- Unanticipated opposition in 1st Chamber of Parliament (~ 'House of Lords')
- Ongoing diplomatic negotiations about (minor) changes
- Revised law requires renewed approval by
 - 2nd Chamber
 - 1st Chamber
 - Council of State
- After approval, six weeks to allow for referendum
- Earliest expected implementation: before summer recess
- Several laws still need to be amended

Ministerial WorkingGroup Implementation EU-Directive

- Objective: optimal adaptation of new law to existing situation
- Simple implementation of dual review
- Broad composition of working group
- Separate working party for non-sponsored research in conjunction with medical faculties
- Information meetings
- FAQs and regular website updates (www.ccmo.nl)
- Instruction Manual

Instruction Manual

www.ccmo.nl

Chapter 1 Overview of changes

Chapter 2 Prior to the start of the study

Chapter 3 During the conduct of the study

Chapter 4 Appendices

[...]

4.5 EudraCT database manual

4.6 Example of a confidentiality statement

[...]

4.8 CCMO External Review Directive

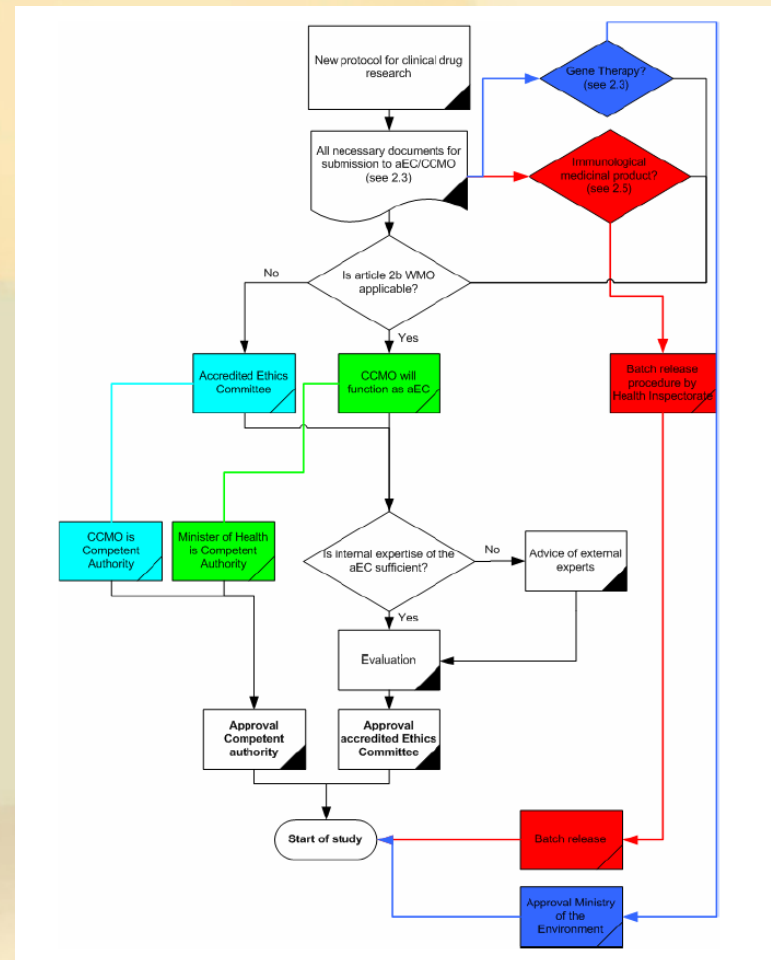
4.9 Example of a Declaration of Feasibility

4.10 Contents of an Investigator's Drug Brochure (IB)

4.11 Example of a Full Investigational Medicinal Product Dossier (IMPD)

4.12 Serious Adverse Events (CIOMS) form

4.13 Example of annual progress report for MERB



Misconceptions about MERB-Reviews and IMPDs:

‘Local MERBs
don’t have the
expertise to
review my drug’

Misconceptions about MERB-Reviews and IMPDs:

‘When my drug
is reviewed by a
local MERB, it’s
secrecy is lost’

Misconceptions about MERB-Reviews and IMPDs:

‘IMPD should
contain complete
information
about drug
manufacturing’

Facts

- No more than about 20 MERBs are left in the Netherlands
- All these MERBs are accredited:
 - Official governmental bodies
 - Bound to full confidentiality vs proprietary information, intellectual property etc
 - Supervised by Ministry of Health
- Sufficient expertise for drug review
 - Accredited clinical pharmacologist / hospital pharmacist in each MERB
 - Training courses by National Institute for Public Health and the Environment (RIVM)
 - Additional evaluations by RIVM at request of MERB

Facts

- IMPD should contain enough information to ensure that product is safe
 - GMP-compliant production
- For registered products* official label text ('1b') sufficient
- EU-Directive: 'IMPD need not be an extensive document'
- Unnecessary to provide *every* aspect of manufacturing to MERB
- Examples of IMPD provided in Handbook

*registered administration mode and indications

Conclusions

- Most aspects of EU-Directive already fully operational since 2000
- Implementation of (remainder of) EU-Directive expected before (?) summer 2005
- Implementation facilitated by Ministerial Working Group consisting of practical field workers (industry, CROs, academia, government)
- Decentralized system, to ensure flexible, non-bureaucratic reviews