WMO 2005

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

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acknowledment
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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

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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

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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

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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

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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)

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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

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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)

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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

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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

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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

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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

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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

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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

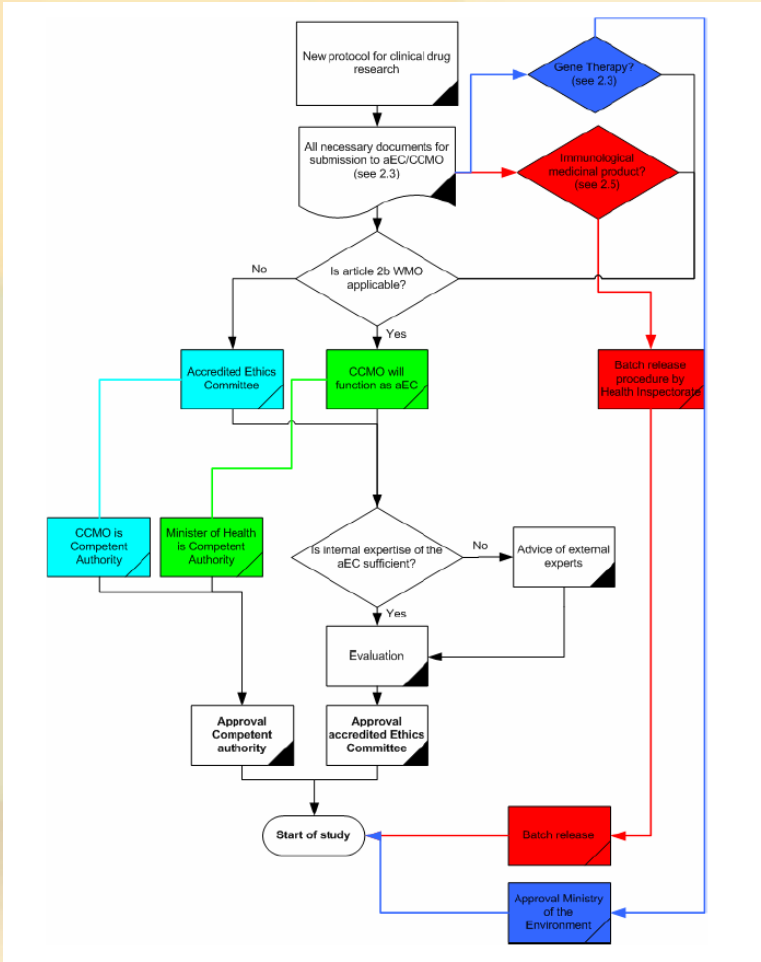
4.9 Example of a Declaration of Feasibility

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



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Misconceptions about MERB-Reviews and IMPDs:

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

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Misconceptions about MERB-Reviews and IMPDs:

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

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Misconceptions about MERB-Reviews and IMPDs:

‘IMPD should contain complete information about drug manufacturing’

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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 proprietory 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

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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

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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

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