WMO 2005

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

Prof dr Joop van Gerven, neurologist
Centre for Human Drug Research, Leiden
Member of WorkingGroup Implementation
EU-Directive of Dutch Health Ministry

acknowledgment
Mrs M.J.F. Elenbaas-Thomas LL.D.,
Dutch Health Ministry
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 Working Group 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.cccmo.nl)
- Instruction Manual
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