Trial Approval in Early Drug Development: Current Experiences in The Netherlands
(Phases 0, I, IIA)

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Ethical Review Processes in The Netherlands

- Competent Authority:

  Central Committee on Research Involving Human Subjects (CCMO)

- Ethics Committees

  1 special CCMO EC for:

  - gene therapy
  - RNA interference
  - antisense oligonucleotides
  - (stem) cell therapy
  - xenotransplantation
  - vaccines
  - nontherapeutic intervention studies with minors or incapacitated adults

  30 EC's, accredited by the CCMO

  - 24 tied to 1 or more health care institutions
  - 6 run by non-profit foundations

Process for obtaining clinical trial authorization in The Netherlands

Parallel submissions of the research protocol to:

1. The CCMO
2. The EC chosen to review the research protocol

The CCMO must notify the EC and the sponsor within 14 days if it has any objections

The EC has 60 days plus one clock stop to reach a decision

Negative EC decisions may be appealed at the CCMO

System widely regarded fast and efficient, especially for EDD

See letter in The Times of January 14, 2009, p.21

Laws and regulations relevant to protocol reviews in The Netherlands

- Medical Research Involving Human Subjects Act (WMO, 1999)
- Revised WMO, incorporating Directive 2001/20/EC (GCP), effective March 1, 2006
- ICH Guidelines
- EMEA Guidelines
- FDA Guidelines

Protocol Reviews in The Netherlands, 2007

Total Reviews:	1841	
CCMO:	**45**	
Clinical Trials with Medicinal Products:	582	= 32%
CCMO:	**6**	
Phase-1 Clinical Trials	119	= 20%
CCMO:	**2**	
Reviewed by EC of BEBO Foundation	68	= 57%

EC of BEBO Foundation has gained pioneering role in reviewing Phase-1 protocols in The Netherlands

Ethics Committee of BEBO Foundation

- 26 members in total, working in 2 equivalent and interchangeable panels. Each panel meets once a month, total of 24 meetings per year. Extra meetings on request
- Short time lines. Protocol/amendment reviews within 10 days after submission
- Sponsor / CRO is heard during meeting
- Chairman or vice-chairman on call for emergencies 24 hrs/day, 7 days /week.
- Rapid and concise procedures for reviewing SUSAR's/SAE's and amendments
- Monitoring of study progress and study outcomes

BEBO POLICIES FOR EDD STUDIES

- Protocol must contain clear justifications of design, starting dose, dose escalation steps, dosing intervals and risk mitigation procedures
- Starting dose based on NOAEL and/or MABEL, as deemed appropriate
- Dosing in first cohort of all FIH studies : Day I: only two subjects, one receiving active treatment, one receiving placebo

  Monitoring for 24 hours. If no safety concerns, dosing of other subjects of this cohort
- Subsequent cohorts (single and multiple dose) will each be dosed on one day, with intervals allowing serial assessments in a safe and practicable fashion

BEBO POLICIES FOR EDD STUDIES

- Dose escalation steps in EDD studies to be decided on a case-by-case basis, taking into account all available *a priori* knowledge. If this knowledge is insufficient or whenever knowledge requires, dose escalation will proceed in steps no greater than 2-fold

- After each dose escalation, Interim Safety Reports must be prepared and submitted to the EC to obtain approval for study continuation

- After completion of each study leg, Interim Safety Reports must be prepared and submitted to the EC to obtain approval for study continuation

BEBO REQUIREMENTS FOR APPROVAL OF AMENDMENTS

- Directive 2001/20/EC, art. 10, sub (a) lets sponsor decide if an amendment is substantial. If so, sponsor shall notify CA and EC

- BEBO: ALL amendment proposals require additional approval of EC. Chairman of EC judges whether amendment is substantial or not. Review procedures for the two categories are different

  A guide on what may be considered substantial amendments can be found in “Clinical Research with Medicinal Products in The Netherlands, Ministry of Health, Welfare and Sport, The Hague, 2005, Chapter 3.1

- Reason: EC responsible for safety and well-being of volunteers. Undesirable to let sponsor decide what is substantial

BEBO REQUIREMENTS FOR REPORTING SUSAR's / SAE's

- Directive 2001/20/EC, art. 17 requires SPONSOR to notify CA and EC about serious adverse reactions, within 7 days if fatal or life-threatening, within 15 days for all others
- BEBO requires to be notified immediately (<24 hrs) by the INVESTIGATOR of any serious adverse event or reaction. Investigator must put study 'on hold' and await a further decision by the EC

  The basis for this requirement is the Dutch WMO, art 10.1,: 'If the research takes a course that is less favourable to the volunteers than initially foreseen, the investigator must inform the EC and the volunteers immediately. At the same time, the research must be put on hold and cannot be continued until the EC has given consent to do so'.
- Reason: EC responsible for safety and well-being of volunteers.

  Unacceptable to continue dosing/other protocol burdens

SUSAR's / SAE's reported to BEBO from 'own' EDD studies

	SUSAR's	On Hold
2006	10	3
2007	6	0
2008	7	2

Note: SUSAR's / SAE's reported by sponsors from 'other' studies are also monitored, including yearly listings

If deemed necessary, EC will take corrective actions for ongoing 'own'. studies

Other pivotal observations on trial approval in EDD

- Laws, regulations and guidelines always lag behind

  As a result, EC's confronted with innovative new approaches are on their own to make risk/safety assessments, etc.
- When legal/regulatory/guideline actions are undertaken, opportunities for comments/suggestions are often limited
- Rationales and/or explanations are usually scarce; key practical issues are not addressed; contact possibilities to obtain advice are limited – if at all
- Regulatory documents on the same topic but from different organisations may show large discrepancies

Bad examples: EMEA Position paper on Microdosing, 2004 and
FDA Guidance for Exploratory IND Studies, 2006

Other pivotal observations on trial approval in EDD

Sponsor tries to get as much as possible in one large, multi-facetted protocol (also known as umbrella protocol)

Example: **single ascending doses**
multiple ascending doses
fast and slow metabolizers
food interaction
drug interaction
impact of age on safety, tolerability and PK
impact of gender on safety, tolerability and PK
concomitant effect measurements

similar legs in patients

Sponsor tries to cut corners / widen boundaries

CONCLUSIONS ON EC OBLIGATIONS

- Stay abreast of
  - Laws, regulations, guidelines ,etc.
  - Appropriate scientific literature
  - Changing societal / ethical insights
- Exert constant alertness and be prepared to detect
  - contradictions, misinterpretations, errors, fraud, etc.
- Find defensible balance between risk acceptance and advancement of drug development
- Always consider the position and well-being of the volunteer in the trial

Thank you for your attention