Selected ethical aspects of international clinical trials

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Regulatory perspective on clinical trials

- Clinical trials should provide sound scientific evidence for benefit/risk assessment for medicinal products
- Requirements for clinical trials are defined
  - by ethical principles (WMA DoH, WHO/CIOMS,…)
  - in Guidelines (ICH, EMA/CHMP,…)
  - by EU Regulations and Directives, national law

Regulatory perspective on clinical trials outside EU

- EU legal requirement: Directive 2001/83/EC, Paragraph 8 of the Preamble of Annex 1
  Clinical trials conducted in third countries and used in Marketing Authorisation Applications in the EEA or in applications for a Scientific Opinion under article 58 of the Regulation (EC) No. 726/2004, must be conducted on the basis of principles equivalent to the ***ethical principles and principles of good clinical practice*** *applied to clinical trials in the EEA.*
- EMA guidance: "Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities" (EMA/121340/2012)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012
EMA/121340/2011
The European Medicines Agency Working Group on Clinical Trials conducted outside of the EU/EEA

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities

Released for Consultation	26 May 2010
End of consultation	30 September 2010
Agreed and Endorsement by CMD	14 June 2011
Agreed by EMA Working Group on Clinical Trials conducted outside of the EU/EEA	05 July 2011
Endorsement by CHMP	19 October 2011
Endorsement by EMA Management Board	15 December 2011
Endorsement by Heads of Medicines Agencies	24 February 2012
Date coming into effect	1 May 2012

Keywords	***Clinical trials, GCP, Marketing Authorisation Applications, EMA, EU, Ethics, conducted outside of the EU***

Regulatory perspective: Selected topics

- EMA guidance defines framework, procedures and proposed regulatory actions
- Reflection paper provides consensus position
- From Table of contents:
  - **4. Clarification of the practical application of ethical standards for clinical trials on medicinal products for human use in the context of the European Medicines Agency activities**
  - **4.1. Ethics committee and national regulatory authority oversight**
  - 4.2. Information/Consent procedure
  - **4.3. Confidentiality**
  - 4.4. Fair compensation
  - **4.5. Vulnerable populations**
  - 4.6. Placebo and active comparator
  - **4.7. Access to treatment post trial**
  - 4.8. Applicability of data to EEA population

Ethics committees

- Local or national ethics committee should review the trial. Ethics committees have to
  - be independent
  - be pluralist, multidisciplinary and representative of stakeholders
  - include expertise in vulnerable populations (paediatric, mental disorders, …)
- In many countries a trial application has to be made to a regulatory authority
  - In Germany trial application must be approved by BfArM
- Review by additional ethics committees is optional
  - in multicentre studies a central ethics committee could review the study in addition to local or national ethics committees

Ethics committees: Regulatory action

- Failure to submit a protocol to an independent EC is a serious violation of ethical standards. EU regulatory authorities should disregard data obtained in a such unethical manner when submitted in support of a MAA.
- Approval by ethics committee and national regulatory authority must be provided. Description of adherence to ethical standards should be provided in study report and assessed by regulatory authorities.
- EU Regulatory Authorities should identify studies that may give rise to special ethical concern (e.g. design, vulnerability of study subjects) and where applicable seek additional assurance that the trial have been ethically conducted.

Biobanks and confidentiality

- Confidentiality must be maintained.
- Participants are entitled to know any information collected on their health. Participants may choose not to receive or not receive information about their health.
- Biological sample retention and consent procedure for analysis and re-analysis should be according to the protocol.
- Samples cannot be used for purposes different of the ones described in the protocol without a new written informed consent.
  - In exceptions, where consent is impossible, impractical or where validity of research would be compromised, ethics committee approval is necessary.

Biobanks: Regulatory action

- EU regulatory authorities should disregard reports which fail to properly protect the confidentiality of the trial subjects, when submitted in support of a MAA.
- EU regulatory authorities should identify studies that may give rise to special concern regarding confidentiality (e.g. arising from the use of genetic information or bio-banked samples).
- From a scientific and public interest perspective use and re-use of biological samples is highly appreciated to capture important information for optimization of therapies
  - Biobank use in European Network of Paediatric Research (Enpr-EMA).
  - Steps toward mechanism-based and individualized medicine (EMA Patients', consumers' and healthcare professionals' expectations survey, Doc ref. EMEA/40926/2009).

Vulnerable groups

- Inclusion of participants from vulnerable populations should be fully justified and research in vulnerable groups should be only undertaken when there is a reasonable likelihood for direct benefit to the subject or group concerned.
- Vulnerability due to poverty, lack of adequate health care systems or lack of access to medicines and exploitation of a vulnerable group for benefit of EU patients is of main concern.
- Category of vulnerability and therefore justification may vary (e.g. impoverished persons, patients with incurable diseases, those incapable of giving consent,…).

Vulnerable groups: Regulatory action

- The inclusion of vulnerable subjects in a clinical trial without the approval of the ethics committee and without implementation of the appropriate consent processes is a serious violation of ethical standards. EU regulatory authorities should disregard data obtained in such an unethical manner when submitted in support of a MAA.
- Justification of inclusion and specific measures implemented to protect rights and welfare of vulnerable groups should be described in the protocol, the clinical study report and made public in the European Public Assessment Report.
- EU regulatory authorities should identify studies that may give rise to special ethical concern regarding the inclusion of vulnerable populations and where applicable seek additional assurance that the inclusion of such populations was justified and their rights and welfare protected.

Post-study arrangements

- Differences in patients‘ access to medicinal products needs to be considered by sponsor, ethics committees and regulatory authorities.
- For patients who participated in a trial continued access to beneficial product is crucial.
- Post-trial access to treatment or care provided by the sponsor cannot substitute for shortcomings of national or regional health care systems.
- Transparency on post-trial access is paramount. Ethics committees, national regulatory authorities and participating patients need to be fully informed about post-trial arrangements and benefits.

Post-study arrangements: Regulatory action

- EU regulatory authorities should identify studies that may give rise to special ethical concern regarding access to treatment post trial and where applicable to seek additional assurance that the solution was appropriate and ethically acceptable.
- Information on post-trial access will be summarized in the European Public Assessment Report.