Interpretation of the definition of non-interventional trials under the current legislative framework ("Clinical Trials Directive" 2001/20/EC)

G. Schnetzler
on behalf of the ENCePP Task Force
Task

• To provide a common interpretation of the understanding of the definition of ‘non-interventional trial’
  – In the context of the current legislative framework
  – Based on widely accepted methodological definitions and clinical practice
• To illustrate the interpretation with examples
Procedure

• Action commissioned at the ENCePP plenary session of Nov 2010
• Call for volunteers in Jan 2011
• Task force reunions (TC) on Feb 3, Feb 28, Mar 15, Apr 14
• Consultation with the ENCePP members (until May 27)
• Adoption by the Steering Group (June 23)
# List of TF participants

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Background

• Article 2c of the Directive 2001/20/EC (CTD):
  – Use of medicinal product according to MA
  – No assignment to therapeutic strategy other than current practice
  – No additional diagnostic or monitoring procedures
• Clarification for post-authorisation safety studies in Eudralex Vol 9A:
  – Interviews, questionnaires and blood samples may be considered as normal clinical practice
• Inconsistencies exist in the interpretation of a non-interventional trial in the EU Member States\(^1\)
  – Studies have been delayed or not been conducted at all due to differences in interpretation of the definition

Study versus Trial

‘Study’: systematic assessment of events without interfering with their course

‘Trial’: element of experimentation (prospective data collection)

‘Interventional clinical trial’: allocating treatment a priori (e.g. by randomisation) → governed by CTD

• Ethics committee approval ≠ CTD governance
Fundamental principle

- Good science and protection of individual in both interventional and non-interventional research

Diagram:
- Investigator
  - Observation, Monitoring, Recording
  - Assigning, Allocating, A priori determination of
    - Treatment:
      - Observational, non-interventional study
      - classical, experimental clinical trial
Retrospective studies are by definition ‘non-interventional’:

• Purely observational database review and/or research
• Retrospective review of records where all the events of interest have already happened
  – e.g. case-control, cross-sectional, and purely retrospective cohort studies
• Studies in which the prescriber later becomes an investigator but prescribing has already occurred
  – e.g. retrospective data collection from individual medical records at the site of the investigator
Assessment of current use

The following prospective studies should never be considered interventional:

• Registries in which the data collected derive from routine clinical care

• Studies which evaluate patterns of the usage of medicines
  – drug utilisation studies including potential off-label use
  – measuring the effectiveness of risk management measures
  – measuring effectiveness of therapeutic interventions in current practice
  – health outcome assessments
Prospective data collection

To be considered non-interventional in the case of:

• Prospective cohort studies in which the prescription of the medicine is independent from the inclusion of the patient in the study
  – May involve additional diagnostic or monitoring requirements

• A retrospective study to which a prospective element is subsequently introduced
  – Further variables that are not in the existing dataset requiring additional research, for instance linked databases or additional blood draws

• Long-term extension studies with patient follow up beyond trial protocol specified time for observation and active collection of additional data
  – Such as death or event free survival
Determinants to define “current practice”

• A diagnostic, monitoring or therapeutic procedure can be considered current practice if at least one of the following is fulfilled:
  – Routinely performed by a proportion of healthcare professionals
  – Not deemed obsolete
  – Performed according to evidence based medicine criteria
  – Defined in guidelines issued by a relevant medical body
  – Mandated by regulatory and/or medical authorities
  – Reimbursed by the national or private health insurance
ENCePP interpretation of non-interventional trial

• Fully in line with Directive 2001/20/EC

• Facilitates observational studies on medicines, thereby protecting and promoting public health
Next steps

• Presentation to the CTFG, July 6-7, 2011
• Publication in a medical journal (aim: Q4 2011)
  – share interpretation and determinants of non-interventional studies with researchers, ethics committees and regulatory authorities
Example 1: Case control studies

- Reviews of events, including treatment, all of which have already happened
- Detailed interviews with patients is still non-interventional
  - There is no experimental element in the study
  - Everything of interest has already happened
  - The purpose of the interview is only to further scrutinise factors surrounding events purely as an observer, with no possible impact on the events
Example 2: Patient Registry

- Prospective data collection over time on subjects, independent of use of medicine according to MA
- No protocol defined treatment or management or allocation of patients and patients visits
  - considered routine clinical care
  - inclusion in the registry will have no impact on the therapeutic strategy
Example 3: Cohort study

• May seek to compare the safety and/or effectiveness of a particular medicinal product with that of another medicine and one of the medicines may be used in conditions that are outside of its MA
  – Retrospective data collection is always non-interventional
  – Prospective data collection is non-interventional if assignment to a particular treatment arm is not decided in advance by a trial protocol
  – If additional diagnostic or monitoring procedures are involved, at least one of the criteria determining current practice has to be fulfilled
Example 4: Safety review of class of medicines

- One product has a specific requirement for regular diagnostic test to monitor AE while other products of same class do not
- MAH have been requested to perform a cohort study to estimate the real-life incidence of the AE across the whole class of products
- The proposed diagnostic/monitoring procedure could be considered as current clinical practice, although it is specified for only one product of the class, and therefore classified non-interventional
Example 5: Drug utilisation studies

• Observing the use of a drug in real life (as opposed to the rigid settings of clinical trials)

• This could include evaluating patterns of use of a medicinal product, including capturing off-label use and can even be conducted with this specific aim

• Research is purely observational, as there is no experimentation involved