



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

	Name	Representing
1	Joerg Hasford	IBE, Ludwig-Maximilians-Universitaet
2	Stephen Evans	Hygiene and Tropical Medicines/PhVWP
3	Nicholas Moore	Bordeaux, ENCePP SG Sponsor
4	Michelle Ellefson	HIV Programme, Denmark
5	Loreto Carmona Ortells	Sociedad Espanola de Reumatologia
6	Gabriel Schnetzler	Prism Ideas (Consultancy)
7	Gillian Hall	Gillian Hall (Consultant)
8	Sabine Straus	Dutch MEB/PhVWP
9	Ingemar Persson	Swedish MPA, ENCePP SG Sponsor
10	Dolores Montero Corominas	Agencia Española de Medicamentos y Productos Sanitarios / PhVWP
11	César de la Fuente	Agencia Española de Medicamentos y Productos Sanitarios
12	<i>Stella Blackburn</i>	<i>EMA, ENCePP SG Sponsor</i>
13	<i>Peter Arlett</i>	<i>European Medicines Agency</i>
14	<i>Fergus Sweeney</i>	<i>European Medicines Agency</i>
15	<i>Camilla Smeraldi</i>	<i>European Medicines Agency</i>
16	<i>Kevin Blake (chair)</i>	<i>European Medicines Agency</i>
17	<i>Ana Rodriguez Sanchez Beato</i>	<i>European Medicines Agency</i>
18	<i>Sophia Mylona</i>	<i>European Medicines Agency</i>

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 States¹
 - 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

Investigator

Observation
Monitoring
Recording

Assigning
Allocating
A priori determination of

Treatment

Treatment

Observational,
non-interventional study

classical, experimental
clinical trial

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

Retrospective studies

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