European Network of Centres
for Pharmacoepidemiology and Pharmacovigilance

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

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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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13	*Peter Arlett*	*European Medicines Agency*
14	*Fergus Sweeney*	*European Medicines Agency*
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16	*Kevin Blake (chair)*	*European Medicines Agency*
17	*Ana Rodriguez Sanchez Beato*	*European Medicines Agency*
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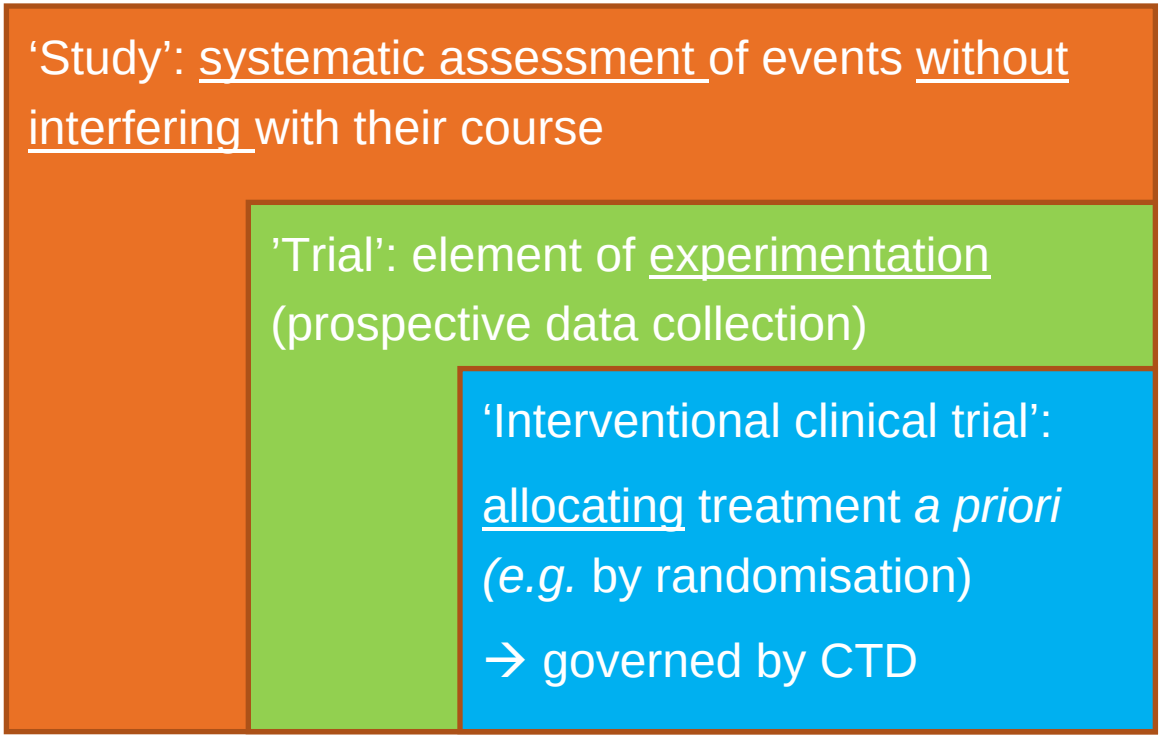
Background

- 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

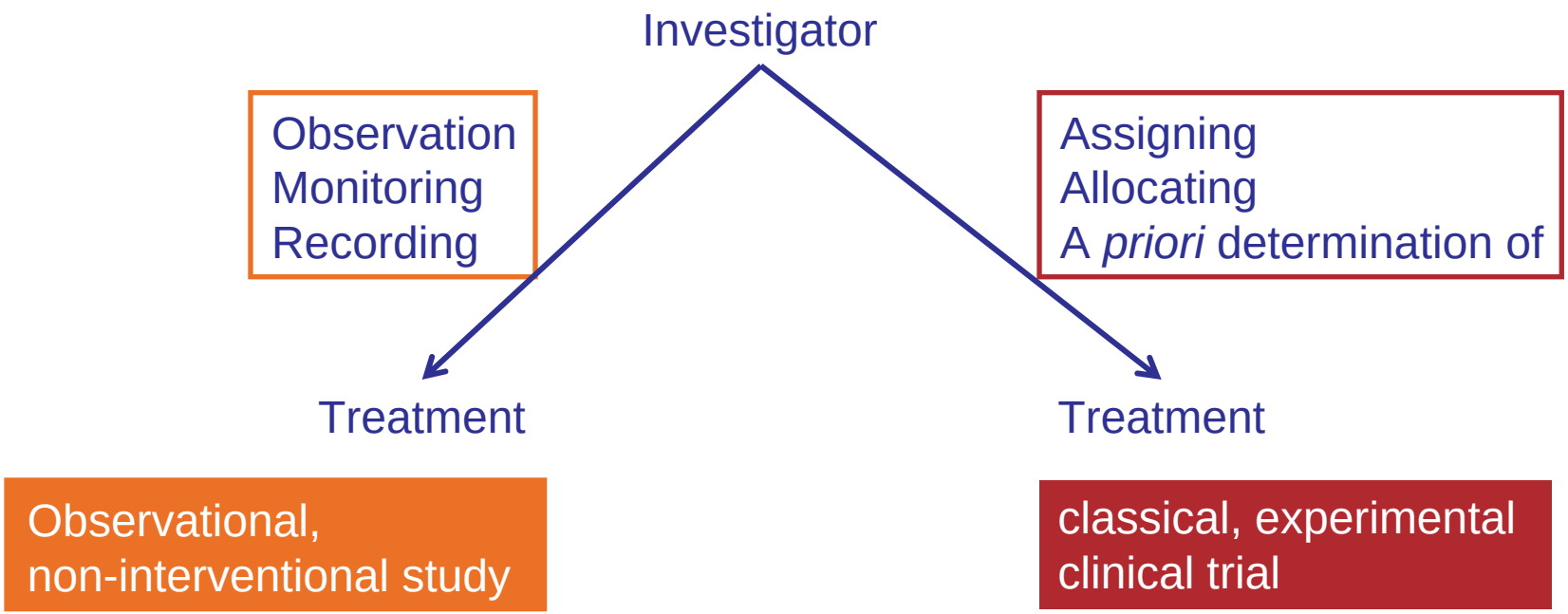
1. Kubiak C, de Andres-Trelles F, Kuchinke W et al. Common definition for categories of clinical research: a prerequisite for a survey on regulatory requirements by the European Clinical Research Infrastructures Network (ECRIN). Trials 2009;10:95

Study versus Trial



- Ethics committee approval ǂ CTD governance

Fundamental principle



- 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