European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCEPP CONSIDERATIONS ON THE DEFINITION OF NON-INTERVENTIONAL TRIALS UNDER THE CURRENT LEGISLATIVE FRAMEWORK ("CLINICAL TRIALS DIRECTIVE" 2001/20/EC)

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BACKGROUND

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance[1] (ENCePP) was started in 2006 as a key initiative from the Heads of Medicines Agencies and EMA's European Risk Management Strategy.[2] ENCePP aims to improve pharmacoepidemiological research and risk-benefit monitoring of medicines in the European Union by increasing research capacity and promoting principles of scientific standards, transparency and scientific independence. The network gathers available expertise and research experience across Europe and currently comprises more than one hundred centres, networks and data sources in seventeen countries. Participation in ENCePP and all related activities is voluntary.

At its November 2010 plenary meeting, ENCePP partners expressed concerns on the current definition of a 'non-interventional trial' within Directive 2001/20/EC[3] (also known as the Clinical Trials Directive) and how this definition is being interpreted differently amongst EU Member States and National Competent Authorities, leading to difficulties in the conduct of such trials (particularly when conducted in more than one Member State).

The aim of this ENCePP position paper is to promote a common understanding of the definition of 'non-interventional trial' in the context of the current legislative framework and based on widely accepted methodological definitions and clinical practice.

CURRENT DEFINITION OF 'NON-INTERVENTIONAL TRIAL'

According to paragraph one of Article 1 of Directive 2001/20/EC, non-interventional clinical trials are excluded from the scope of that Directive.

A 'non-interventional trial' is defined in Article 2(c) of Directive 2001/20/EC as follows:

"a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data."

In a Question and Answer document dated March 2011 and published in Chapter V of Eudralex Volume 10[4] it is further stated that for a trial to be considered as non-interventional, the requirements specified in the legislation need to be cumulatively fulfilled.

The statement in the Q & A document continues that the purpose for excluding non-interventional trials from the scope of Directive 2001/20/EC is that such trials are typically of a lower risk than interventional clinical trials. Moreover, this restriction shall ensure that medical activities which are *normal clinical practice* and as such part of the general medical surveillance of a patient are excluded from the scope of the Directive 2001/20/EC.

A clarification of the definition is also provided in Eudralex Volume 9A,[5] where as regards to post-authorisation safety studies, the following is stated:

"(…) In this context it is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice. Based on these definitions a fundamental distinction can be made between non-interventional (observational) and interventional post-

authorisation safety studies. The latter are considered clinical trials falling under the scope of the Directive 2001/20/EC."

It must also be noted that certain national legislation (in the transposition of the EU Clinical Trials Directive in national legislation) further contributes to the interpretation of the definition of a non-interventional trial and/or add additional requirements for approval. Differences in interpretation mainly relate to the interpretation of what constitutes 'intervention' in terms of blood samples, questionnaires or other measurements.[6] However, national legislation and requirements for approval also differ among Member States in terms of a need to submit to National Competent Authorities for approval; the level at which Ethics Committee approval is required (national or local); and; for example; in Portugal there is a requirement for authorisation from the Portugese Data Protection Authority for non-interventional post-authorisation safety studies.

PROBLEM STATEMENT:

Experience has shown that the current definition leaves room for interpretation by stakeholders such as investigators, independent ethics committee members and regulatory authorities in the different EU Member States.[7] Furthermore, the recent focus of having to cumulatively fulfil three requirements for a study to be considered 'non-interventional' can lead to classification errors being made as it diverts from the more fundamental question of whether a study, methodologically, is a clinical trial that needs to meet the requirements of the Clinical Trial Directive. Failure to meet the definition of 'non-interventional' results, by default, in assignment of the status of interventional trials to observational studies that collect real life data. As a consequence, studies have been delayed or not been conducted at all due to differences in interpretation of the definition in the Directive in terms of what might be considered issues that present low risk to study participants such as more frequent diagnostic or monitoring procedures than would be applied within normal clinical practice.

Pharmacoepidemiology is the field of public health research that studies the effects of medicinal products in large populations, mostly after these products have come to the market. For example, the IPPHS study was a prospective case-control study that investigated the risk of occurrence of primary pulmonary hypertension (PPH), a disease with high lethality, in association with anorectic agents.[8] It included patients with PPH diagnosed between 1 September 1992 and 30 September 1994 with data collection tools that included interviewing cases and controls and recording some clinical parameters. The study was a key element in the first EU review of the benefit/risk balance of anorectic agents initiated in 1995. Under the most recent interpretation of the Clinical Trials Directive, this study would have been considered as an interventional trial, a status which may have significantly delayed or even impeded its implementation.

The major goal of ENCePP is to facilitate the conduct of high quality multinational pharmacoepidemiological and pharmacovigilance studies that serve to elucidate the risk-benefit profile of a medicine in the real-life setting as compared to use within the framework of an interventional clinical trial. ENCEPP partners have, therefore, highlighted the need to promote a common understanding of the current definition of 'non-interventional trials' with specific regard to the most common methodologies used for the conduct of observational studies.

ENCEPP AGREED POSITION:

Observational research and ethical review

The key objectives of Directive 2001/20/EC are to ensure good science and quality of data and analyses, and to maximise the protection of the participating research subjects. However, similar to clinical trials, ensuring scientific quality and the protection of personal integrity of study subjects are also important objectives in observational, pharmacoepidemiological research. In line with its aim of supporting the highest research standards, ENCePP considers that in addition to meeting legislative requirements, studies need to adhere to a set of principles that meet with the requirements of scientific and ethical reviews.[9] ENCePP wishes to emphasise, however, that a requirement for Ethics Committees approval is separate to classification as falling within the scope of Directive 2001/20/EC. It does not, therefore, of itself, imply that a study should be considered subject to the Clinical Trials Directive even in cases where potentially complex ethical considerations may be involved (e.g. further analyses of already drawn blood). Similarly, there may be ethical considerations around the methods to be used for the analysis of collected data.

Trials and studies

In classical, experimental clinical trials, there are fundamental interventions, which include applying strict criteria for inclusion and exclusion of the subjects, allocating treatment *a priori (e.g.* by randomisation), and enforcing study requirements according to a protocol. Observational, epidemiological (including pharmacoepidemiological) studies are fundamentally different in these respects. Treatment of the subject is not *determined* or *assigned* by study procedures, but instead non-interventional research involves its *observation and monitoring* and recording what is happening or has happened in the clinical setting. Although the term trial is often used as a synonym for study, ENCePP considers the term 'trial' implies an element of experimentation and a prospective approach in the collection of data, whereas a 'study' is a systematic assessment of events that unfold without interfering with their course.

In interpreting the definition of a non-interventional trial as per Directive 2001/20/EC in the context of observational research, it should, therefore, be considered that in the majority of cases the term 'trial' is not applicable and the term 'study' as defined in the previous paragraph is more appropriate. Any definition must be primarily driven by consideration of the methodological instruments applied and, therefore, have a scientific base. This implies 'studies' are readily distinguishable from 'trials' and should not lead to any ambiguity in terms of the scope of the currently applicable legislative framework.

Examples of non-interventional studies

Taking into account the previous considerations, ENCePP considers the following as examples of retrospective studies that should not be considered in terms of Directive 2001/20/EC being applicable:

- Purely observational database review and/or research.
- Retrospective review of records where all the events of interest have already happened (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).

Similarly, the following prospective studies should never be considered as falling within the scope of Directive 2001/20/EC:

- Registries in which the data collected derive from routine clinical care.

- Studies which evaluate patterns of the usage of medicines, including potential off-label use or measuring the effectiveness of risk management measures in current practice, such as collection of data on drug utilisation and occurrence of health outcomes.

The following situations are, however, examples of studies that involve prospective data collection and for which the potential applicability of the Directive needs close consideration to decide whether or not a given study is ultimately classified as a non-interventional trial or an interventional trial (refer Appendix for further detailed examples):

- Prospective cohort studies that involve additional diagnostic or monitoring requirements but in which the prescription of the medicine that is being investigated is independent from the inclusion of the patient in the study.
- A retrospective study to which a prospective element is subsequently introduced (e.g. the researcher wants to evaluate further variables that are not in the existing dataset and, therefore, prospective additional research is undertaken. This might range from further analyses in linked databases to additional blood draws or other additional diagnostic or monitoring events).
- Long-term extension studies in which patients that received treatment with a medicinal product in a completed randomised clinical trial are followed beyond the time specified by the clinical trial protocol for the observation and the active collection of data on safety or other outcomes (e.g. death, event free survival, etc).

Requirements for non-interventional trials

In these cases the current Volume 10 of Eudralex interpretation of the definition of non-interventional trial specifies that the three requirements in the Directive need to be met simultaneously. ENCePP, however, considers the following criterion as the key to classifying a trial in terms of it being non-interventional and falling outside the scope of the Clinical Trials Directive i.e. "*The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study".* As such, any intervention in terms the prescribing of the medicinal product itself is independent of inclusion in the study and whatever has happened/will happen in terms of treatment with the medicine *per se* will not be modified by inclusion in the study.

In cases where this criterion is met, ENCePP understands the further consideration required to determine if a trial should ultimately be classified as non-interventional relates to establishing whether "*additional diagnostic or monitoring procedures*" are applied to the trial subjects as compared to normal clinical practice. The terms of the marketing authorisation may serve as a reference point for this consideration. ENCePP has also elaborated the following set of principles based on the current applicable legal framework and on current scientific and medical evidence that could serve as a guidance, in addition to the previously cited explanation given in Eudralex Volume 9A, providing examples of additional interventions, such as '*interviews, questionnaires and blood samples'* that '*may be considered as normal clinical practice'*.

Clinical practice can be seen as any medical procedure, which is performed by an adequately qualified person on a patient. *Qualified person* relates to professional education and training for specific medical procedures, as defined by law and regulation in the individual Member States and their mutual recognition within the European Union (Directive 2005/36/EC)[10]. *Medical procedures* can be medical diagnostic tests, interventions or treatments.

Current practice is less precisely defined and current clinical practice regarding the diagnosis, intervention, and follow-up of a specific medical problem can vary between healthcare

professionals and can differ depending on the setting (e.g. outpatient vs. inpatient clinics[11], district hospital vs. teaching hospital[12] and between EU member states[13]).

Current clinical practice

The following criteria could help to determine whether a diagnostic, monitoring or therapeutic procedure could be classified as current practice, particularly in the context of prospective data collection: the procedure is routinely performed by a proportion of healthcare professionals; is performed according to evidence based medicines criteria; is defined in guidelines issued by a relevant medical body; is mandated by regulatory and/or medical authorities; and/or is reimbursed by the national or private health insurance. The requirement is for at least one of these criteria to be fulfilled.

The following are general principles for procedures to still be seen as non-interventional:

- The use of validated patient reported outcomes is non-interventional, where evidence based medicine criteria and/or other relevant guidelines recommend their use for diagnostic or monitoring purposes or to measure outcomes.
- Interviews and questionnaires should not lead to a change in behaviour or influence treatment and should be as short as needed to reach the objectives of the non-interventional trial.
- Further analysis of already drawn blood need not be seen as interventional, although such analyses have to be approved by ethics committees.

CONCLUSION

Classification as a non-interventional trial within the current legislative framework should be scientifically-based and determined by the methodological instruments involved. This will readily determine if a study is observational with no experimentation involved and, therefore, even if use of the term trial is appropriate. If further consideration is still required in terms of whether a study might potentially fall within the scope of Directive 2001/20/EC, then if treatment with the medicine has already happened or if such treatment that will happen is not assigned *a priori* in a protocol and the same applies for the therapeutic strategy, including the diagnostic or monitoring procedures involved, and the therapeutic strategy itself can be considered as current clinical practice, then the study should be classified as non-interventional.

A non-interventional trial may, therefore, be interpreted as:

"a study where the medicinal product(s) is (are) prescribed independent to inclusion of the patient in the study and as part of a therapeutic strategy, including diagnostic and monitoring procedures, which is not decided in advance by a study protocol but is applied according to the current clinical practice"

This position is fully in line with Directive 2001/20/EC and aims to further facilitate post-authorisation medicines research, thereby protecting and promoting public health.

1 http://www.encepp.eu/

2 European Risk Management Strategy: 2008-2009 work programme adopted.
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2009/11/WC500010971.pdf

3 European Parliament and Council. DIRECTIVE 2001/20/EC (EU Clinical Trials Directive). http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF. 2001.

4 European Commission. Eudralex Volume 10- Guidance documents applying to clinical trials Q&A version 8 (March 2011). http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm

5 European Commission. Guidelines on Pharmacovigilance for Medicinal Products for Human Use: Eudralex Vol 9A. European Commission- Eudralex Eudralex Vol 9A. 2008. http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm

6 European Commission-European Medicines Agency. Report on the Conference on the Operation of the clinical Trials Directive (Directive 2011/20/EC) and Perspectives for the Future. http://www.eortc.be/services/doc/EUCTD/EC-EMEA_report_CT_20071003.pdf. 2007

7 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.

8 Abenhaim LA, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C, Wouters E, Aubier M, Simonneau G, Bégaud B. for the International Primary Pulmonary Hypertension Study Group. Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension. N Engl J Med 1996; 335: 609-616.

9 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology. http://www.encepp.eu/standards_and_guidances/index.html

10 The European Parliament. Directive 2005/36/EC on the recognition of professional qualifications. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:255:0022:0142:en:PDF. 2005

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13 European Commission. Cancer screening in the European Union. Report on the implementation of the council recommendation on cancer screening. First report. http://ec.europa.eu/health/ph_determinants/genetics/documents/cancer_screening.pdf. 2008.

APPENDIX: Practical examples of studies that may be classified as 'non-interventional trials'.

Example 1: Case-control studies are reviews of events, including treatment, all of which have already happened. In case-control studies, however, it is rather usual to perform detailed interviews with patients in order to explore whether or not they were exposed in the past to certain drugs or other variable of interest. These sometimes long, specific interviews may be viewed as outside routine practice and therefore as an "additional procedure" (if a subject was not included in the study they would not be having the interview). According to the current definition of a non-interventional trial inclusion of such interviews in a case-control study might result in the study being classified as a clinical trial falling within the scope of Directive 2001/20/EC if it is considered that they constitute an additional diagnostic or monitoring procedure being applied to patients. It is, however, paramount to apply consideration of the methodologies involved in a case-control study in the first instance to avoid such a classification as interventional trial that everything of interest has already happened and the purpose of the interview is only to further scrutinise factors surrounding events purely as an observer, with no possible impact on the events themselves. There is no experimental element in the study. This emphasises the point that retrospective reviews of events that have already happened should never be considered in terms of whether or not Directive 2001/20/EC is applicable as to do so diverts from the bigger picture that what is being conducted is observational research.

Example 2: A registry collects data prospectively over time on subjects with certain shared characteristics, which may be a disease or an outcome (disease registry) or a specific exposure (exposure or drug registry). Some of drug registries recommend including the highest number of patients treated for safety purposes, independently of whether or not the medicines are used according the Summary of Product Characteristics (SmPC) or not (e.g. orphan indications, when the use of the medicine is limited by the prevalence of the disease, etc...). If the current definition of a non-interventional trial is applied in a rigid manner and it is considered that a drug is being used outside the terms of its marketing authorisation, such registries could be mis-classified as clinical trials falling within the scope of Directive 2001/20/EC. If, instead, it is considered in the first instance whether or not "*the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice"* and it is confirmed that there is no protocol defined treatment or management or allocation of patients and patients visits, then it is the case that what is happening is routine clinical care and inclusion in the registry will have no impact on the therapeutic strategy. This implies, therefore, that what is being conducted is purely observational research and as such is a non-interventional trial. Furthermore, although by definition a patient may be included in a drug-registry only once a drug has been prescribed the key consideration has to be whether or not "*the prescription of the medicine is clearly separated from the decision to include the patient in the study".* If the medicine is prescribed within routine clinical care and inclusion in the study will not impact on the therapy, this again classifies what is being conducted is purely observational research and as such a non-interventional trial.

Example 3: A cohort study (either retrospective or prospective) 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 it's marketing authorisation. Such a study would not fulfil all the criteria laid down in Directive 2001/20/EC for being classified as 'non-interventional trials'. If the study is a retrospective review of data and everything of interest has already happened, then there is no experimental element to the study at this stage and simply looking back at what happened when a drug was used off-label cannot be considered as a clinical trial falling within the scope of the Clinical Trials Directive. It must, therefore, be considered only as a non-interventional trial. If the study is to be conducted prospectively, then what is paramount in classifying the study is that the decision to include a patient in a particular treatment arm is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. If this is the case, then inclusion in the study *per se* has not impacted on the decision to prescribe one medicinal product instead of the other and should not impact on the subject remaining on that treatment. This means the study is simply observing what will happen and as such may be classified as a non interventional trial. If, however, there are additional diagnostic or monitoring procedures involved, then further consideration of the applicability of the Clinical Trials Directive is required. The need for such further consideration does not imply a particular prospective cohort study will ultimately be considered as a clinical trial. Fulfilling at least one of the following criteria could help to determine whether a diagnostic or monitoring procedure could be classified as current practice: the procedure is routinely performed by a proportion of healthcare professionals; is not deemed obsolete; is performed according to evidence based medicines criteria; is defined in guidelines issued by a relevant medical body; is mandated by regulatory and/or medical authorities; is reimbursed by the national or private health insurance.

Example 4: Consider a review of the safety of a class of medicinal products after one of the substances belonging to this class has been associated with a particular adverse event that is detectable only with a particular diagnostic procedure. The terms of the marketing authorisation for the drug known to be associated with the adverse event and, therefore, the SmPC have been varied to include a requirement for the specific diagnostic procedure to be conducted at regular intervals. For the other drugs belonging to the same class the introduction of this requirement is under evaluation by regulatory authorities. In the context of this evaluation, marketing authorisation holders have been requested to perform a cohort study to estimate the real-life incidence of the adverse event across the class of products before a final regulatory decision is taken. Such a study might consist of two groups of patients, those taking the drug which is associated with the adverse event and those taking other drugs belonging to the same class of products. In both groups a baseline performance of the relevant diagnostic procedure would be necessary along with periodic repeating of the same investigation with the at a pre-determined time interval to detect the adverse event of interest. If this is considered as the implementation of an additional diagnostic or monitoring procedure then according to the current definition of non-interventional trial, this cohort study could automatically be classified as falling within the scope of Directive 2001/20/EC. Close consideration should, however, be given first as to whether or not the proposed diagnostic/monitoring procedure is truly outside of current clinical practice, taking into account the SPC of the drug known to be associated with a risk of the outcome of interest. If it is considered that the proposal in fact falls within current practice then the study may be classified as a non-interventional trial.

Example 5: Drug utilisation studies are aimed at observing the use of a drug in the real life (as opposed to the rigid settings of clinical trials). Typically data relating to indications, dosages and duration of use are gathered and analysed. By definition, the observer should not interfere with practice because the aim of the study is to capture reality as it is. Drug utilisation studies are useful tools in evaluating the patterns of use of a medicinal product, including capturing off-label use and can be conducted with this specific aim. In these circumstances therefore, if the current

definition of non-interventional trial is applied, the fact that a study is intended to study the use of drugs (although not their effects) outside the terms of their marketing authorisation could be interpreted as if these studies fall within the scope of Directive 2001/20/EC. If, however, methodological principles are applied first, it will be seen that such a classification should never occur as there is no experimentation involved and the research is purely observational and, therefore, non-interventional.