EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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# The ENCePP Code of Conduct

## FOR SCIENTIFIC INDEPENDENCE AND TRANSPARENCY IN THE CONDUCT OF PHARMACOEPIDEMIOLOGICAL AND PHARMACOVIGILANCE STUDIES

The ENCePP Code of Conduct was adopted on 7 May 2010 by the Steering Group of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The terms of the Code of Conduct will be reviewed by the ENCePP Steering Group periodically after its adoption.

| **Steps taken** | **Date** |
|---|---|
| **Key elements of the Code of Conduct** agreed by the ENCePP Working Group on *Independence and Transparency* | 21 November 2008 |
| **1st draft Code of Conduct** agreed by Drafting Group of the ENCePP Code of Conduct | 8 May 2009 |
| **2nd draft Code of Conduct** agreed by ENCePP Working Group on *Independence and Transparency* | 17 June 2009 |
| **Final draft Code of Conduct** approved by ENCePP Implementation Advisory Group | 27 October 2009 |
| **Public consultation** | 16 November 2009 – 5 January 2010 |
| **Adoption of the final draft** | 7 May 2010 |

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# 1. Background

In recent years, the European Medicines Agency (EMA) has concentrated on developing a more proactive approach to pharmacovigilance as part of the European Risk Management Strategy[1]. ENCePP originates from the agency's endeavour to enhance the scientific and operational expertise and capacity in the fields of pharmacoepidemiology and pharmacovigilance across Europe and to improve pharmacoepidemiological research and post-authorisation safety surveillance of medicines by offering access to a robust network of resources.

The ENCePP Code of Conduct, hereinafter referred to as the "Code", has been primarily developed by the ENCePP Working Group on *Independence and Transparency* and has been subsequently adopted by the ENCePP Steering Group. Development and adoption of the Code followed a transparent process including a public consultation involving a wide range of stakeholders[2].

# 2. Rationale and Scope

### *Rationale*

The aim of the Code is to maximise transparency and to promote scientific independence throughout the research process of pharmacoepidemiology and pharmacovigilance studies. By applying the principles of transparency and scientific independence, the Code aims to strengthen the confidence of the general public, researchers and regulators in the integrity and value of pharmacoepidemiology and pharmacovigilance research.

### *Scope*

The Code of Conduct sets out rules and principles for studies, primarily pharmacoepidemiology and pharmacovigilance studies, with an emphasis on non-interventional post-authorisation studies (see also definitions of post-authorisation study and non-interventional study in Annex 1). This includes - but is not restricted to - active surveillance studies, registries, drug-utilisation studies, and any other types of observational methodologies. However, the definition of pharmacoepidemiology and pharmacovigilance studies may also include clinical trials (see Annex 1).
The Code does not provide rules or guidance on methodological aspects or scientific standards to be used for specific studies or study types. Adherence to the Code will not guarantee validity or accuracy of study data. However, knowledge of this Code of Conduct and a documented commitment of applying the rules and principles to a study by the investigator and study funder will help regulators and other stakeholders in the assessment of the reliability of study findings.

The use of this Code is voluntary but is mandatory if a study is to be awarded the title "ENCePP study" (see Chapter 3 for further details on ENCePP studies).

[1] The European Risk Management Strategy (ERMS) is a joint effort between the EMA and the Heads of Medicines Agencies (HMA) started in July 2002 aiming at strengthening the safety-monitoring in the EU/EEA of medicinal products for human use. More information is available at http://www.hma.eu/43.html.

[2] Stakeholders including regulatory authorities, learned societies, health care professionals and patients' organisations as well as the pharmaceutical industry were given the opportunity to express their view on the Code in a public consultation. Specifically, the National Competent Authorities of the EU/EEA through the Heads of Medicines Agencies and the Committee for Medicinal Products for Human Use (CHMP) as well as the CHMP's Pharmacovigilance Working Group (PhVWP), the US Food and Drug Administration, the International Society for Pharmacoepidemiology (ISPE) and other learned societies, the EMEA/CHMP Working Group with Healthcare Professionals' Organisations, the EMEA Human Scientific Committees' Working Party with Patients' and Consumers' Organisations, and the European Federation of Pharmaceutical Industry and Associations (EFPIA) and other Industry organisations were involved.

### *Main principles*

The Code lays down rules and recommendations as regards:

- **scientific independence**, by ensuring best practice in the relationship between investigators and study funders, including protocol agreement and publication of results; and
- **transparency** throughout the research process and when reporting results.

## 3. Implementation of the Code in the context of ENCePP studies

Adherence to the Code is one of the prerequisites for studies to qualify for the title "ENCePP study". Applying a set of transparency measures, both with regard to operational and methodological aspects, ENCePP studies will permit a high level of public scrutiny, ultimately increasing trust in the value of the study results.

More specifically, any study can qualify as an "ENCePP study" provided that the (primary) lead investigator[3] belongs to an entity that is included in the ENCePP Inventory of Research Centres[4] and that the "CoRe requirements" are met as detailed below.

*CoRe* requirements

- *Co*de of Conduct: Signed declaration and checklist.
- Methodological Standards for Study Protocols: Signed checklist[5].

*The signed declaration and checklists and the study protocol must be provided to the ENCePP Secretariat before the study commences. The declaration and the checklists will be made publicly available.*

- *e*-Register of Studies[6]

*The study needs to be included in the electronic ENCePP Register of Studies before it commences.*

The primary interest of ENCePP lies in pharmacoepidemiological and pharmacovigilance studies and more specifically in non-interventional studies.

Further information on the application process for "ENCePP study" qualification is available at http://www.encepp.eu.

### *Application of the Code and Compliance of ENCePP Studies*

To confirm compliance with the provisions of the Code, the (primary) lead investigator of the study must complete the checklist (Annex 2) and sign the declaration (Annex 3). Originals of the signed checklist and declaration together with a copy of the agreed full study protocol[7] shall be provided to

[3] This requirement refers to the primary lead investigator in case of a multi-site study and to the lead investigator if the study is conducted at a single site.

[4] The ENCePP Inventory of Research Centres forms part of the ENCePP Database of Research Resources and can be accessed at http://www.encepp.eu/encepp/resourcesDatabase.jsp.

[5] The *Checklist for Methodological Standards for ENCePP Study Protocols* is available at http://www.encepp.eu.

[6] The electronic ENCePP Register of Studies is currently under development. Until its release, studies can be registered at http://www.encepp.eu.

[7] For the purpose of this document, a *full* study protocol is a version of the protocol which includes enough detail in order to answer all questions in the *Checklist of Methodological Standards for ENCePP Study Protocols*.

the ENCePP Secretariat, who will archive them for at least five years after the date of the final report. The ENCePP Secretariat will check the documentation for completeness and confirm the *a priori* eligibility of the study to be considered as an ENCePP study. The declaration and the checklist will be made publicly available.

Investigators and funders who, for a particular study, wish to claim "ENCePP study" status, commit to adhering to the rules of this Code throughout the research process including the publication of the research results.

At the same time, the (primary) lead investigator and the study funder should ensure that the research contract makes appropriate reference to the Code and that by signing the research contract the funder commits to abide by the rules of the Code (see also Chapter 8).

### *Withdrawal and Breach*

The (primary) lead investigator should inform the ENCePP Secretariat without delay if the study deviates from and/or no longer follows the rules of the Code. In this event he should cease describing the study as an ENCePP study. Failure to comply with the above may be considered a breach of the declaration (Annex 3).

In the event of a breach, the concerned study shall be deprived of the title "ENCePP study".

In the event of either voluntary withdrawal or removal of the "ENCePP study" status for breach of the Code, the ENCePP Secretariat may identify the respective studies together with the cause for such change in status, i.e. either voluntary withdrawal or deprivation for breach, in the annual reports and on the ENCePP website.

## 4. Legal framework and approved guidelines

In addition to the rules and principles laid down in the ENCePP Code of Conduct, studies performed in line with the Code need to comply with relevant legislation, as applicable.

The Declaration of Helsinki[8] and the provisions on processing of personal data and the protection of privacy as laid down in Directive 95/46/EC and Regulation 45/2001 of the European Parliament and of the Council need to be followed.

For interventional research, the Clinical Trials' Directive (Directive 2001/20/EC) applies.

As post-authorisation studies concern authorised medicinal products, relevant European and national legislation applies. Specifically, Marketing Authorisation Holders will need to comply with Directive 2001/83/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council.

This Code should not be considered as a stand-alone document but should be read in conjunction with other relevant guidance. Notably, this Code takes into account the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP, Revision 2, 2007) and refers to relevant parts thereof, as appropriate. Other relevant guidance including Volume 9A of the Rules Governing Medicinal Products in the European Union -

[8] World Medical Association declaration of Helsinki (see also chapter 16)

Pharmacovigilance for Medicinal Products for Human Use, the STROBE Statement (Guidelines for Reporting Observational Studies), the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors (2009), the Guidelines for Good Clinical Practice (Commission Directive 2005/28/EC) and the International Guidelines for Ethical Review of Epidemiological Studies of the Council for International Organizations of Medical Sciences (CIOMS) should be taken into account when conducting pharmacoepidemiological studies.

## 5. General Provisions

By agreeing to follow the Code, investigators and study funders commit to adhere to the following general principles:

- The primary purpose of a study shall be to generate data of potential scientific or public health importance and not to promote the sale of a medicinal product;
- The design of the research shall not be aimed towards producing a pre-specified result;
- A contract shall be concluded between the (primary) lead investigator or the coordinating study entity and the study funder clearly defining the research assignment and addressing in sufficient detail critical areas of their interaction, remuneration, protocol agreement, analysis of results and publication of results;
- Remuneration shall only be granted as specified in the research contract and shall not depend on the study results;
- The results of a study shall always be published, preferably in a peer-reviewed journal, or made available for public scrutiny within an acceptable time frame, regardless of the (positive or negative) results and the statistical significance;
- Relevant information on the research process and results as specified in this Code shall be publicly available.

## 6. Declaration of Interest

All parties to be involved in the conduct of a study shall declare existing direct or indirect interests of a commercial, financial or personal nature that might impact their impartiality in relation to the study. Details of any and all participation by parties with such an interest shall be documented and made publicly available. Once the protocol has been finalised, no person with a financial interest in a particular outcome of the study shall take part in any study activity that could influence the results or interpretation thereof.

## 7. Ensuring Transparency

A maximum level of transparency on relevant information pertaining to the study should be ensured. This includes information on the study protocol and any revisions thereof - and the publication of study findings. Access to this information should be provided as required in the Code to regulators, health care professionals and the scientific community, as well as patients and the general public as appropriate.

The following means of ensuring transparent research are required by the Code:

- Registration of the study in a publicly accessible register of studies prior to the study start (for ENCePP studies, registration in the ENCePP Register of Studies is required), thereby making publicly available information on the study including the expected timelines, and updating the register with the results (or references to publications) on study completion;
- Accurate and detailed documentation of relevant steps throughout the research process, especially changes to the study protocol from study start and the explanations thereof;
- Agreement to make available on request relevant information including:
    - reports from independent reviewers,
    - a detailed description of how the raw data were transformed into the data set used for analysis as well as the data set for analysis and all scheduled interim and final study findings irrespective of positive or negative results once the final study report is available (see also chapter 12),
    - the content of the research contract (actual financial figures may be redacted[9]).
- State in advance and in publications the affiliations of the investigators and any conflicts of interest.

## 8. Research Contract

The contractual arrangement between the (primary) lead investigator or the coordinating study entity and the study funder should be concluded by signing a legally binding contract prior to the first step in the research process that is the subject of the assignment (see also the definition of 'research contract' in Annex 1).

The research contract shall specifically refer to the ENCePP Code of Conduct and shall include the statement "The parties to this agreement and individuals acting on their behalf hereby commit to adhere to the rules of the ENCePP Code of Conduct in their entirety". The statement should be translated into the language of the contract. The relevant version of the Code at the time of the signature of the research contract should be annexed to the contract for reference.

The following aspects should be addressed in the research contract:

- The main objectives and a brief description of the intended methods of the research that is the subject of the contract.
- The name of the study and a clear assignment of tasks and responsibilities should be stated.
- The procedure for achieving agreement on the study protocol as well as any involvement of the funder in the development of the protocol. The research contract should refer to the study protocol taking into account the elements of the *Checklist of Methodological Standards for ENCePP Study Protocols* (for details on the research contract see Chapter 4) in its development.
- The amount of the financial support and the payment scheme.
- Ownership of, and access to, the data produced during the study. The provisions on data ownership and access to data addressed in Chapter 12 shall apply.
- A communication strategy for the scheduled interim (if applicable) and final results.

[9] Financial figures might be redacted by being blacked out or by being otherwise distorted or rendered unrecognisable provided that it remains clear that a redaction has been made.

- The contract should provide for the rights and obligations as detailed in Chapters 9 (Rights and Obligations of Researcher and Study Funder) and 14 (Publication/Reporting of Study Results).

In case of complaints from third parties questioning the compliance of a particular ENCePP study with the provisions of this Code, the ENCePP Secretariat may request to see the research contract to verify whether it is, or is not, in breach of the Code (actual figures may be redacted).

## 9. Rights and Obligations of Researcher and Study Funder

The content of the assigned research project and the design of the protocol, including the analysis plan, shall be established by agreement between the study funder and the (primary) lead investigator. However, the (primary) lead investigator shall be ultimately responsible for the study including the design of the protocol, the conduct of the study, the analysis and interpretation of the study results and the preparation and publication of the study outcome. The (primary) lead investigator shall keep the funder informed about the study progress in terms of recruitment, where relevant, data collection, any modification of the protocol and the reasons for it, but should not communicate results other than final or scheduled interim results. In the event of a potential serious public health issue, relevant regulatory authorities and the funder should be informed without delay.

Relevant legislation should be followed, as applicable (see also chapter 4).

Detailed provisions on the study conduct and the reporting and publication of the study results can be found in chapter 13 and 14.

## 10. Registration of Studies

The (primary) lead investigator, on behalf of the coordinating study entity, undertakes to register the study before it commences in a publicly available register of studies. Information on the study, constituting a study synopsis and including information on the researchers, i.e. the primary lead investigator and the lead investigator(s), as appropriate, their affiliations as well as the study funder, should be made publicly available. Studies for which the status “ENCePP study” is applied for must be registered in the ENCePP Register of Studies, but other studies, not seeking formal "ENCePP status", are also free to use the ENCePP Register. The ENCePP Register will facilitate compliance with the Code by allowing the uploading of the study protocol, including information on conflicts of interest and, at the end of the study, communication of results.

Studies for which the status “ENCePP study” is applied for must be registered in the ENCePP Register of Studies.

The entry of the study in the register should be regularly updated as appropriate.

## 11. Development of the Study Protocol

The protocol shall be developed before the study commences, by individuals with appropriate scientific background and experience, taking into account the elements of the *Checklist of Methodological Standards for ENCePP Study Protocols* (for details on the research contract see Chapter 4).

The protocol must be designed to ensure scientifically valid and sound results are generated independently from any potential conflicting interest of the funder or the researcher. To achieve this aim, the protocol needs to pre-define certain information before the study starts, as outlined in the *Checklist of Methodological Standards for ENCePP Study Protocols,* including a timetable for the progress and completion of the study and describing milestones (e.g. interim reports) and deadlines.

Any amendments or updates to the protocol after the study start should be documented in a traceable and auditable way including the dates of the changes. Changes to the protocol that may affect the interpretation of the study shall be identifiable and reported as such in publications and in the publicly available register where the study is included, and should be considered when interpreting the findings. This includes additions or amendments to the objectives or endpoints after the study start. An explanation for the change(s) to the protocol should be recorded with the protocol alterations or provided upon request once the study results have been published.
Except for changes to protect the safety of study subjects, changes to the protocol should be agreed in writing with the funder. Changes for reasons such as to promote marketing and/or advertising strategies shall not be acceptable and shall result in removal of the title “ENCePP study”.

### *Protocol Agreement*

The research contract between the (primary) lead investigator and/or coordinating study entity and the study funder shall outline the procedure for achieving agreement on the study protocol. Irrespective of the origin of the study protocol, the (primary) lead investigator shall have final responsibility for its content. If the study has been requested by a particular competent authority, all parties involved in the development of the protocol are responsible for ensuring that the study meets the requirements of the competent authority. In these circumstances, the competent authority might be involved in the development of the protocol according to its regulatory practices.

Involvement of the funder in the design of the protocol shall be specified in the research contract. Information on all parties involved in the writing and adoption of the protocol, including a brief description of their contribution, shall be made publicly available.

### *Availability of the Study Protocol*

The original version of the full study protocol, i.e. the version at the time of study start, together with the final version shall be made publicly available, without delay after the final study report. However, the (primary) lead investigator may decide to publish the protocol at an earlier point in time if he so wishes and provided that the study funder agrees.

For an ENCePP study, the original version of the protocol shall be provided through the ENCePP Register of Studies at the time of registration (see also Chapter 10), but may not be immediately accessible to the public unless the (primary) lead investigator so chooses. The final version should be provided after the final study report and the ENCePP Secretariat will make both versions publicly available.

## 12. Data Ownership and Access to Data

The research contract shall clearly specify data ownership (see Chapter 8). Intellectual ownership by the parties directly involved in the planning and conduct of the study as well as the analysis and interpretation of the study data should be taken into account and should be provided for in the

contract. In principle, data shall belong to both the investigator(s) and the funder. As regards the relation between data ownership and publication of results please refer to Chapter 14.

Both the study protocol and the research contract should address rules for access to raw data, processed data and final results generated under the study. Any identifiable data should be maintained under secure conditions in line with data protection legislation (see also Chapter 4).

The (primary) lead investigator should ensure that all data collected and generated in the study are recorded in a way that allows verification of the published results whilst respecting data protection legislation. Access should be provided on request to the data set used for analysis as well as a detailed description of how the raw data were transformed into the data set for analysis, and all scheduled interim and final study findings irrespective of positive or negative results once the final study report is available. Access may be requested by regulators, health care professionals and the scientific community.

## 13. Study Conduct

Any step in the research process shall follow the agreed procedures laid down in the study protocol and shall be directed towards the generation of sound and valid findings. The investigator(s) shall be responsible for the conduct of the study within the remits of their assignment, including the data collection and analysis, the interpretation of the study results as well as the preparation of study reports and publication of the study outcome.

Once the original version of the full protocol has been finalised, no person with a direct financial interest in a particular outcome of the study shall take part in any study activity that could influence the results or interpretation thereof in a particular direction.

### *Data Analysis*

A statistical analysis plan shall be described in, or annexed to, the study protocol. Any deviations from the analysis plan should be clearly documented and a reasonable scientific explanation should be provided in line with the provisions for changes to the study protocol (see chapter 11).

Outcomes resulting from changes to the analysis plan after data analysis has begun, e.g. formation of new sub-groups based on knowledge of (initial) study results, may not be used for the purpose of verifying or rejecting a hypothesis of a causal association. A caveat regarding this view is that important safety concerns, even if based purely on subgroup analyses, should be documented and evaluated appropriately.

### *Study Steering Group*

If an independent steering group is foreseen for the purpose of providing scientific advice and guidance and/or to oversee the conduct of the study, the members of this steering group shall declare existing direct or indirect interests of a commercial, financial or personal nature and should only be appointed if no direct conflict of interest exists.

If they have a conflict of interest, other parties and stakeholders including the study funder may only participate in meetings of the steering group as invited observers. Observers may participate in the discussions of the steering group; however, they cannot be involved in any decision-making steps.

Representatives of the study funder shall have a demonstrated expertise and scientific knowledge in the area and/or methods of the research.

The composition of the steering group including observers participating in its meetings should be made publicly available.

## 14. Publication/Reporting of Study Results

In publications, the section 'conflicts of interests' should specify that the study has been conducted according to the Code.

A dissemination and communication strategy should be pre-defined as part of the research contract. Any deviation should be duly justified.

A clear summary of the main results of a study, whether positive or negative and including results from prematurely terminated studies, should always be made available to the public according to the timetable agreed in the research contract. In addition, for ENCePP studies, an abstract of the study findings shall be provided through the ENCePP register of studies within 3 months following the final study report. The (primary) lead investigator may ask the ENCePP Secretariat to delay the publication of this abstract for a limited period pending response to peer-review comments.

A full report of all results with a scientific or public health impact must be made publicly available without delay. In case of a (suspected) public health impact, relevant legal provisions shall be followed and the respective competent authority(ies) shall be informed forthwith and in advance of publication.

The outcome of a study shall always be presented in an objective and truthful manner providing a comprehensive and accurate description of the findings. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests. For the content of the report(s), it is recommended to follow the ISPE GPP and the STROBE statement.

If necessary, the published results shall be updated, e.g. in case of re-analyses or additional analyses, including an explanation for the update.

Presentations to a limited audience at meetings will not suffice as the only or main means of communication.

The (primary) lead investigator shall have the right to independently prepare publications of the study results irrespective of data ownership (see also Chapter 12). The study funder shall be entitled to view the final results and interpretations thereof prior to submission for publication and to comment in advance of submission within a reasonable time limit, e.g. one month, as agreed in the research contract and without unjustifiably delaying the publication. Requests that interpretation of the results or their presentation be changed must be based on sound scientific reasons. The (primary) lead investigator is free not to take the comments of the funder into account and, in the event of such a refusal, the funder may only require that the presentation of the results be changed to delete confidential information (see also Chapter 15). Any comments of the funder should be made publicly available.

In line with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors (2009), the authors of the study publication(s)

should be those individuals who have made substantial intellectual contributions to the research. As is usually demanded by respected peer-reviewed journals, information on the actual role of all authors and the study funder should be provided. In addition, affiliations and conflicts of interest should be disclosed. The lead author shall accept responsibility for the overall content of the study publication and the accuracy and integrity of the data presented (even if medical writers have been involved) as well as for any conclusions drawn from the data.

### *Scientific Review*

It is good practice to invite review of the study results and any publications and/or communications thereof by independent experts regardless of whether a study steering group has been established.

The report(s) of the reviewer(s) should be documented. If the reviewer(s) recommend(s) changes, the (primary) lead investigator should either revise the results and publications, or provide a rationale why the original version should be retained. The reports and related information e.g. regarding the implementation of the reviewers' recommendations should be made available upon request.

## 15. Confidentiality

A maximum level of transparency should be sought in relation to any information pertaining to the research process, including the disclosure of relevant information on the study protocol, and any revisions thereof, and the publication of study findings (see Chapter 7).
What constitutes confidential information should be determined before the study commences, and specified either in the research contract or a separate agreement between the relevant parties. Data and results derived from a study shall be regarded as confidential only in relation to relevant data privacy law.

## 16. References

**Checklist of Methodological Standards for ENCePP Study Protocols**, currently a draft is released for public consultation at http://www.encepp.eu.

**Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products** (Official Journal L 91, 9/4/2005 p.13-19 ), available at http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:en:PDF.

**Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use** (Official Journal L 121, 1/5/2001 p. 34 - 44), available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1_en.htm.

**Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use** (Consolidated version: 30/12/2008), available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1_en.htm.

**Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data**, available at http://ec.europa.eu/justice_home/fsj/privacy/law/index_en.htm.

**Guidelines for Good Pharmacoepidemiology Practices (GPP)**, International Society for Pharmacoepidemiology, (Revision 2: April 2007), available at https://www.pharmacoepi.org/resources/guidelines_08027.cfm.

**International Ethical Guidelines for Epidemiological Studies**, The Council for International Organizations of Medical Sciences (CIOMS), 2009, ISBN 92 9036 081 X, superseding the 1991 International Guidelines for Ethical Review of Epidemiological Studies which are available at http://www.cioms.ch/frame_1991_texts_of_guidelines.htm.

**Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18. December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data**, available at http://ec.europa.eu/justice_home/fsj/privacy/law/index_en.htm.

**Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency** (Consolidated version : 6/7/2009), available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1_en.htm.

**STROBE statement:** von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. **The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.** J Clin Epidemiol. 2008 Apr;61(4):344-9.

**Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors (ICMJE)**, 2008, available at http://www.icmje.org/urm_main.html.

**Volume 9A of the rules governing medicinal products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use** (September 2008), available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9_en.htm.

**World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects**, 1964, last amended 2008, available at http://www.wma.net/en/30publications/10policies/b3/index.html.

## Annex 1 (Definitions)

## Definitions

### Clinical Trial

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy.

### Confidential Information

Confidential Information means all information, facts, data and any other matters communicated between the investigator(s), the coordinating study entity and the study funder in the framework of the study undertaken which are clearly identified or marked as being confidential at the moment of their disclosure.

Information on the identity of the study funder is not considered confidential information.
Data derived from a study shall be treated confidentially only in relation to relevant data privacy law.

### Conflict of Interest

In the context of this document, conflicts of interest include any direct or indirect interests of a commercial, financial or personal nature - other than purely scientific motivation - which might compromise the impartiality of the persons contributing to a study and may have an effect on relevant decisions, including the choice of the study design, interpretation of data, and publication of results etc.

### Contract Research

Outsourced research, including either the complete research process or specific steps therein, such as the design of a protocol, data collection that is conducted by an independent contractor on behalf of a funder.

### Coordinating Study Entity

A legal person, institution or organisation which takes responsibility for the design and/or the management of a study. The (primary) lead investigator is the person authorised to represent the coordinating study entity.

### ENCePP Study

Studies, primarily pharmacoepidemiological and pharmacovigilance studies, performed taking into account relevant methodological research standards as agreed by ENCePP and in line with the rules and requirements for the independent and transparent conduct of pharmacoepidemiological and pharmacovigilance research laid down in the ENCePP Code of Conduct, whose (primary) lead

investigator belongs to an entity that is included in the ENCePP Inventory of Research Centres, and which are registered before they commence in the ENCePP register of studies.

### ENCePP Code of Conduct

A set of rules and principles laying down the obligations, responsibilities and good practices to guide the interaction between research centres, pharmaceutical industry and regulators, as well as rules and principles for the conduct of studies, primarily pharmacoepidemiological and pharmacovigilance studies to be followed throughout the research process in order to maximise transparency and scientific independence.

### Lead Investigator

A person with the scientific background and experience required for the conduct of a particular pharmacoepidemiological or Pharmacovigilance study. The lead investigator is responsible for the conduct of a study at a study site.

### Non-interventional Study

See Volume 9A.

### Pharmacoepidemiology

The study of the utilisation and effects of drugs in large numbers of people. To accomplish this study, pharmacoepidemiology borrows from both pharmacology and epidemiology.

### Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems.

### Post-Authorisation Study

Any study conducted with a medicinal product authorised in the European Economic Area (EEA).

### Primary Lead Investigator

If a study is conducted at several study sites by a team of investigators, the (primary) lead investigator is the investigator who has overall responsibility for the study across all sites.

### Research Contract

A legally binding agreement between the (primary) lead investigator or the coordinating study entity and the study funder on the research assignment. This includes grant agreements with public funding bodies and studentship agreements.

### Study Funder

A legal person or a group of legal persons who provide(s) the financing for a study.

## Study Protocol

A document that describes the objective(s), design, methodology, statistical and ethical considerations as well as organisation of a study. The term protocol refers to the initial protocol, successive versions of the protocol and protocol amendments.

## Study Start

Start of data collection as defined in the study protocol.

## Transparency

Transparency is based on openness, communication and disclosure of or making available information whilst respecting the protection of both personal data as well as commercially confidential information. Research may be labeled as transparent if relevant aspects of the research are open in the sense of open access to information on the research process and data thereby facilitating an objective assessment of the quality and independence of the research and validity of the research results.

## Annex 2 (Checklist)

## Checklist of the ENCePP Code of Conduct for ENCePP Studies

The purpose of this checklist is to emphasize the core elements of the ENCePP Code of Conduct that are relevant at the time of study start. The act of completing this checklist confirms that the study for which the status "ENCePP Study" is applied for complies – at the time of submission - with the key requirements of the Code. Of note, completion of the checklist does not release researchers of ENCePP studies from their obligation to adhere to the entirety of the provisions of the Code.

The checklist must be completed by the (primary) lead investigator of the study for which the status "ENCePP study" is applied for. The (primary) lead investigator must:

- Tick all boxes of the checklist thereby confirming compliance of the study with core requirements of the Code.
- If applicable, provide additional information as requested.
- Sign the checklist.

*The undersigned declares upon honour the following answers on behalf of the organisation that he/she represents. Signature should be by the (primary) lead investigator.*

| **1. General** | **Check** |
|---|---|
| The study has been designed<br>➢ in line with the general principles outlined in the Code (see chapter 5 of the Code), and<br>➢ providing for a maximum level of transparency (see chapter 4 of the Code). | ☐<br>☐ |
| **2. Research contract** | **Check** |
| A research contract between the (primary) lead investigator and/or the coordinating study entity and the study funder has been concluded prior to study start. | ☐ |
| The statement "The parties to this agreement and individuals acting on their behalf hereby commit to adhere to the rules of the ENCePP Code of Conduct in their entirety" is included in the research contract and the latest version of the Code at the time of the signature of the contract is annexed. | ☐ |
| The contract includes the following information:<br>➢ The main objectives and a brief description of the intended methods of the research as well as a clear assignment of tasks and responsibilities.<br>➢ The procedure for achieving agreement on the study protocol as well as the involvement of the funder in the development of the protocol.<br>➢ The amount of the financial support and the payment scheme.<br>➢ Ownership of and access to the data produced during the study. | ☐<br>☐<br>☐ |

| | |
|---|---|
| ➢ A communication strategy for the scheduled interim (if applicable) and final results. | ☐<br>☐ |
| **3. Registration of studies** | **Check** |
| The study has been registered[10] in the ENCePP Register of Studies. | ☐ |
| **4. Study protocol** | **Check** |
| A full study protocol[11] has been developed before study start. | ☐ |
| The latest version of the full study protocol is uploaded to the ENCePP Register of Studies[12]. | ☐ |
| A system is in place to allow for documentation of changes to the original version of the study protocol in a traceable and auditable way. | ☐ |
| Information on all parties involved in the writing and adoption of the protocol including a brief description of their contribution is being made publicly available. | ☐ |
| A detailed statistical analysis plan is described and included in or annexed to the study protocol. | ☐ |
| **5. Data ownership and access to data** | **Check** |
| A system has been put in place in order to record the data collected and processed in the study in a way that allows verification of published results. | ☐ |
| Appropriate plans and agreements, if necessary, are being or have been made to grant, upon request, access to data and results as detailed below to regulators, health care professionals and the scientific community once the final study report is available: | |
| ➢ Data set used for analysis. | ☐ |
| ➢ Detailed description of how the raw data were transformed into the data set for analysis. | ☐ |
| ➢ All scheduled interim and final study findings irrespective of positive or negative results. | ☐ |
| **6. Declaration of interest** | **Check** |
| Declarations of interests of all parties involved in the conduct of the study are collected and documented (including members of the study steering group, if such group is being established). | ☐ |
| Details of participation in the study of parties with a conflict of interest (if any) are documented and are being made publicly available. | ☐ |
| All persons with a financial interest in a particular outcome of the study are excluded from participation from any study activity which could influence the results or interpretation thereof in a particular direction. | ☐ |

[10] A study is deemed registered in the ENCePP Register of Studies once the application has been approved by the ENCePP Secretariat.

[11] For the purpose of the Code of Conduct, a *full* study protocol is a version of the protocol which includes enough detail in order to answer all questions in the *Checklist of Methodological Standards for ENCePP Study Protocols*. The *Checklist of Methodological Standards for ENCePP Study Protocols* is available at http://www.encepp.eu.

[12] When uploading the protocol in the Register, it may not be immediately accessible to the public unless the (primary) lead investigator so chooses.

| 7. Study Steering Group | Check |
|---|---|
| If a study steering group has been/will be established, the following rules are/will be applied: | |
| ➢ No expert with a conflict of interest is appointed as a member of the steering group | ☐ |
| ➢ The composition of the steering group is being/will be made publicly available | ☐ |
| Please tick all of the above boxes in section 7 if no steering group is foreseen for the study, as well as the following box. ☐ | |

| 8. Publication/Reporting of studies | Check |
|---|---|
| Appropriate plans and agreements, if necessary, have been made (e.g. as part of the dissemination and communication policy) ensuring publication of results | |
| ➢ including results from prematurely terminated studies. | ☐ |
| ➢ independent of statistical significance and whether the results are positive or negative. | ☐ |
| ➢ in form of a clear summary of the main results. | ☐ |
| ➢ in form of an abstract to be provided to the ENCePP Secretariat within 3 months after the final study report. (Note that requests for delays are possible pending response to peer-review comments). | ☐ |
| ➢ in form of a full report of all results with a scientific or public health impact without delay (taking into account relevant legal provisions in case of a suspected public health impact). | ☐ |
| ➢ independently by the (principle) lead investigator irrespective of data ownership. | ☐ |
| ➢ providing for the possibility of review by the study funder prior to submission – but without unjustified delay. | ☐ |
| ➢ considering comments from the study funder and enabling the study funder to request changes to the presentation of the results to delete confidential information. | ☐ |
| ➢ making publicly available comments of the funder. | ☐ |
| ➢ taking into account the provisions for authorship of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors (2009). | ☐ |

| 9. Confidential information | Check |
|---|---|
| A definition of what constitutes confidential information has been agreed between the parties of the research contract. | ☐ |
| The definition of confidential information does not consider data and results as being confidential despite in relation to relevant data privacy laws. | ☐ |

Name of the coordinating study entity: _____

Name of (primary) lead investigator: _____

Date: _____ (xx/yy/zzzz)

Signature: _____

Stamp (if applicable)

# Annex 3 (Declaration)

## Declaration on compliance with the ENCePP Code of Conduct for ENCePP Studies

The (primary) lead investigator and a person authorised to sign on behalf of the coordinating study entity hereby declare for the purpose of conducting the study <include study name and identifier/registration no.>

- to follow the rules and principles for the independent and transparent conduct of pharmacoepidemiological and pharmacovigilance studies of the ENCePP Code of Conduct adopted on --/--/---- <include revisions>;
- to inform the ENCePP Secretariat, without delay, of any change or decision to change that constitutes a deviation from the provisions of this Code.

It is of note that the (primary) lead investigator and the person authorised to sign on behalf of the coordinating study entity may be identical.

Name of (primary) lead investigator:

_____

Date: _____ (xx/yy/zzzz)

Stamp and signature:

Name of the coordinating study entity: _____

Address:

_____

_____

Name of person authorised to sign on behalf of the coordinating study entity [if different from (primary) lead investigator]:

_____

Date: _____ (xx/yy/zzzz)

Stamp and signature:

The (primary) lead investigator should also complete, sign and date the Checklist of the ENCePP Code of Conduct for ENCePP Studies (Annex 2).

The agency is unable to accept electronic signatures and will not accept photocopies of the completed declaration and checklist.