EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

London, 21 November 2011
EMA/929209/2011

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
Revision no. 1	12 September 2010
Revision no. 2	21 November 2011

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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.

[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 (see http://www.encepp.eu/public_consultation/index.html). 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.

Whether a study will be conducted in line with the Code or not is to be decided by the respective researchers and funder. The use of this Code is only mandatory if a study is to be awarded the title "ENCePP study" (see Chapter 3. for further details on ENCePP studies) or if an obligation to adhere to the Code has been imposed in the research contract.

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.

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

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

- Code of Conduct: Signed declaration and checklist.
- Checklist 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.

Some of the provisions of the Code relate to research that is (partially) financed from external sources, e.g. studies commissioned by pharmaceutical companies, research grants etc. Studies that are conducted based on the investigator's own general resources, i.e. self-funded studies, are in principle also eligible for the ENCePP study status.

[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 *ENCePP Checklist for Study Protocols* is available at http://www.encepp.eu/encepp_studies/documents/ENCePPChecklistforStudyProtocols.doc.

[6] The electronic ENCePP Register of Studies can be accessed at http://www.encepp.eu/encepp/studiesDatabase.jsp

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 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.

For studies that are (partially) financed from external sources, the provisions in Chapter 8 in relation to the research contract apply.

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

[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 *ENCePP checklist for Study Protocols*.

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

Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP, Revision 2, 2007) and refers to relevant parts thereof, as appropriate. The Code is further complemented by the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which provides a framework of scientific guidance towards the conception and execution of pharmacoepidemiology and pharmacovigilance 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;
- For studies that are (partially) financed from external sources, 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;
- For studies that are (partially) financed from external sources, 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 shall be made publicly available or on request as specified in this Code.

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. To this end, all parties should complete the Declaration of Interest Form for ENCePP Studies (see Annex 5) which should be documented and made publicly available (see also chapter 10. 'Registration of Studies'). 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 once the final study report is available (see chapter 12. and 14. as well as Annex 4 *Implementation Guidance for Sharing of ENCePP Study Data* for details),
  - for studies that are (partially) financed from external sources, the content of the research contract (actual financial figures may be redacted[9]),
  - for self-funded studies, a declaration on the use of own resources, making clear reference to the study and the (primary) lead investigator(s) and signed by (an) authorised representative(s) of the participating study entity/ies.
- State in advance and in publications the affiliations of the investigators and any conflicts of interest.

8. Research Contract[10]

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". Where this is not possible, a separate agreement with the funder may be concluded provided it clearly references the particular study, includes the above statement on adherence to the Code and states that this adherence with the relevant version of the Code is an additional requirement to those in the (clearly referenced) research contract. 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.

For studies that are entirely financed from public funding schemes, it is sufficient to include a reference to the Code in the project proposal or equivalent document, i.e. any document that includes a description of the study to be funded and that has been endorsed or is otherwise recognised by the funding body. Reference to the Code should be such that acceptance of the project proposal (or equivalent document) by the funding body constitutes agreement to adhere to the provisions of the Code including the requirement for unrestricted freedom of the investigator to publish.

The following aspects should be addressed in the research contract:

[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.
[10] This chapter only applies to studies that are (partially) financed from external sources.

- 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 *ENCePP checklist for Study Protocols* (for details on the research contract see Chapter 4) in its development.
- The amount of the financial support and the payment scheme.
- Intellectual property rights arising from the study and access to study data. The provisions on intellectual property rights and access to data addressed in Chapter 12. shall apply.
- A communication strategy for the scheduled interim (if applicable) and final results.
- The contract should provide for the rights and obligations as detailed in Chapters 9. (Rights and Obligations of Researcher and Study Funder) and 14. (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[11]

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 declarations of interest and, at the end of the study, communication of results. The results should be updated, as necessary, e.g. with findings from

[11] This chapter only applies to studies that are (partially) financed from external sources.

re-analyses of the study data and including additional research conducted by third parties with shared data (for the provisions on data sharing see chapter 12.).

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 *ENCePP checklist for Study Protocols*.

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 *ENCePP checklist for Study Protocols*, including a timetable for the progress and completion of the study and describing milestones (e.g. interim reports) and deadlines. Feasibility studies that were carried out in advance, if any, should be described in the protocol. Feasibility studies should not include pre-analyses of data which indicate the likely direction of the results and such studies prior to protocol finalisation would invalidate ENCePP Study status.

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

For studies that are (partially) financed from external sources, 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 at which time the ENCePP Secretariat will make both versions publicly available.

12. Ownership of results and Sharing of Data

For studies that are (partially) financed from external sources, the research contract shall clearly specify ownership of intellectual property rights, including data and results, arising from the study (see Chapter 8.). For the avoidance of doubt, the use of secondary data in studies does not confer rights over these data. Results arising from the analysis of the data generated in the study shall either be owned together by both the investigator(s) and the funder, or belong to the investigator(s), and should be used in line with the provisions of the Code. 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 results generated under the study. Any personally 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. The (primary) lead investigator should provide on request a detailed description of how the raw data were transformed into the data set for analysis and should take all possible steps to provide for audits by competent authorities. The (primary) lead investigator should furthermore be prepared to share upon request the data set used for analysis and all scheduled interim and final study findings - irrespective of positive or negative results - once the final study report is available and provided data sharing does not infringe the rights of any third party, e.g. license for secondary data. Investigators should respond to requests for access to data in line with the *Implementation Guidance for Sharing of ENCePP Study Data* (see Annex 4).

Access to data may be requested by a third party for the purpose of corroborating the study results in the interest of public health, and provided that the additional research with the shared data is compliant with the Code's provisions for transparency (see *Implementation Guidance for Sharing of ENCePP Study Data*, Annex 4 for details). The access request needs to be made on specific grounds and should include a sound justification as well as a protocol on the research to be conducted or the plan for quality control checks, as applicable in order to corroborate the study results. In principle, data should be shared if the grounds on which access is requested cannot be addressed otherwise (see also chapter 14.). Access to data should also be provided in response to requests to confirm compliance with the Code or in the context of an audit by a competent authority.

Investigators should describe the procedure for access to the analytical data set in, or as an Annex to, the study protocol, indicating the degree to which data can be shared and, if access is restricted, including a justification why access is limited.

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. 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. For studies that are (partially) financed from external sources, this strategy should be included as part of the research contract. Any deviation should be duly justified.

A clear summary of the main results of the 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 or as specified in the study protocol. In addition, for ENCePP studies, a synopsis of the study findings shall be provided through the ENCePP register of studies within 3 months following the final study report[12]. Delays to this deadline in relation to ongoing peer-review will not be accepted[13]. If necessary, the abstract should be updated with the reviewer(s)

[12] Of note, for studies that are (partially) financed from external sources, the deadline of 3 months relates to the submission of the final study report to the study funder.
[13] This is in line with the outcome of the ENCePP Workshop with Medical Journal Officers on 29 June 2011 (minutes are available at http://www.encepp.eu/events/documents/Minutes_Journaleditorsworkshop_29Jun2011.pdf), where it was confirmed that making publicly available an abstract of the study findings will not jeopardise publication in peer-reviewed journals later on.

comments, once available. If the final report is not published together with the abstract, the timelines for its publication should be specified in the abstract.

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.

On a case by case basis, the (primary) lead investigator may be asked to provide the trail of journal submissions to demonstrate compliance with the Code's requirement to always publish the study results.

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. This includes results from research conducted by third parties using shared data from ENCePP studies (see chapter 12.).

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

For studies that are (partially) financed from external sources, the (primary) lead investigator shall always 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, 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 and Corroboration of Results

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.

The (primary) lead investigator should respond to requests by third parties made with the aim to corroborate the reported study outcomes in the interest of public health. On a case-by-case basis, this may involve sharing of study data with the requesting party (see also chapter 12.).

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, for studies that are (partially) financed from external sources, should be specified either in the research contract or in a separate agreement between the relevant parties. Data and results from a study shall be regarded as confidential only in relation to relevant data privacy law.

16. References

ENCePP checklist for Study Protocols, available at http://www.encepp.eu/encepp_studies/documents/ENCePPChecklistforStudyProtocols.doc.

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.

ENCePP Guide on Methodological Standards in Pharmacoepidemiology, available at http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE.pdf.

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

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.

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

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

Analytical data set

The analytical data set is defined as the minimum set of data required to perform the statistical analyses leading to the results reported for the study and which, together with a complete audit trail describing the manipulation of raw data to obtain the analytic dataset, would be sufficient to allow a third party to repeat or corroborate the results. This can be raw data, provided this is in line with data protection legislation, or an aggregation of the data. For raw data, the complete audit trail should always be available as well. In the context of the Code's requirement for data sharing, the analytical data set can be the full data set or a subset thereof if sufficient to address the data access request.

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.

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

According to the International Society of Pharmacoepidemiology (ISPE)[14], pharmacoepidemiology may be defined as 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, including any annexes thereto, 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.

[14] http://www.pharmacoepi.org/about/index.cfm

Secondary Data

Data previously collected for another purpose and stored in medical charts or electronic records.

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)

Annex 3

(Declaration)

Annex 4

(Implementation Guidance on Sharing of ENCePP Study Data)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EMA/409316/2010
ENCePP Secretariat

Revision 1, dated 21 November 2011

ENCePP Code of Conduct – Implementation Guidance for Sharing of ENCePP Study Data

The purpose of this document is to define clear criteria for sharing data of ENCePP studies[1] as well as for the procedure for handling requests for access to data by third parties. The guidance follows the principle of maximum transparency whilst respecting the need to guarantee data privacy and to avert the potential for misuse of shared data. It complements the ENCePP Code of Conduct[1] which defines requirements for the conduct of studies to maximise transparency and promote scientific independence throughout the research process.

It is stressed that studies need to comply with relevant legislation, as applicable.

I Background

Studies that have been awarded the ENCePP study seal are recognised by ENCePP as being conducted at a high level of openness and public scrutiny. Researchers and study funders of ENCePP studies have committed to comply with a set of transparency requirements including sharing of study data upon request. The Code lays down the following provision requiring researchers of ENCePP studies to provide access to the study data:

> *(…) Both the study protocol and the research contract should address rules for access to raw data, processed data and results generated under the study. Any personally 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. The (primary) lead investigator should provide on request a detailed description of how the raw data were transformed into the data set for analysis and should take all possible steps to provide for audits by competent authorities. The (primary) lead investigator should furthermore be prepared to share upon request the data set used for analysis and all scheduled interim and final study findings - irrespective of positive or negative results - once the final study report is available and provided data sharing does not infringe the rights of any third party, e.g. license for secondary data. Investigators*

[1] Further information on the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), ENCePP studies and the ENCePP Code of Conduct can be found at http://www.encepp.eu/.

should respond to requests for access to data in line with the Implementation Guidance for Sharing of ENCePP Study Data *(see Annex 4).*

Access to data may be requested by a third party for the purpose of corroborating the study results in the interest of public health, and provided the additional research with the shared data is compliant with the Code's provisions for transparency (see Implementation Guidance for Sharing of ENCePP Study Data, *Annex 4 for details). The access request needs to be made on specific grounds and should include a sound justification as well as a protocol on the research to be conducted or the plan for quality control checks, as applicable in order to corroborate the study results. In principle, data should be shared if the grounds based on which access is requested cannot be addressed otherwise (see also chapter 14). Access to data should also be provided in response to requests to confirm compliance with the Code or in the context of an audit by a competent authority.*

Investigators should describe the procedure for access to the analytical data set in, or as an Annex to, the study protocol, indicating the degree to which data can be shared and, if access is restricted, including a justification why access is limited. (…)

II Data requirements

It is acknowledged that the degree to which access to study data can be granted depends on the need to comply with data protection legislation (both at European and national level) as well as on the nature and origin of the data. Ideally and in line with the principle of maximum transparency, data are made available as openly as possible.

In any event, the degree to which access is provided should be sufficient to allow addressing the specific issue (see also chapter V) raised by the third party requesting access (hereafter referred to as applicant). To this end, the Code of Conduct requires to provide access to the *analytical data set* and a *detailed description of how raw data were transformed into the data set for analysis*.

II.1 Analytical data set

For the purpose of the provision on data sharing as specified in the ENCePP Code of Conduct and this document, the analytical data set is defined as the minimum set of data required to perform the statistical analyses leading to the results reported for the study and which, together with a complete audit trail describing the manipulation of raw data to obtain the analytic dataset, would be sufficient to allow a third party to repeat or corroborate the results. In principle, this can be raw data, provided this is in line with data protection legislation, or an aggregation of the data. For raw data, the complete audit trail should always be available as well. If sufficient to address the issue based on which access to data is requested, it is acceptable to only make available a subset of the full analytical data set.

II.2 Data privacy restrictions

To protect the privacy of the study subjects, often it will be necessary to remove personal identifiers from the data set before it can be released to third parties[2]. Studies investigating rare diseases, small geographic areas or involving sensitive information present particular challenges and may require substantial modifications. Such modifications shall not be considered a breach to the Code's

[2] Practical guidance on preparing raw clinical data before sharing them has been published by Hrynaszkiewicz I, Norton ML, Vickers AJ, Altman DG, Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers, BMJ 2010;340:doi:10.1136/bmj.c181.

requirement to share data. It is also acceptable if access can only be granted on-site and/or involves confidentiality or data sharing agreements.

II.3 Detailed description of how raw data were transformed into the data set for analysis

In order to further increase transparency for ENCePP studies, the Code requires an audit trail documenting the steps undertaken to transform the data collected in the study (raw data) into the data set used for analysis. This description should be made available alongside the analytical data set if necessary to answer the question for which access to data has been requested.

III Time restrictions

Access to data should be granted whether all data or related results have been published or not. However, access may only be requested after the final study report is available. If possible, sharing of data should not be limited in time. As a minimum, researchers should provide for the possibility to share data up to a period in line with the requirements for the study archive in the Guidelines for Good Pharmacoepidemiology Practices (GPP)[3].

IV Applicant

In principle, any third party may request access to data in line with the provisions of the Code and this document. The applicant requesting access to data should be clearly identifiable (name of individual, affiliation and contact details) and should agree to follow the transparency requirements of the ENCePP Code of Conduct, including provision of declarations of interest (for further detailed see chapter VII).

V Purpose for sharing study data

Requests for access to data must be made on specific grounds either

- with the aim to corroborate the study results in the interest of Public Health,
- to confirm compliance with the ENCePP Code of Conduct, e.g. to demonstrate that the audit trail established in line with the Code's requirements does allow corroboration of results, or
- in the context of an audit by a competent authority.

Sufficient information needs to be provided to confirm that the request is made for one of the above-mentioned purposes, including a sound justification and, in case of a request with a view to corroborate study results, a protocol on the research for which the data will be used or a plan for quality control checks, as applicable .

The original researcher may require the conclusion of a data sharing agreement with the applicant restricting the use of the shared data to one of the above-mentioned purposes and/or the protocol. It is at the discretion of the original researchers to grant access to their data in case of requests outside the scope described above, e.g. for use in other research projects such as independent patient meta-analysis.

[3] According to revision 2 of the GPP (April 2007) the study archive should be kept for a period of five years after final report or first publication of study results, whichever comes later.

V.1 Corroboration of study results

Access to data with the aim to corroborate published results and interpretations thereof should be provided

- if there is evidence of conflicting results of different/separate studies addressing the same research question. In this case, access to data may be restricted for the sole purpose of identifying differences (e.g. methodological) that explain the discrepancies between the reported outcomes.
- in case of suspected methodological issues which might impact on the study outcome, such as accounting for confounding factors.

V.2 Audits

In order for the findings of a study to be used to support regulatory decision making it is essential that the respective competent authority can have access to the underlying data and conduct audits. To this end and as is good practice, researchers of ENCePP studies should ensure that all data generated in the study are recorded in a way that allows corroboration of the published results. All possible steps to provide for audits by competent authorities should be taken.

VI Replying to requests for data sharing

Researchers of ENCePP studies should describe the procedure for providing access to data as part of or annexed to the study protocol. If such procedure provides for access criteria, these should be no stricter than those described in this document.

VI.1 Approaches for replying to data access requests

Researchers should as far as possible take an open and collaborative approach to data sharing with the aim to corroborate the results of their study. On a case-by-case basis, researchers may choose to reply to access requests in different ways, some of which do not involve sharing of data, including:

1. **Written response:** The original researcher provides a response in writing to the applicant addressing the issue based on which access is requested.
2. **Re-analysis by original researcher:** The original researcher provides the applicant with the outcome of additional data analyses to address the issue raised.
3. **Collaboration:** Both the applicant and the original researcher jointly investigate the issue raised.
4. **On-site access:** Data are shared at the premises of the original researcher only, with or without having concluded a data sharing agreement.
5. **Provision of data:** The study data are submitted to the applicant with or without having concluded a data sharing agreement.
6. **Analysis by an independent third person:** Post-hoc analyses are performed by an independent third person, e.g. statistician or other.

Any of these approaches is in principle acceptable provided that it suffices to address the issue raised by the applicant, and ensures full transparency. In case of studies using secondary data, it may be necessary for the applicant to directly apply for access to the relevant database in line with applicable

licence and governance rules (see chapter *VI.3* for further details). For audit purposes in line with chapter *V.2*0 on-site access should be granted.

If the applicant has a (perceived) conflict of interest, researchers may decide to reply to the access request in a way that that does not involve actual sharing of data, e.g. using an independent third party to carry out the re-analysis of the data.

If the applicant does not agree with the level of access provided, the matter should be referred to the ENCePP Steering Group for arbitration (see also chapter VIII). Irrespective of the approach chosen to reply to a request, the description of how the raw data were transformed into the data set for analysis (see chapter II.3) should always be made available if requested.

VI.2 Financial considerations

Researchers may ask the applicant for compensation of the costs incurred for providing access to and/or additional analysis of data. The amount of the compensation has to be reasonable and needs to be communicated to the applicant prior to sharing the data.

VI.3 Licensing and governance rules

In studies utilising secondary data, i.e. data previously collected for a another purpose and stored in medical charts or electronic records, access to data might be subject to a licence or governance rules which prevent researchers from sharing their data sets with third parties. As a principle, all steps should be taken to ensure the success of a request for data sharing in the most cost-effective way possible, e.g. if feasible, researchers should consider bilateral agreements and provide access to the applicant on-site. Should this not be possible, the applicant can be advised to obtain a licence or to apply for approval at a research committee or to fulfil any other condition required under the governance rules.

VII Compliance of research with shared data with the Code's transparency requirements

There is no guarantee that re-analysing the study data will produce results of a better quality than the original study. The outcome of the re-analysis should always be read in the context of the original results taking into account that it has been done post-hoc.

In order for the applicant to meet the claimed purpose of improving Public Health, the research conducted with the shared data needs to be equally transparent as the original study. Therefore, any research or review conducted with the shared data should be compliant with the transparency requirements of the ENCePP Code of Conduct:

- Making available the study protocol for the re-analysis of the data including the statistical analysis plan. It is acceptable to include reference to the protocol of the relevant ENCePP study.
- Compliance with the Code's requirements of declarations of interests.
- Compliance with the Code's requirements as regards the recording and access to data and relevant steps throughout the research process and to take all possible steps to provide for audits by competent authorities.
- Making publicly available the results in line with ENCePP requirements. In particular, the origin of the data should be acknowledged in line with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors. In addition to the

requirements of the Code the original researcher should be consulted before the publication of the results in order to enable him/her to provide comments.

- Registration in a publicly available register: Notwithstanding the general need to comply with the Code, the requirement for registration of the study in a publicly available register shall only apply if the additional research qualifies as a stand-alone study. In any event, information on post-hoc research with shared ENCePP study data including the study report and publications of the results should be linked to the original study in the ENCePP register of studies (see also chapter 10 and 14 of the ENCePP Code of Conduct). To this end, it is the responsibility of the applicant for access to data to provide all relevant material to the original researchers or the ENCePP Secretariat who should add this information to the ENCePP study register.

VIII Role of the ENCePP Steering Group & arbitration

Whenever there is disagreement between the applicant for access to data and the original researcher the matter should be referred to the ENCePP Steering Group who will act as an arbiter.

In the first two years following the launch of the ENCePP study seal, all requests for access to data should also be sent to the ENCePP Steering Group via the ENCePP Secretariat for information. Upon receipt of a data sharing request, researchers should respond to the request in line with this Guidance or consult the Steering Group about an appropriate response. If the applicant agrees with the chosen approach, the request should be tabled at the next Steering Group meeting for information only. If the applicant and the original researcher cannot agree on a suitable approach, the ENCePP Steering Group will validate the request against the access criteria as specified in this guidance and decide about an appropriate approach to reply to the request. If the level of detail of the request is not sufficient, further information may be requested from the applicant as appropriate.

Once the Steering Group has decided on a data access request, the ENCePP Secretariat shall inform the researcher of the ENCePP study and the applicant accordingly. The decision of the Steering Group is binding for the researcher of the ENCePP study and non-compliance will be considered a breach with the ENCePP Code of Conduct.

If, for any reason, access to data is refused, the communication of the related data access request including an explanation for its refusal should be made publicly available on the ENCePP Study Register unless the applicant withdraws his/her request.

IX References

ENCePP Code of Conduct, (Revision 2: 21 November 2011) available at http://www.encepp.eu/code_of_conduct/index.html.

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

Hrynaszkiewicz I, Norton ML, Vickers AJ, Altman DG, **Preparing raw clinical data for publication: guidance for journal editors, authors, and peer reviewers**, BMJ 2010;340:doi:10.1136/bmj.c181.

Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors (ICMJE), 2010, available at http://www.icmje.org/urm_main.html.

Annex 5

(Declaration of Interest Form for ENCePP Studies)