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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 are reviewed by the ENCePP Steering Group periodically after its adoption.

Steps taken	**Date**
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Revision 2	21 November 2011
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Table of contents

1. Introduction

ENCePP originates from the collective endeavour to enhance the scientific and operational expertise and capacity in the fields of pharmacoepidemiology and pharmacovigilance across Europe. It also aims to support pharmacoepidemiological research and post-authorisation safety surveillance of medicines by offering access to a robust network of resources. The secretariat of ENCePP is provided by the European Medicines Agency (EMA).

The ENCePP Code of Conduct, hereinafter referred to as the "Code", has been developed by the ENCePP Working Group on Independence and Transparency. The aim of the Code is to promote and support scientific independence and transparency throughout the pharmacoepidemiology and pharmacovigilance research process and, consequently, to strengthen the confidence of the general public, scientific community and all stakeholders in the integrity and value of the research. Following its first release, the Code has been regularly revised based on feedback and experience.

The latest revision 4 aims to clarify and support the practical implementation of the Code's key principles of scientific independence and transparency. The Code addresses the need to avoid research being influenced by commercial, financial or institutional interests of study funders where there is potential to threaten scientific independence. It proposes strategies to separate the power and influence of study funders from researchers' responsibilities for scientific integrity. The Code also addresses potential personal interests of researchers.

2. Scope

The Code 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 type of observational methodology based on secondary use of already existing data and on primary data collection. The definitions of pharmacoepidemiology and pharmacovigilance studies also include interventional clinical trials (see Annex 1).

Throughout any pharmacoepidemiology or pharmacovigilance study the highest level of scientific independence and transparency is recommended and all researchers undertaking studies are encouraged to adhere to the principles of the Code. Adherence to the principles of this Code will increase trust of stakeholders, who will have full information on which to base assessment of the study findings. Research entities that are included in the ENCePP Inventory of Research Centres are encouraged to formalise their commitment to adherence to the Code through obtaining the ENCePP Seal, which permits a high level of public scrutiny of the Code's operational and methodological aspects. The procedure to obtain the ENCePP Seal is described on the ENCePP website[1].

The provisions of the Code apply to research that is (at least partially) financed (including in kind contributions) from external sources, e.g. studies commissioned by pharmaceutical companies, research grants etc. where researchers, study funders and other involved parties agree to adhere to the Code.

Studies that are funded by the investigator's own organisation, i.e. self-funded studies, should in general also adhere to the principles of the Code.

[1] http://www.encepp.eu/encepp_studies/index.shtml

For studies funded by pharmaceutical companies and requested by a regulatory body, all parties involved in the development of the protocol are responsible for ensuring that the study meets the regulatory 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.

The Code does not provide rules or guidance on methodology or scientific standards applicable to specific studies or study types. The ENCePP Guide on Methodological Standards in Pharmacoepidemiology[2] should be consulted for this purpose.

Throughout the Code, provisions that ENCePP considers to be applied to all studies without exceptions are identifiable through the modal verb "shall" whereas provisions that ENCePP considers to be recommended and applied whenever possible are identifiable using the modal verb "should".

3. Core principles of the Code

3.1. Scientific independence

Scientific independence is needed to ensure best practice in the relationship between investigators, study funders, and contract research organisations (CROs)/coordinating study entities from protocol agreement to publication of results.

Scientific independence means that:

- the primary purpose of the study shall be to generate evidence of potential scientific or public health importance and not to promote the use of a medicinal product or any specific outcome;
- the design of the research shall aim at minimising any potential bias;
- any financial, commercial, institutional or personal interest in a particular outcome of the study (i.e. in the results and their interpretation) at the level of the organisation(s) initiating or funding the study and of the coordinating study entity and/or the researcher(s) conducting the study, shall not influence any decision on the scientific aspects of the study in any direction, including data collection and analysis, interpretation and dissemination of the study results (see also definition of conflicts of interest in Annex 1).

3.2. Transparency

Transparency is based on openness, communication and disclosure of (or making available) information, whilst respecting the protection of both personal data and commercially confidential information. Research may be labelled as transparent if relevant aspects of the research are publicly available, and there is open access to information on the research process, the data sources and the method, described in sufficient detail to make it replicable, thereby facilitating an objective assessment of the quality and independence of the research and validity of the research results.

The highest level of transparency on relevant information pertaining to the study shall be ensured. This includes providing information on the study protocol and any revisions thereof, and the publication of study findings.

The study shall be registered in the EU PAS Register® thereby making information on the study (such as expected timelines) publicly available (see Chapter 4.5.).

[2] http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

4. Provisions for implementation of the Code

4.1. Rights and obligations of researcher(s) and funder(s)[3]

The content of the 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, and the coordinating study entity where applicable. However, the (primary) lead investigator shall be ultimately responsible for 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 including justification, but shall not communicate results, other than final or scheduled interim results, or serious public health issues that require informing relevant regulatory authorities and the funder without delay.

4.2. Declarations of interest

The core team members involved in the conduct and outcomes of a study shall declare existing direct and potential indirect interests of a commercial, financial, institutional or personal nature that might impact their impartiality in relation to the study. Core team members involved in the conduct of a study include the (primary) lead investigator, the epidemiologists, patient representatives, the data and study managers, the main statistician, the coordinating study entity, and future authors of the study report and of any publications arising from the research. To this end, these parties shall complete the Declaration of Interest Form (see Annex 5) which should be made publicly available in the EU PAS Register® at the time of involvement in the study.

4.3. Research contract[4]

The primary (lead investigator) will always be a person without financial, commercial or institutional interests in a particular outcome of the study that could influence in any particular direction any decision on the scientific aspects of the study, including the data collection and the analysis, interpretation and dissemination of the study results.

A contract shall be signed between the (primary) lead investigator or the coordinating study entity and the study funder clearly defining the research project and addressing in detail critical areas of their interaction such as remuneration, feasibility assessment, protocol agreement, study registration with regulatory authorities, ethic committees and other bodies (as applicable by national law), data analysis and publication of study results.

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 research project (see also the definition of 'research contract' in Annex 1).

Remuneration shall only be granted as specified in the research contract and shall not change the direction of the study results.

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 in the

[3] This chapter only applies to studies that are (fully or partially) financed from external sources.
[4] This chapter only applies to studies that are (fully or partially) financed from external sources.

contract, a separate agreement with the funder may be concluded provided it clearly references the study, includes the above statement on adherence to the Code and states that this adherence to 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 specified in 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.

If multiple studies are funded through a single project the reference to the Code shall be included in the project proposal or equivalent document, and the provisions of the Code shall apply to each individual study.

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 of the core team members involved in the design and conduct of the study.
- The procedure for achieving agreement on the study protocol as well as any involvement of the funder and competent authority 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[5] in its development.
- The amount of the financial and/or service in kind 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 4.8. (Ownership of results and sharing of data) shall apply.
- A communication strategy for the scheduled interim (if applicable) and final results including relevant milestones.
- The contract should provide for the rights and obligations as detailed in Chapters 4.1. (Rights and Obligations of Researcher and Study Funder) and 4.7.2. (Reporting of Study Results).

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

[5] http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml

4.4. Study protocol

4.4.1. General provisions

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 that 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 kept to a minimum and described in the protocol. Feasibility studies based on secondary use of data shall not include pre-analyses of data. Any substantial protocol amendments based on the results of feasibility studies shall be based on scientific grounds and not aimed at influencing the study results in any particular direction.

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. A justification for the change(s) to the protocol should be recorded with the protocol alterations.

Changes for reasons such as to promote marketing and/or advertising strategies shall not be acceptable.

4.4.2. Protocol agreement

For studies that are (at least 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 the final responsibility for its content, including protocol amendments to address validation of databases chosen to provide data (where applicable). For studies requested by a competent authority to meet regulatory requirements the final protocol, including protocol modifications, should be agreed between the (primary) lead investigator, the funder and the competent authority.

Any involvement of the study funder in the design of the protocol (e.g. as epidemiologist employed by the pharmaceutical industry) shall be specified in the research contract and in the study protocol. 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 in the abstract of the study results published in the EU PAS Register® or the final publication.

4.4.3. Availability of the study protocol

The original version of the protocol, or a redacted version if justified, should be provided through the EU PAS Register® at the time of registration, including publication of any subsequent revisions. The final version should be provided after the final study report.

4.5. Registration of the study

Any post-authorisation study shall be registered in the EU PAS Register® by the (primary) lead investigator or any individual on their behalf, or on behalf of the coordinating study entity, before the study starts. The EU PAS Register® will facilitate compliance with the Code by allowing the uploading of the study protocol, including declarations of interest, information on the researchers, i.e. the (primary) lead investigator and contributing investigator(s), as appropriate, their affiliations as well as the study funder, and, at the end of the study, communication of results. The results should be updated, as necessary, e.g. with findings from re-analyses of the study data and including additional research conducted by third parties with shared data.

The entry of the study in the register should be regularly updated as appropriate to capture and justify any changes during the study, such as protocol amendments, and to include an abstract of the study results or links to all publications arising from the study on study completion.

The responsibility for the study record in the EU PAS Register® shall ultimately lie with the (primary) lead investigator. However, the study record may be managed by the marketing authorisation holder in agreement with the (primary) lead investigator to comply with regulatory requirements.

4.6. Study conduct

4.6.1. General provisions

All steps 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 project, 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 protocol has been finalised, no person with a commercial, financial or institutional interest in a particular outcome of the study shall take part in any study activity that could influence the results or interpretation thereof in any particular direction; where no other technical expertise for the conduct of the study exists in the study team this may be obtained externally, including from the study funder, in a transparent process which ensures that the results are not influenced in a particular direction.

4.6.2. Data Analysis

A statistical analysis plan or section shall be described in, or annexed to, the study protocol. Any deviations from the analysis plan after finalisation of the protocol shall be clearly documented and a reasonable scientific explanation should be provided in line with the provisions for changes to the study protocol.

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 the prior hypotheses of causal association stated in the protocol, but can be used to generate further hypotheses, or fully to describe the association between exposure and outcome. It should be noted that important safety concerns and adverse events, even if based purely on subgroup analyses, should be documented and evaluated appropriately.

4.6.3. Study steering group or committee

If an independent steering group or committee is foreseen for the purpose of providing scientific advice, data monitoring, guidance and/or to oversee the conduct of the study, the members shall declare existing direct or indirect interests of a commercial, financial, institutional or personal nature and shall only be appointed if no commercial, financial or institutional interests in a particular outcome of the study exist. Roles and responsibilities of the members should be specified in a study specific document.

If they have a commercial, financial or institutional interest in a particular outcome of the study, other parties and stakeholders including the study funder may only participate in meetings of the steering group as invited specialists. Specialists 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 demonstrated expertise and scientific knowledge in the area and/or methods of the research.

The composition of the steering group, including specialists participating in its meetings, should be made publicly available (e.g. via the EU PAS Register®).

4.7. Study results

4.7.1. 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 as to 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 aimed at corroborating 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.

4.7.2. Reporting of 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. For the content of the report(s), it is recommended to follow the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society of Pharmacoepidemiology (ISPE) and the STROBE[6] and RECORD[7] statements, and also the Good Pharmacovigilance Practices (GVP) template for study reports.

Presentations to a restricted audience at meetings will not suffice as the only or main means of communication and a dissemination and communication strategy for the study results should be pre-defined. For studies that are (at least 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, shall always be made available to the public according to the

[6] http://www.strobe-statement.org
[7] http://www.record-statement.org

timetable agreed in the research contract or as specified in the study protocol. An abstract of the study findings in English shall be provided through the EU PAS Register® within three months following the final study report. Delays to this deadline in relation to ongoing peer-review will not be accepted. If necessary, the abstract should be updated with the reviewer(s) 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 emerging safety issues with (suspected) public health impact, relevant legal provisions of Good Pharmacovigilance Practices (GVP) module IX (see Chapter 6. below) shall be followed and the respective competent authority(ies) shall be informed forthwith and in advance of publication.

4.7.3. Publications

For studies that are (fully or 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. 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 should 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 refusal, the funder may only require that the presentation of the results be changed to delete confidential information. Any comments of the funder and justification of the investigator should be made publicly available.

In line with the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors (ICMJE), the authors of the study publication(s) should be those individuals who have made substantial intellectual contributions to the research, with authorship of each individual defined by the authorship criteria[8] recommended by ICMJE. Information on the actual role of all authors and the study funder shall be provided. In addition, affiliations and conflicts of interest shall 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 as well as for any conclusions drawn from the data. There should be transparency about the involvement of all others involved in the writing. The section 'conflicts of interests' should specify that the study has been conducted according to the principles of the Code.

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.

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.

4.8. Ownership of results and sharing of data

For studies that are (at least partially) financed from external sources, the research contract shall clearly specify ownership of intellectual property rights, including data and results, arising from the

[8] http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html

study. For the avoidance of doubt, the use of secondary data in studies does not confer rights over these 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 identifiable personal data shall be maintained under secure conditions in compliance with data protection legislation.

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 the results - once the final study report is available and provided data sharing complies with applicable laws and 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 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 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 4.7.2.). 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.

4.9. Confidentiality

The highest level of transparency shall 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 3.2.).

What constitutes confidential information should be determined before the study commences, and, for studies that are (fully or 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.

5. 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[9] and the provisions on processing of personal data and the protection of privacy as laid down in Regulation (EU) 2016/679 and Regulation 45/2001 of the European Parliament and of the Council need to be followed.

For interventional research, the EU Clinical Trials' Directive 2001/20/EC[10] 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 Good Clinical Practices (GCP) where applicable, Good Pharmacovigilance Practices (GVP)[11] (see Chapter 6. below) and other relevant guidance such as Good Pharmacoepidemiology Practices (GPP) (see Chapter 4.7.2.). 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.

[9] World Medical Association declaration of Helsinki (see also chapter 6.)
[10] The application of the new clinical trials Regulation EU No 536/2014 depends on the development of a fully functional EU clinical trials portal and database and is currently estimated to occur in 2019.
[11] Good pharmacovigilance practices (GVP) are the official regulatory guidances to facilitate the performance of pharmacovigilance in the European Union (EU) (see also chapter 6.)

6. References

ENCePP Checklist for Study Protocols, available at http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml

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://data.europa.eu/eli/dir/2005/28/oj.

Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council (Official Journal L 159, 20/06/2012 p.5-25), available at http://data.europa.eu/eli/reg_impl/2012/520/oj.

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://data.europa.eu/eli/dir/2001/20/oj.

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 (Official Journal L 311, 28.11.2001, p. 67–128), available at http://data.europa.eu/eli/dir/2001/83/oj.

Good Pharmacovigilance Practices (GVP) module VIII on post-authorisation safety studies (PASS) available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c.

Good Pharmacovigilance Practices (GVP) module IX on signal management available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c.

ENCePP Guide on Methodological Standards in Pharmacoepidemiology, available at http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml.

Guidelines for Good Pharmacoepidemiology Practices (GPP), International Society for Pharmacoepidemiology, (Revision 3: June 2015), available at http://onlinelibrary.wiley.com/doi/10.1002/pds.3891/pdf.

Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors, available at http://www.icmje.org/icmje-recommendations.pdf.

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 (Official Journal L

8, 12.1.2001, p. 1–22), available at
http://data.europa.eu/eli/reg/2001/45/oj.

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 (Official Journal L 136, 30.4.2004, p. 1–33), available at
http://data.europa.eu/eli/reg/2004/726/oj.

Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (Official Journal L 119, 4.5.2016, p. 1–88), available at
http://data.europa.eu/eli/reg/2016/679/oj.

World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, 1964, last amended 2013, available at
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/.

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 processing 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 experimental 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, institutional 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 such as the choice of the study design, the analysis or interpretation of data, or the reporting of results.

For the purpose of this Code, *commercial* interest should be understood as the legitimate interest of an organisation selling a medicinal product involved in the study; *financial* interest should be understood as the legitimate interest of an organisation in the costs of a medicinal product involved in the study, or whose corporate financial value can be impacted by the activity of selling/buying the medicinal product ; *institutional* interest should be understood as the legitimate interest of an organisation with a responsibility for health policies (e.g. vaccination policies).

The outcome of a specific study being in one direction or another is not intended to be a commercial interest of the CRO or academic institution involved in the research contract.

Contract Research Organisation

A contract research organisation (also called clinical research organisation, CRO), is a person or an organisation (including commercial, academic and non-profit) that provides services to industry and other stakeholders such as governmental organisations, foundations or hospitals on a contract basis

and within the scope of clinical research (experimental or observational) as well as other activities in connected domains.

Coordinating Study Entity

A legal person, institution or organisation which takes responsibility for the design and/or the management of a study, including contract research organisations (CROs). Where applicable, the (primary) lead investigator is the person authorised to represent the coordinating study entity.

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 and funders, 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 Good Pharmacovigilance Practices (GVP) module VIII.

Pharmacoepidemiology

According to the International Society of Pharmacoepidemiology (ISPE), pharmacoepidemiology may be defined as the study of the utilisation and effects of drugs in large numbers of people. To accomplish its objectives, pharmacoepidemiology applies methods 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, with a lead investigator at each site, then 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 project. This includes grant agreements with public funding bodies and studentship agreements.

Scientific independence

Any financial, commercial, institutional or personal interest in a particular outcome of the study (i.e. in the results and their interpretation) at the level of the organisation initiating or funding the study and of the researcher(s) conducting the study, shall not influence any decision on the scientific aspects of the study in any particular direction, including the data collection and the analysis, interpretation and dissemination of the study results.

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) some or all the financing for a study.

Note: Although being frequently the same entity, the study funder is not necessarily the study sponsor. The study sponsor (as defined for clinical trials) is the person who takes on responsibility for the initiation and management (or for arranging the initiation and management) of and the financing (or arranging the financing) for a clinical study. In some jurisdictions the term study sponsor may be used to designate the institution taking the responsibility for studies undertaken by its staff.

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. Start of data collection is the date from which the recruitment of study patients/participants starts, or, in case of secondary use of data, the date on which the data extraction starts.

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 labelled 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 Study Data

Annex 5

Declaration of Interest Form