EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# ENCePP Code of Conduct – Revision 4

WG2 proposal - agenda item 6

16th ENCePP Plenary, 21 November 2017

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# Content

- Why do we need a revision?
- Overview of the proposed amendments
- Details on the key amendments
- Discussion – perspective from industry and academia

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- **Why do we need a revision?**
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# Background – What the Code is supposed to do

1. The Code sets out the guiding principles of **scientific independence** and **transparency** throughout the research process in pharmacoepidemiology and pharmacovigilance studies, with focus on **non-interventional post-authorisation studies**;
2. Aim of the Code is
   - to **reduce the risk of** (*financial, commercial, institutional, personal*) **conflicts of interests** and the perceived or actual impact on research through its guiding principles;
   - to **strengthen the confidence** of the general public, of researchers and regulators in the integrity and value of pharmacoepidemiology and pharmacovigilance research, irrespective of the funding source;
   - to ensure **highest quality standards** are adhered through the ENCePP Seal process, though the Code itself does not provide rules or guidance on methods or scientific aspects (Seal links the Code with the checklist for protocols and methods guide);

# Why do we need a revision? (1)

ENCePP work plan 2017-2019 mandated WG2 to explore how the Code could be further strengthened with:

1. Additional **tools to support good governance** of pharmacoepidemiological research, taking into account the provisions and governance models of the ADVANCE Code of Conduct developed for collaborative vaccine studies (private-public partnerships);
2. Experience with the **practical application** of the ENCePP Code of Conduct
   - The Code was written before the pharmacovigilance legislation came into force in 2012;
   - The Code was written as a contractual arrangement between the funder and PLI; some of the Code's provisions are mandatory ("shall") whereas other provisions may be interpreted as voluntary ("should") which creates **ambiguity and double-standards**;

# Why do we need a revision? (2)

- The rules focus on **transparency** and **handling of conflicts of interest** to reduce the risk of bias and the impact on research between investigators and industry as study funder;
- However, the principle of **scientific independence is not defined,** and **should extend to self-funded research** with *institutional* and *personal interests* of the investigators in a particular study outcome (e.g. academic competition, intellectual beliefs etc.) which the Code does not address;

3. Some provisions are repetitive, e.g. in context of transparency requirements and the EU PAS Register;

# Why do we need a revision? (3)

4. The **ENCePP Seal concept** links the Code's principles of scientific independence and transparency with the ENCePP methods guide and the protocol checklist to ensure research is independent, transparent and adheres to highest quality standards in protocol development;
   - However, the **low uptake** of the Seal (45 studies in 10 years) is a concern;
   - Some provisions of the Code sound like being restricted to researchers applying to the Seal, which was not in the intention; this leads to **double-standards** and **misinterpretations**;

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# The main provisions

Scientific independence
Transparency

*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*

*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 such as remuneration, protocol agreement, data analysis and publication of study results*

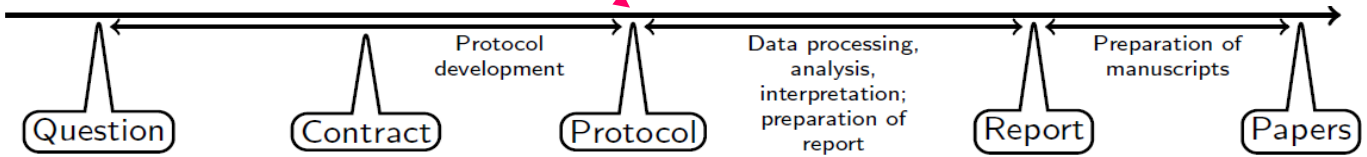
*The original version of the protocol shall be provided through the [EU PAS] Register at the time of registration [prior to study start], but may not be immediately accessible to the public unless the (primary) lead investigator so chooses.*

*Once the protocol has been finalised, no person with a financial, commercial or personal 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. (...) 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 (...). 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 (...)*

*A clear summary of the main results of the study (...) should always be made available to the public*

*The final version [of the protocol] should be provided after the final study report at which time the ENCePP Secretariat will make both versions publicly available*

*The [EU PAS] Register should be used as a repository for reports including those pending publication*




Courtesy of Dr. Rosa Gini, presented at LI CONGRESSO AIE Modena, 25-27 October 2017

# Overview of the proposed amendments - Objectives of Rev 4

1. **Definition** and clarification on the practical implementation of **"scientific independence"**
   - Clarification on the primary lead investigator (PLI) role, ensuring scientific independence throughout the research process;
   - After protocol finalisation external technical expertise for study conduct is allowed in a transparent process ensuring that the results are not influenced in a particular direction;
2. **ENCePP Seal** is **maintained**, but procedures related to the Seal application are moved to a **separate document** *"The ENCePP Seal – Concept and Application"*
   - Cross-reference in section 3 of the Code, document to be published ENCePP website;
   - Existing Seal studies remain unchanged, including EU PAS Register functionalities;
3. **Improved operability** of the Code
   - Separate principles from processes in relation to transparency and the Seal
   - Clarify 'shall' (*must*) and 'should' (*recommended*) provisions where legally possible

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# Proposed definition of scientific independence

- Proposed definition for inclusion:

  *"All decisions on the scientific aspects of the study must be **independent of any financial, commercial, institutional or personal interest** of the researcher(s) conducting the study and of the organisation initiating or funding the study in a particular outcome of the research.*
  *These scientific aspects include the framing of the research question, its translation into a study design and the analysis, interpretation and dissemination of the study results".*

- This definition moves the core of the principle **from the nature of the persons** (having/not having a conflict of interest) **to their actions** (acting/not acting independently of one's interests);

# Provisions to support scientific independence

- Separate powers of the study funder from the powers of the PLI; the Code excludes staff from the funding organisation (e.g. study drug manufacturing or government) from being part of the study team after protocol finalisation; include a statement that **researchers employed by the funding organisation cannot take the PLI role** (currently is implied but not clear);
- Acknowledge that personal interests can never be ruled out; include a statement that they should be disclosed, and that a researcher with personal interests, but not commercial, financial, or institutional interests, **is allowed** to take the PLI role
- Clarify that the PLI alone has the final responsibility of the protocol, except **for studies requested by a regulator** (i.e. imposed or required PASS), where the **final protocol agreement** should be **between PLI, competent authority and MAH**
- Make **publicly available the declaration of interests forms** of PLI and key investigators in the study team via the EU PAS Register (currently this is only required for Seal studies);

# ENCePP Seal

- Separate provisions related to the Seal (procedures) and incorporate the key principles (adherence to the entirety of the Code's provisions on transparency and scientific independence, including scientific standards) in the core document;
  - **Maintain the Seal as visible hallmark for adherence to the Code** at researchers' discretion;
  - Remove references to the Seal procedures in the Code document;
  - Seal **conditions remain unchanged;**
  - Maintain existing Seal studies, the Seal logo and related EU PAS Register functionalities;

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# Discussion and questions to ENCePP Plenary

**Do you endorse the proposed revisions to the Code** and publication in Q1/2018 with:

- Clarifications on scientific independence, including the proposed
  - Definition and
  - Provisions regarding:
    - Separate powers of PLI from power of funding organization;
    - Allow PLI role only to researchers with personal interests (no commercial, financial or institutional interests);
    - Clarify that protocol agreement is more complex if the study is requested by a regulator;
    - Make conflict of interest declaration compulsory;
- Seal related procedures moved in a separate document but maintenance of the Seal concept and conditions on a voluntary basis?
- Other proposed changes?

# Any questions?

## Further information

[Insert relevant information sources or contact details as applicable.]

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