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REVIEW

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The ENCePP Code of Conduct: A best practise for scientific independence and transparency in noninterventional postauthorisation studies

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Abstract

Purpose: The ENCePP Code of Conduct provides a framework for scientifically independent and transparent pharmacoepidemiological research. Despite becoming a landmark reference, practical implementation of key provisions was still limited. The fourth revision defines scientific independence and clarifies uncertainties on the applicability to postauthorisation safety studies requested by regulators. To separate the influence of the funder from the investigator's scientific responsibility, the Code now requires that the lead investigator is not employed by the funding institution.

Method: To assess how the revised Code fits the ecosystem of noninterventional pharmacoepidemiology research in Europe, we first mapped key recommendations of the revised Code against ISPE Good Pharmacoepidemiology Practices and the ADVANCE Code of Conduct. We surveyed stakeholders to understand perceptions on its value and practical applicability. Representatives from the different stakeholders' groups described their experience and expectations.

Results: Unmet needs in pharmacoepidemiological research are fulfilled by providing unique guidance on roles and responsibilities to support scientific independence. The principles of scientific independence and transparency are well understood and reinforce trust in study results; however, around 70% of survey respondents still found some provisions difficult to apply. Representatives from stakeholders' groups found the new version promising, although limitations still exist.

Conclusion: By clarifying definitions and roles, the latest revision of the Code sets a new standard in the relationship between investigators and funders to support scientific independence of pharmacoepidemiological research. Disseminating and training on the provisions of the Code would help stakeholders to better understand its advantages and promote its adoption in noninterventional research.

KEYWORDS

conflict of interest, ethics, observational studies as topic, pharmacoepidemiology, pharmacovigilance, practise guideline, research

1 | INTRODUCTION

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was set up in 2008 to strengthen methodological standards, transparency, and scientific independence that supports the evaluation of medicines in Europe.[1] The ENCePP Code of Conduct, referred to hereafter as the Code, was first released in 2010 to set out a framework for good practise in the relationship between investigators and study funders, irrespective of whether the study funder was a public body, industry, or a regulatory authority.[2] The purpose was ultimately to improve the integrity of pharmacoepidemiological research, for the benefit of public health.

The ENCePP Code of Conduct is a tool supporting the dialogue between stakeholders in pharmacoepidemiological studies. The objective of this paper is to present the main provisions of the Code, focussing on the most recent revision, and to discuss the perspectives of the relevant stakeholders on its value and applicability.

KEY POINTS

- The Code is a unique source of practical guidance on scientific independence and transparency in the relationship between investigators and funders.
- The Code's fourth revision supports the scientific integrity of noninterventional postauthorisation research.
- Compliance with the Code protects researchers and study funders from threats to scientific independence related to commercial, financial, institutional, or personal interests.
- Researchers, from the funding organisation shall not participate in study activities that could influence the results or their interpretation in any particular direction.

2 | THE ENCEPP CODE OF CONDUCT

2.1 | The initial concept

The initial concept for the Code was a contractual framework between the study funder and the primary lead investigator that would seek to guarantee transparency and scientific independence. However, because of the different languages and legal systems existing across Europe, a standard template for the research contract between a research institution and a study funder was not deemed feasible, and the Code was launched as a set of principles and provisions to be integrated in each study contract. The contract was to be signed before the development of the study protocol.

A key requirement was the publication of study results, whether negative or positive, under the responsibility of the primary lead investigator. Transparency was granted by the creation of a publicly accessible electronic register, which later became the European Union (EU) Post-Authorisation Studies (PAS) Register (EU PAS Register), in which the study protocol was to be uploaded before data collection and in which the study report was to be uploaded when the study is finalised.

Since 2010, several revisions of the Code were published in light of experience with its uptake by stakeholders and in efforts to facilitate the implementation of its requirements on access to study data, declaration of interests, and funding sources; to improve its readability; and to provide clarifications.

Despite these revisions and whilst becoming a key reference for the conduct of pharmacoepidemiological studies over the years, the Code continued to experience limitations in its use. In hindsight, chief amongst them was the lack of definition of scientific independence, which made it difficult to verify its implementation by involved parties, despite their commitment. Secondly, the concept of the "ENCePP Seal," developed as an option to formalise both the commitment to the Code and the application of ENCePP methodological standards,[3,4] was often misunderstood as suggesting that some provisions *of the Code* were optional and would only apply if the Seal was requested. Thirdly, the principle of conflict of interest referred almost exclusively to financial or commercial interests without considering the importance of the influence that institutional or personal interests may have on outcomes of research.[5] And finally, the Code had initially been created before the EU pharmacovigilance legislation came into force in 2012 and experience with the implementation of this meant that clarifications were needed as to how some provisions would apply to postauthorisation safety studies (PASS).[6] A major revision of the Code was therefore undertaken in 2017 and completed in 2018.

2.2 | The fourth revision

The key changes to address these deficiencies in the fourth revision are as follows. The spirit of the revision was to further move the balance from principles to practical solutions.

2.2.1 | New definition of scientific independence

After much deliberation, scientific independence is now defined as follows: that any financial, commercial, institutional, or personal interest in a particular outcome of the study (ie, 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.

2.2.2 | More clarity on different categories of interest

Four categories of relevant interests are described: commercial, financial, institutional, and personal. In particular, it is now specified that commercial interests refer to the interests of organisations marketing the drug under study. The provisions of the Code now invest the four categories in a more articulated way.

Indeed, in the previous version of the Code, the requirement was that after protocol finalisation, no person with a commercial, financial, institutional, or personal interest in a particular outcome of the study could take part in any study activity that could influence the results or interpretation in any particular direction. This provision was considered as having undesired consequences and was modified in the current revision. Currently, all members of the study team are first requested to declare all existing direct and potential indirect interests of a commercial, financial, institutional, or personal nature that might impact their impartiality in relation to the study, and their declarations must be made available in the EU PAS Register. Second, specific provisions concern commercial, financial, or institutional interests only: persons with such interests may not take the role of the primary lead investigator and may not participate in activities after protocol finalisation that may impact the results or their interpretation, unless no other specific technical expertise needed for the conduct of the study can be obtained in the study team. In addition, they may not have a decision-making role in the meetings of the steering group (if applicable), where they may be invited as specialists.

2.2.3 | Supporting applicability in regulatory studies

For studies requested by a regulatory authority to which legal requirements apply, the Code specifies that the final protocol should be agreed between the primary lead investigator, the study funder and the competent authority, even if the final responsibility of the protocol remains with the primary lead investigator. This provision complements the Good Pharmacovigilance (see: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices) Practices (GVP) Module VIII requirement that the study protocol should be developed by individuals with appropriate scientific background and experience.[6]

2.3 | Comparison with other guidelines

In order to assess how the fourth revision fulfils an unmet need in pharmacoepidemiological research, we mapped the main recommendations of the revised Code with those of the International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practices (GPP)[8] and of the ADVANCE Code of Conduct.[9] Table 1 provides the main recommendations from each guideline for the main topics addressed by the Code.

Although there are similarities between the three guidelines, there are also important differences explained by their differing objectives: the Code aims to establish the concepts of scientific independence and transparency in the relationship between investigators and study funders, the ISPE GPP aims to ensure the scientific quality and integrity of pharmacoepidemiological studies and the ADVANCE Code of Conduct aims to support effective collaborations in postauthorisation vaccine studies. An important difference exists between the Code and the ISPE GPP as regards the principle of scientific independence. The latter states that (a) organisations and individuals conducting and sponsoring the research shall be fully responsible for the research; (b) for projects sponsored by one organisation (such as a pharmaceutical company or government agency) but implemented by another (eg, academic institution), the responsibility for scientific integrity is shared between the collaborating institutions; and (c) the primary lead investigator is responsible for the overall content of the research. The European legislation defines the term "sponsor" as *an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial*.[10] This makes the previous statements difficult to map to the context of noninterventional studies in Europe, and as a result, no support in the relationship between funders and investigators on the topic of scientific independence is provided. The Code therefore represents a unique source of guidance on this critical aspect of pharmacoepidemiological research in Europe. A recent commentary endorsed by the ISPE Board outlined points to be incorporated in academia-industry agreements in order to facilitate collaborative pharmacoepidemiological research.[11] It does not provide recommendations on how to implement these considerations as these will depend on the specific research setting. The ENCePP Code of Conduct provides such practical recommendations for the European situation, but they may also be considered for other settings if applicable.

2.4 | Clearer distinction between the Code and the ENCePP Seal

Researchers not requesting an ENCePP Seal but intending to comply with the Code must follow exactly the same provisions as those requesting the Seal. In order to convey this message, all the procedures required to obtain the ENCePP Seal were removed from the Code and transferred into a separate document.[7]

3 | STAKEHOLDERS' OPINION

3.1 | Survey of stakeholders

After release of version four, a survey of stakeholders was conducted to evaluate how potential users understand and apply the Code in practise. This survey was only marginally referring to the revised version, and the topic was more generally the high-level concept of the Code. Five categories of stakeholders were identified: patient and consumer organisations, health-care professionals, pharmaceutical industry, public health body or regulators, and researchers (academic, contract research organisations, and other type of research professionals not employed by pharmaceutical industry). They were invited to provide feed-back on the following five dimensions:

TABLE 1 Recommendations from the ENCePP Code of Conduct, the ISPE Guidelines for Good Pharmacoepidemiology Practice (GPP), and the ADVANCE Code of Conduct for postauthorisation studies.

Topics	ENCePP Code of Conduct	ISPE Guidelines for Good Pharmacoepidemiology Practice (GPP)	ADVANCE Code of Conduct
Objective	To support scientific independence and transparency throughout the research process; to strengthen the confidence in the integrity and value of the research.	To help ensure the quality and integrity of research; to facilitate transparency and ethical integrity.	To support effective collaborations and clear governance for the conduct of collaborative postauthorisation vaccine studies.
Scope	Noninterventional postauthorisation studies	All types of pharmacoepidemiological (PE) research.	Postmarketing vaccine benefit-risk monitoring activities.
Guiding principles	Scientific independence and transparency	Sound PE research, framework for conducting and evaluating PE studies, appropriate utilisation of technical resources, transparency, ethical integrity	Best science, strengthening public health, transparency
Participants	Protocol developed by individuals with appropriate scientific background and experience, but after protocol finalisation, no person with commercial, financial, institutional, or personal interest in any outcome of the study should be part of any study activity that could influence results or interpretation.	Personnel should have education, training or experience necessary to perform the assigned functions.	All study team members to be qualified and to act in accordance with values of honesty, accuracy, and objectivity.
Rights and obligations	Primary lead investigator (PLI) ultimately responsible for study protocol, study conduct, and analysis, interpretation, and publication of results; study funder to be kept informed of study progress (eg, progress with recruitment but not interim results).	Organisation(s) or individuals conducting and sponsoring the research to be fully responsible; roles and responsibilities to be described. Responsibility for scientific integrity to be shared by collaborating institutions. Right for the study sponsor to inspect the contractor's facilities and perform audit.	No undue influence of any financial, commercial, institutional, or personal interest in a particular outcome of the study. Clear and transparent roles and responsibilities.
Declaration of interests	Direct and indirect commercial, financial, institutional, or personal interests to be declared by core team members and made public.	Potential conflicts of interest, financial and nonfinancial, to be disclosed in manuscripts.	Documented autonomy of study team members for making decisions in their organisation. Regulatory updated declarations of interest to be disclosed. Study protocol to include sections on funding, affiliations, and potential conflicts of interest. Actual or potential conflicts of interest to be addressed at the planning phase and their management to be included in research contract.
Research contract	PLI to be without financial, commercial or institutional interest that could influence study in any particular direction.	If shared responsibility, research contact to delineate roles and responsibilities of study sponsor and contractor.	Should not lead investigators to act against the Helsinki declaration or applicable legislation. Clarity and transparency. ADVANCE CoC to be referred to.

(Continues)

TABLE 1 (Continued)

Topics	ENCePP Code of Conduct	ISPE Guidelines for Good Pharmacoepidemiology Practice (GPP)	ADVANCE Code of Conduct
	Full compliance with ENCePP CoC to be referred to in contract. List of aspects to be addressed.		List of elements to be included.
Study protocol	To be developed with appropriate scientific background and experience. ENCePP Checklist for study protocols to be consulted. Process for protocol agreement on design options between PLI and study funder to be agreed beforehand. Protocol to be published in EU PAS Register before start of study. Amendments to be documented.	To be drafted as one of first steps in research project and to be amended or updated throughout the course of study. Detailed description of content of protocol, to be included in case no regulatory guidance exists. Significant deviations to be documented in writing. Registration of protocol in public site is welcomed without the option to retract the protocol.	To be drafted as one of first steps in research project and developed with persons of relevant expertise. Process for decision making to be agreed beforehand. Contribution of each party to study design, protocol writing, and study work programme to be described. Independent scientific review by external experts. To be amended as needed and changes to be identifiable. To be registered in publicly available database before data collection.
Study registration	Study to be registered in EU PAS Register by PLI and entry to be regularly updated	Registration of PE research in public site (EU PAS Register, clintrial.gov) is welcomed.	Study to be registered in publicly available database before start of data collection or extraction.
Study conduct	Once the protocol is finalised, no person with commercial, financial, or institutional interest in any outcome of the study to be part of any study activity that could influence the results or interpretation thereof in any particular direction, except if technical expertise needed. Post hoc analyses to be done only to generate further hypotheses. Members of steering group must be without direct or indirect commercial, financial, or institutional interests. Persons with interests may be appointed as invited specialists without involvement in decision making. Composition of steering group to be made publicly available.	PI to be responsible for overall content of the research. Decisions to terminate the study to be based on good scientific and ethical reasons and documented in writing. Description of procedures for data collection, management, and verification to be followed. All data management and statistical analysis programmes used in analyses to be documented and archived. Analysis to be directed towards unbiased estimation of the epidemiological parameter of interest; use of confidence intervals and sensitivity analyses.	Sensitivity analyses to be planned. Additional analyses based on study results to be presented as such and used only to generate further hypotheses. Plan to handle missing and noninterpretable data to be developed.
Study results	Review of results by independent experts and PLI to address recommended changes and justify why changes are not accepted. PLI to respond to requests by third parties.	Description of format and content of study report to be included.	Interpretation of study results to be the responsibility of the study team. Important safety concerns to be documented and evaluated.

(Continues)

TABLE 1 (Continued)

Topics	ENCePP Code of Conduct	ISPE Guidelines for Good Pharmacoepidemiology Practice (GPP)	ADVANCE Code of Conduct
	Study report to follow ISPE GPP, STROBE, RECORD, and GVP.		Deviations from study protocol to be clearly documented. STROBE statement to be followed. Draught report to undergo independent scientific review.
Dissemination and publication	Dissemination strategy to be predefined Summary of results in the EU PAS Register within 3 months. PLI has the right to prepare publication irrespective of data ownership; study funder entitled to view the final results and interpretations and provide comments. ICMJE guidelines to be followed.	Ethical obligation to disseminate findings of potential scientific or public health importance. Procedures for communications of the intent, conduct, results, and interpretation of epidemiology results to be predetermined. Recommendations for format of results to be reported. ICMJE guidelines to be followed.	PI and study team to be allowed by contract to publish independently from study funder. All study results to be made available and intermediate results to be presented or published based on procedure agreed in advance; significant results of public health importance to be published rapidly with statement of their preliminary nature; regulatory and public health authorities to be rapidly informed of study results. Source of funding, affiliation, and potential conflicts of interests to be presented. Study report or summary of results to be included in publicly accessible database. ICMJE guideline to be followed.
Data ownership and sharing.	Rights of ownership of data and results to be included in research contract. Rules for access to raw data, processed data, and results to be specified in protocol and research contract. Verification of published results to be allowed Data transformation steps to be described on request. Analytical data set to be shared based on justification of public health interest and compliance to the Code of Conduct or audit by authority.		Open and collaborative approach to be adopted. Data to be shared only after study report finalised. Data sharing to be based on a written request justifying public health interest. Decision to share data to be taken by study team Analysis of shared data to follow ADVANCE CoC.
Protection of human subjects, confidentiality	Confidential information to be defined in advance and specified in research contract or separate document.	Approval by IRB or IEC to be obtained with exceptions in some countries. Confidentiality to be maintained; personal identifiers to be removed or protected.	Protocol to describe data protection and incentives for study subjects. Applicable legislation to be followed.

Abbreviations: CoC: Code of Conduct; GVP, EU Good Pharmacovigilance Practices; ICMJE, International Committee of Medical Journal Editors; IRB, institutional review board; IEC, independent ethics committee; PI, principal investigator (GPP); PLI, primary lead investigator (ENCePP CoC).

- *Usefulness*: for which types of studies the Code was considered to be beneficial
- *Clarity*: whether the Code was considered to be clear
- *Trust*: whether application of the Code was increasing trust in a study
- *Participation*: whether the respondent would more likely participate in a study if it were compliant with the Code
- *Redundancy*: whether the Code was perceived as redundant with other guidelines

For some dimensions, the questions were tailored to stakeholder categories to match their perspective and expected level of expertise in the field of noninterventional postauthorisation studies. The full questionnaire is available as supplement. The survey was conducted online with the EU Survey tool and distributed by the European Medicines Agency (EMA). A snowball sampling strategy was enacted, and in particular, ENCePP partners and stakeholder representatives and observers within the Steering Group were requested to share the survey link with individuals within and outside of their own organisations.

After 1 month, a total of 87 responses were received. The most represented category of respondents (43 or 49%) was "researchers," and the least represented one was "patients and consumer organisations" (6 or 7%). On average, respondents assessed their knowledge about noninterventional postauthorisation studies as "fairly good" (33 or 37.9%) or "expert" (31 or 35.6%).

In the "usefulness" dimension, the majority of the respondents overall indicated that the Code would benefit all or most of all studies (66 or 76%)

Regarding "clarity," patients and healthcare professionals were asked (a) if they understood and (b) if they found important the principles of scientific independence and transparency, and the answers were largely positive to both questions (14 or 87.5% and 15 or 93.7%, respectively). Respondents from the other categories were asked to rate the Code in terms of easiness to understand and apply. The former was judged positively by a large majority of respondents (92%), whilst in the latter, a negative judgement prevailed in all categories (70%) but more so amongst pharmaceutical companies (88%). In the dimension of "trust," a large majority of respondents in all categories (83%, 69% in pharmaceutical industry) responded that the Code would reinforce their trust in the study results. In the "participation" dimension, a large majority (71%) declared that studies applying the Code were likely to encourage their participation (in the role corresponding to their category), except for pharmaceutical industry, where half of the respondents (50%) replied with a neutral or negative answer. In the dimension of "redundancy," the overlap with other guidelines was difficult to judge by half of the sample of patients and health professionals and by 42% in the category of public health body or regulators. Amongst those providing an answer, the majority (38 or 43.7% of the whole sample) considered that the Code is a good complement to other guidelines. A complete report of the survey is available in the EU PAS Register (EUPAS26545).

3.2 | ENCePP stakeholders' perspective

The following section provides the perspective of the different stakeholder groups of ENCePP based on the individual experience of the co-authors: H.D. is a senior member of ENCePP Working Group 2 and one of the coauthors of the initial Code; X.F. is a member of the Board of the European CRO Federation; P.V. and K.A. are representatives of their respective stakeholder groups in the ENCePP Steering Group; V.S. is an appointed expert and former alternate member of the Pharmacovigilance Risk Assessment Committee (PRAC).

3.2.1 | Academic perspective

Scientific independence and transparency are considered well established principles in academic research. However, there has been increasing realisation of the ways in which unconscious bias can occur.[2,5,12-14] Some of these problems relate to the quality of the research process (eg, adherence to the principles of stating hypotheses in advance, clarifying the protocol in advance, not selecting preferred results, following best practise in analysing and reporting results, always publishing results whether positive or negative). Transparency involves all stakeholders being able to verify that best practise in research process has been followed. Other problems relate to real or perceived pressure from study funders or ambiguity in how the interpretation of results or their reporting is influenced by particular interests in study outcomes. Scientific independence therefore needs to be visibly strengthened. These problems have damaged public confidence in scientific integrity of researchers and the validity of research results, and thus academic stakeholders can only welcome a Code, which not only promotes scientific independence and transparency but also gives researchers a way of publicly certifying their own adherence to these principles and an externally validated way of negotiating with funders how compliance with them can be substantiated in practise.

The disadvantages of the Code from an academic perspective have been mainly the time resources needed to comply with the transparency provisions of the Code and to enact the Code in the funding contract. Rather than following the Code for all studies, it is likely to be felt to be particularly important and worth the time investment where the funder is industry. Multistakeholder engagement in the protocol refinement process is likely to be a path to greater relevance and impact of the research, but it also imposes a greater complexity of understanding and managing interests.

A grey area is still the exact point at which the contract is signed in relation to prior feasibility studies and the exact nature of those feasibility studies since the period before the contract is not covered by the Code. Some protection in studies, which go ahead to contract, is given by including prior feasibility studies transparently as part of the protocol.

From an academic perspective, a greater awareness and more explicit value placed on the Code by medical journals would be helpful, both in justifying the expenditure of resources in following the Code and in negotiating compliance with the Code with funders. Academics

and journals however are aware that compliance with the Code is currently self-policed, and the resulting impact on public confidence may not be as high as desired. Further development of a compliance monitoring mechanism could be envisaged.

Finally, from an academic point of view, the issue of scientific independence and transparency will never be fully resolved, whilst industry retains so much of the responsibility for conducting medication safety (and benefit) research. If regulatory agencies were to fund more of this to be done in the public sphere, with industry contributing to a public funding pot, which was distributed via an independent public mechanism, this could meet the requirement of scientific independence and achieve efficiencies that are impossible with the current product-centred pharmacovigilance system.

3.2.2 | Industry perspective

There is general agreement on the key principles of scientific independence and transparency; however, the practical implementation of these principles for industry-funded studies performed for regulatory purposes is challenging.

In the previous version of the Code, a key issue was the interpretation that the Code did not allow involvement in the study conduct after protocol approval, even when the study funder was legally responsible to comply with regulatory requirements. From an industry perspective, the sponsor's or marketing authorisation holder's legal accountability cannot be transferred to a third party. Related to this, another aspect was that the epidemiological expertise of researchers employed by industry that adds value to a study as does the expertise from academic researchers was not really considered. In this respect, the Code's focus on conflicts of interest of the study funder was considered as not balanced, and conflicts of interest that may arise from personal interests of researchers seemed to be perceived less of a threat to scientific integrity.

For all these reasons, a revision of the Code was welcomed by industry in order to get a more clear definition of scientific independence; ensure that industry can fulfil its legal obligations in following the Code; allow some flexibility in the study team structure, as defined in the research contract; and support better collaboration, as well as increase the trust, between all involved stakeholders.

With the updated current version of the Code, some of the previous critics should be now obsolete. The changes introduced may ease the use of the Code when industry is the funder, even if this will be difficult to quantify. This is why it could be interesting to develop a metrics that would help to assess how often the Code is implemented, for which types of studies (required by regulators or not), from which funder. This could be implemented in the EU PAS Register. This would most probably be easier to implement than assessing the real compliance with the content of the Code.

3.2.3 | Contract research organisation perspective

The Code was so far not explicit on whether contract research organisations belonging to ENCePP could participate in a study compliant with the Code beyond protocol finalisation. CROs are usually for-profit private organisations providing scientific expertise in the protocol design, recruitment, monitoring, data management and analysis, study report, and publication of results. The new definition for conflict of interest usefully clarified that 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.

3.2.4 | Regulatory perspective

Since its beginning, the ENCePP network has served as support for the European regulatory environment in the field of epidemiology.[1,15,16] The ENCePP network has also helped to facilitate the introduction of amended regulatory concepts and amended frameworks specifically in the field of epidemiology for the conduct of postauthorisation safety studies (PASS), and especially following also regulatory requirements coming into force with the EU pharmacovigilance legislation in 2012.[17-19] Evolution of the ENCePP network continues to support the work of EU regulatory agencies mirroring also the increased demand for generation of post-approval data.[17,20] ENCePP guidance documents are seen as important resource and form part of recommended references and resources of regulatory guidance such as GVP Modules.

The Code may be applied to studies requested or imposed by regulatory authorities. A recent review showed that only a limited number of PASS protocols discussed at EMA's PRAC had the ENCePP Seal, implying declared application of the Code.[21] Studies imposed on MAHs as a condition of marketing authorisation are generally overseen by regulators with the possibility to influence study design and protocol development. From a regulatory perspective, the application of the Code might be seen as less relevant if regulatory oversight is ensured. However, strengthened transparency and independence with regard to the role of investigators may still be important, although it is acknowledged that regulatory agencies would prioritise regulatory compliance and implementation of provisions imposed for such studies. This implies that primary lead investigators are not completely independent in terms of the conduct of imposed studies as objectives and aspects of study designs are rather inflexible based on binding conditions. Early engagement with all stakeholders in protocol discussions might ensure understanding of the regulatory requirements and avoid deviation from study concepts and delays in protocol approval by regulators.

The provisions of the Code foreseeing that studies requested by regulators are not only agreed with the study funder but also with the competent authority(ies) strengthens the scientific independence of the primary lead investigator, which seems particular important for studies funded by stakeholders with interests in the products investigated. Whilst it might be considered as additional burden, the opportunity to engage with the primary lead investigator at the early stages of protocol discussions might also help to improve the process of protocol agreement, to foster timely involvement in discussions of methodological, operational, and feasibility aspects and to decrease possible information loss when regulatory advice is only conveyed

indirectly via parties interacting between regulators and the responsible study investigator. Such issues led to multiple rounds of regulatory comments on PASS protocols,[21] prolonging the process of protocol approval.

Regulatory agencies also frequently assess results of noninterventional studies that were not conducted based on regulatory requests. For these studies also, assurance of transparency and independence are important factors guiding considerations of assessment of these data.

It has to be further noted that strengthened concepts of transparency and independence of study investigators might help to meet critique that has been expressed regarding the conduct of epidemiological studies, including PASS.[22,23] The generation of epidemiological evidence is sometimes relevant to support the early approval of medicines. This highlights the need for reinforcement of those concepts, to enhance trust in postapproval epidemiological research.[17,24]

Trust building is further supported by increased transparency and the Code's provision to enter studies in the EU PAS Register. Apart from study registration, the Code foresees publication of study protocols and study results. A sample of German national PASS notified to the Federal Institute of Drugs and Medical Devices (BfArM) between January 2015 and June 2018 showed that 90% of the studies had been entered into the EU PAS Register with about 56% of those with a protocol published. For studies for which BfArM received an "end of study" notification between January 2015 and June 2018 about 62% had results published via the EU PAS Register. However, 36% provided only abstract information, and only 25% made comprehensive study reports available. This provides room to further increase transparency in line with the provisions of the Code. A broader and more frequent application of the Code's transparency provisions by all stakeholders is necessary to further strengthen transparency in postauthorisation research, a concept also pursued by the EU pharmacovigilance legislation.[19]

New emphasis has been put on performing joint PASS encompassing studies performed by multiple marketing authorisation holders, which is also covered by the Code. Whilst it is acknowledged that conduct of joint studies may be associated with higher burden for stakeholders, especially during protocol development, from a scientific and regulatory perspective, the conduct of joint PASS is preferred over the generation of fragmented results by multiple stakeholders. This is particularly the case when study objectives relate to a substance or therapeutic class independent of a product or marketing authorisation holder, eg, assessing the impact of risk minimisation measures introduced postapproval through safety referrals. Despite frequently recommended by regulators, the conduct of joint PASS remains sparse.[21] The Code's provisions for practical implementation of scientific independence might help to overcome constraints of individual industry stakeholders who wish to engage in joint PASS concepts.

3.2.5 | Patient and consumer perspective

Despite the importance of the role of ENCePP and the interest that patient advocacy groups expressed in the recent years in drug development, clinical trials, drug safety, and adverse events of their medicines, ENCePP is little known to the European patients and consumer organisations at large, and it would not be arbitrary to include health care professionals.

This assumption was validated by the results of the stakeholder survey mentioned earlier with only 7% of respondents from patient and consumer organisations, compared with 49% of respondents being researchers. The lack of familiarity with the activities and the role of ENCePP amongst the European patient community are reflected in the answers to the survey. Noninterventional postauthorisation studies are less known amongst patients and consumers than amongst the other participant groups. What is worth noting is that despite low level of knowledge about ENCePP, patients and consumers together with the other responder groups confirmed the usefulness dimension of the Code, as being beneficial to all or most of the studies, and the importance of the principles of scientific independence and transparency. It is worth noting that the latter two principles are supported by the vast majority of European umbrella patient organisations, as proven by their advocacy about them.

Patients value highly scientific independence, meant as not linked to any financial or other interests and assuring quality research financed from external sources. Equally, transparency is very important for patient organisations who have claimed recently the publication of all results of clinical studies, regardless of whether they are positive or negative. The adoption by ENCePP of these principles adds to its credibility and its perception by the public as a trustworthy scientific organisation.

Patients are indeed more interested in the results; however, they are much concerned about the methodology to carry out a study, which is affecting its results. To this end, the principles and the set of rules governing the Code increase the confidence and trust of patients and citizens in the integrity and value of studies carried out by ENCePP.

Studies that bear the ENCePP Seal are considered as more trustworthy and having undergone close scrutiny as to compliance with ENCePP principles and rules. However, even if patients and the public generally understand what scientific independence and transparency with regard to medicines mean, there are serious doubts that they fully understand the meaning of these terms in the context of the ENCePP Code of Conduct.

All major European patient umbrella organisations recognise the need of rules governing their relations with the scientific community, study funders, and regulators, and amongst them, concrete and unequivocal recruitment rules, informed consent, and ethical aspects are considered of particular importance. Transparency, clarity, unequivocal terms, and respect of ethical aspects are very important for patients.

As the set of rules and principles for pharmacoepidemiology and pharmacovigilance studies to promote transparency and scientific independence throughout the research, the Code should be well known and understood by all those involved in one way or another with medicines, including the general public as the end users. As the

target audiences of communication on the Code are different, the communication strategy to these audiences should be tailored to their needs and expectations from the studies covered by the Code.

4 | DISCUSSION

The fourth revision of the Code introduced new provisions aimed at supporting scientific independence and transparency in studies funded by an external institution. Its focus is on studies that involve at least two institutions that are tied by a research contract and a remuneration agreement. The study funder is often an institution with a commercial, financial, or institutional interest in the study results, but it often has also the responsibility for selecting the research institution that will lead the study, and it can influence the course of the study itself. The Code therefore foresees a separation between the influence of the funder and the scientific responsibility of the study, and for this reason, the primary lead investigator may not belong to the institution that funds the study (irrespective of the nature of the funding institution). This implies that studies conducted by an organisation based on its own funding may not be compliant with the Code as the precautionary separation between funder's influence and scientific responsibility is not implemented. This does not imply that such studies are invalid.

By forbidding important roles to researchers with personal interests, the previous version of the Code may have led candidate investigators to claim they had no interests rather than conducting an honest analysis of their personal position with respect to the study outcomes. This left the impression that the Code was only focussing on financial and commercial interests. Indeed, there are legitimate inclinations of personal nature that, if undetected, may lead to an unwanted influence. For instance, a finding that is unexpected or novel, or unfavourable to a drug, may be more appealing for publication and may therefore constitute a personal interest of an investigator working in academia.[5]

Although it was not representative of the views of an entire stakeholder group, the survey indicated that all the categories of stakeholders considered the Code as beneficial to all the studies, but practical applicability was indicated as problematic, and judging overlap with other guidelines was considered difficult. We showed, however, that, in comparison with the ISPE GPP and the ADVANCE Code of Conduct, the ENCePP Code of Conduct is a unique source of guidance on scientific independence and relationships between investigators and study funders. A major concern from an industry perspective was that the Code would forbid industry to fulfil its legal obligation in case of regulatory requirements as, after protocol finalisation, the Code excludes participation of researchers from the funding organisation in study activities "that could influence the results or interpretation thereof in any particular direction." It must be noted, however, that this provision does not preclude a regular monitoring of the progress of the study, for example, in terms of monitoring recruitment and data quality such as missing data levels or loss to follow-up. On the contrary, the Code specifies that the investigators have the obligation to keep the funder informed of such data.

4.1 | Limitations of the Code

The expression "commercial interest in an outcome of the study" is clarified in the Code to refer to the legitimate interest of those organisations marketing drugs. However, it may be perceived that research institutes that rely on funding from pharmaceutical companies to thrive (if public or private not-for-profit) or to pursue their legitimate profit (if for-profit), may be subject to indirect, possibly unwanted, influence from their funders. Even though compliance with the Code does protect researchers and funders from this risk within the realm of a single study, it cannot avoid a more subtle influence, because of a perception that funders may select the institution, which will conduct the next study based on the result of previous studies, instead of professional reputation. A related risk is that investigators and researchers may be tempted to interpret evidence of negative results as need for further research, with the objective of attracting new funding. In Europe, according to the current legislation, the funders for pharmacoepidemiology studies requested by regulators are mostly manufacturers themselves, which are therefore the most common funders for European research institutions in pharmacoepidemiology. This makes the risk of indirect influence higher than in the United States, where public funding is substantial. The ADVANCE project attempted to address the indirect influence of study funders, by producing guidance on the selection of research institutions. Three models of selection were proposed, in increasing order of perceived independence: led by the study funder, led by a selection committee, led by an external body.[25]

4.2 | The way forward

The Code is perceived as useful but, at the same time, has to date been seen as potentially difficult to apply in practise. As discussed above, this is partly due to the inherent complexity of the relationships between study funders and investigators. It is hoped that the current major revision will help in clarifying and disseminating the provisions of the Code to support understanding of its advantages and promote its adoption. Examples of translation of principles of the Code into concrete actions should be made available that could also support training activities.[13] To reinforce trust in the actual application of the Code's provisions funders and investigators may decide to enter in the EU PAS Register together with the final study report, a final self-assessment of compliance with the Code, signed by all involved parties. Alternatively, an independent scientific committee overseeing the study conduct could also take the responsibility to review compliance with the Code. A periodic, independent review of a random sample of EU PAS Register records would also be useful. Finally, to address the limitations of the Code and building on previous work, ENCePP could develop specific guidance on the selection of research institutions.

5 | CONCLUSION

The ENCePP Code of Conduct is a tool supporting pharmacoepidemiology studies. Researchers are supported in their relationship with study funders, as scientific collaboration is allowed within limits and under their control, as well as with regulators, as the Code supports dialogue between researchers, regulators, and funders having to comply with a legal obligation. The pharmaceutical industry is supported with guidance on practical aspects of the funding of studies that are considered scientifically independent and transparent, in particular for regulatory obligations. Regulators are supported by increasing their confidence in results of studies conducted to best practise of transparency and scientific independence. And health-care professionals and patients may have more trust in studies that generate the evidence they rely upon for their decisions on pharmaceutical treatments.

ETHICS STATEMENT

The authors state that no ethical approval was needed.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

The views expressed in this article are the personal views of the authors and may not be understood or quoted as being made on behalf or of reflecting the position of their employer organisation or of the European Medicines Agency or one of its committees or working parties.

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