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European Network of Centres for  
Pharmacoepidemiology and  
Pharmacovigilance

## Overview of comments received on the 'Checklist of Methodological Standards for ENCePP Study Protocols – Draft for public consultation' (Doc.Ref. EMEA/540136/2009)

### Interested parties that commented on the draft document released for consultation:

Stakeholder No.	Name of organisation or individual
1	Giampiero Mazzaglia, Health Search, Italian College of General Practitioners
2	Yolanda Alvarez – European Medicines Agency (EMA)
3	European Federation of Pharmaceutical Industries and Associations (EFPIA)
4	Anonymous
5	Dr Norbert Banik, GlaxoSmithKline GmbH & Co. KG, Munich, Germany
6	Centre for Pharmacoepidemiology, Karolinska Institutet, Sweden
7	MHRA Pharmacoepidemiology Research Unit
8	Roche
9	BPI – German Pharmaceutical Industry Association
10	Stan Young, National Institute of Statistical Sciences (NISS), USA
11	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)

**The ENCePP Checklist of Methodological Standards for ENCePP Study Protocols will be reviewed by the ENCePP Steering Group on a regular basis. We would be grateful to receive details of any circumstances where it has been difficult to adhere to the provisions of the Checklist.**



## 1. Overview of comments - Introduction

The comments received are presented as 'General comments' and 'Specific comments on the text'. The corresponding sections and questions relating to the comments refer to the text in the version of the Checklist that was published for public consultation. However, the details may be different in the revised final version due to changes in the text and restructuring. Comments are presented relating to the following 10 sections:

1. Research Question
2. Study population
3. Study design
4. Data sources
5. Exposure measurement
6. Endpoint definition and measurement
7. Biases
8. Analysis plan
9. Quality assurance and feasibility
10. Ethical issues

## 2. General comments

Stakeholder no.	Comment	Outcome
1	An overall detailed document addressing all the relevant issues associated with a pharmacoepidemiological study. Maybe, further details need to be included in a ENCEPP study related with (1) the background information leading to the research question; (2) the potential progress of the study in terms of knowledge of the issue; (3) feasibility (i.e. timelines, monitoring of the progress of the study, possible interim reports)	<p>An overall guidance document as proposed is in preparation by Working Group 1.</p> <p>Studies that qualify as 'ENCePP Studies' need to be registered in the Registry of Studies before the study commences. The Registry will capture information on timelines and a synopsis of the study including information on the background to the research question.</p> <p>Questions to ensure that the study timelines/milestones are specified in the protocol are to be added in the section on quality assurance and feasibility (see general comment below).</p>

Stakeholder no.	Comment	Outcome
3	<p>The draft Checklist on Methodological Standards is simplistic and does not address important topics, such as appropriate statistical adjustment for multiple comparisons, or investigation in cohort studies of balance of baseline covariates between treatment groups compared. The draft Code of Conduct correctly acknowledges (page 3) that “The Code does not include rules or guidance on methodological aspects or scientific standards to be used for specific studies or study types. Adherence to the rules will not guarantee validity or integrity of the study data.” Use of this checklist may help to encourage that certain elements are included in study protocols, but use of the checklist provides no assurance that a proposed protocol or study design is appropriate or scientifically sound.</p> <p>Moreover, the handling of the checklist seems to be not entirely clear. The question is if it is a list of minimum requirements for ENCePP studies, or is this just meant as a checklist to increase the level of transparency, i.e. what happens if the declaration contains a number of questions answered with ‘No’? Is there a response of the ENCePP office intended discussing statements in the sense of a standard response / evaluation process?</p>	<p>The Checklist is not intended to provide assurance that a proposed study is scientifically sound. The lead investigator has the final responsibility for the protocol. No review process is currently foreseen to assess the quality of study protocols. The aims of the Checklist are to stimulate researchers to consider important epidemiological principles when writing a study protocol and to promote awareness and transparency regarding study methodologies and design.</p>
3	<p>It would probably be easier for the user of the Checklist if the questions would be more targeted to specific sections of the protocol and follow the natural sequence of the protocol, not so different to the way we report research findings. For an example, see the flow of the STROBE list or the sequence of the topics in GPP from</p>	<p>The Checklist addresses important methodological aspects and does not aim to be a comprehensive review of the protocol. The number of questions is limited and should be easily answered by the lead investigator who developed the protocol.</p>

Stakeholder no.	Comment	Outcome
	ISPE.	
3	We propose that you add questions about the Funding Contract by reference to Chapter 8 of the Code of Conduct.	The Code of Conduct and the Checklist of Methodological Standards are submitted simultaneously. There is, therefore, no need to duplicate or cross-refer to the same questions.
3	The Code of Conduct requests that the “timetable for study progress and completion of the study describing milestones (e.g. interim reports) and deadlines” is included in the Protocol. The Checklist does not presently inquire about this timetable. We suggest modifying the Checklist by adding questions to ensure that study timelines/milestones are specified in the Protocol.	Agreed. Such questions to be added in section 9 which will be reworded as ‘Quality assurance, feasibility and reporting’.
3	Please consider whether a scientist from the Funder organization should also be a signatory of the checklist.	The lead investigator has the final responsibility for the development of the protocol and is the sole signatory on the Checklist accordingly.
3	The Checklist does not presently cover the Funder’s responsibilities on AE reporting according to Volume 9A. Suggest modifying the Checklist by adding questions to ensure that AE reporting responsibilities are included in the Protocol.	Not agreed. The protocol covers methodological aspects not the regulatory obligations of the funder already described elsewhere. A future ENCEPP guidance document will cover this.
4	It would be easier for Checklist users if the questions would be more targeted to specific sections of the protocol and come in the natural sequence of the protocol (which is not so different to the way we report research findings – for an example see the flow of the STROBE list or the sequence of the topics in GPP from ISPE.	See above
5	Section 4 and 5 are dealing to some extent with	The scope of ENCePP studies includes all pharmacoepidemiological and

Stakeholder no.	Comment	Outcome
	<p>specifications regarding the “exposure”. In the given context, the exposure will be to one or more medicinal products. Even if other exposures are studied, at least one medicinal product needs to belong to the exposures, too in order to make the study fitting in the context at hand (non-interventional pharmacoepidemiological or pharmacovigilance studies). So the term exposure seems to be a bit too generic here, although a general misinterpretation shall rather not happen.</p>	<p>pharmacovigilance studies and not just ‘non-interventional’ studies. In line with this broad scope, it is considered best to keep the generic interpretation of the word to cover multiple types of studies.</p>
8	<p>A scientist from the Funder organization should also be a signatory of the checklist.</p>	<p>See above</p>
9	<p>BPI welcomed the establishment of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) to complementing the existing tools (RMP, EudraVigilance, etc) of the EU pharmacovigilance system, in order to facilitate the generation of highly reliable pharmacoepidemiological data for pharmacovigilance purposes.</p> <p>Overall, the proposals on the ENCePP Code of Conduct and the Checklist of Methodological Research Standards have been well received and generally accepted by BPI Members to be a valuable and important step forward to promote transparency regarding methodologies and design used in pharmacoepidemiological studies performed in the EU. However, one key issue resides which will be critical:</p> <p>According to the ISPE (International Society for Pharmacoepidemiology) guidelines, epidemiologic studies</p>	<p>Agreed. The Code of Conduct has been amended accordingly.</p>

Stakeholder no.	Comment	Outcome
	<p>provide valuable information about the relationship between human health and therapeutic agents. But epidemiologic research for the assessment of drugs shall not only focus on safety aspects, there is an increasing need to also address other questions, especially concerning effectiveness and comparative effectiveness. To get an informative safety profile for a drug according to its risk-benefit assessment, information on benefit is also needed. As the ENCePP Code of Conduct will set out rules for the conduct of Pharmacoepidemiology and Pharmacovigilance Studies, BPI would like to remind that the legal framework in Europe only covers post authorization safety studies according to NtA Vol. 9a Part I N° 7 (PASS). However, setting out principles for methodological research standards shall cover all other topics to be addressed in epidemiologic studies. Many countries, not only in Europe, have gradually assumed responsibility for economic evaluations. Applicability of prospective data collection to different evaluations is essential.</p> <p>BPI therefore would like to recommend to extent the scope of the ENCePP Code of Conduct and to include effectiveness as well as economic evaluations</p>	
10	<p>My impression is that this is like the current STROBE effort. Report what was done to a degree, but make no fundamental demands that the studies be done in a way that the results are more reliable than they current are. Multiple testing problems are not even mentioned. The author can do anything they want on bias. This just says</p>	Noted.

Stakeholder no.	Comment	Outcome
	<p>the author needs to say what they did.</p> <p>I take it that these are the funders and they are essentially saying the status quo is acceptable. The workers, epidemiologist, will love it.</p> <p>They get money and they can carry on business as usual. The false positive machine will continue. The funding agencies and the journals are the managers of the process. It is their responsibility to fundamentally change the system so that results are more reliable.</p>	
11	<p>Overall, the proposals on the ENCePP Code of Conduct and the Checklist of Methodological Research Standards have been well received and generally accepted by EUCOPE Members to be a valuable and important step forward to promote transparency regarding methodologies and design used in pharmacoepidemiological studies performed in the EU.</p> <p>Currently, the “Functioning of the Clinical Trials Directive (CTD) 2001/20/EC” is assessed. EUCOPE has taken part in the Public consultation published by the European Commission. The CTD only applies to „interventional trials”, not to „non-interventional” studies (NIS). As the Commission report states, the main characteristics of NIS are accepted by all Competent Authorities (CAs), but the borderline between „interventional trials” and „non-interventional” studies is drawn differently in individual Member States. Moreover, the report underlines that there are divergent interpretations of the term „non-interventional”, especially with respect to „no additional</p>	Agreed. The Code of Conduct has been amended accordingly.

Stakeholder no.	Comment	Outcome
	<p>diagnostic or monitoring procedure and use of epidemiological methods".</p> <p>Even concerning the design, there is currently a divergent interpretation at Member State level: Some Member States accept controlled studies without systematic allocation of treatment (e.g. without randomization) as NIS. Other Member States interpret all designs with comparison of groups even without randomization as falling under the Clinical Trials Directive.</p> <p>A clear definition, differentiation and harmonization between Member States are urgently needed.</p> <p>The ENCePP Code of Conduct and the Checklist of Methodological Research Standards is therefore a valuable and important step forward to promote transparency regarding methodologies and design used in pharmacoepidemiological studies performed in the EU. However, setting out principles for methodological research standards shall cover not only safety aspects but all other topics to be addressed in epidemiologic studies. Many countries, not only in Europe, have gradually assumed responsibility for economic evaluations. Applicability of prospective data collection to different evaluations is essential.</p> <p>EUCOPE therefore recommends to extend the scope of the ENCePP Code of Conduct and to include effectiveness as well as economic evaluations.</p>	



## 2. 3. Specific comments on text

Section/Question number	Stakeholder number	Comment and rationale; proposed changes	Outcome
<b>Section 1. Research Question</b>			
Section 1	6	<p><b>Comments:</b> --</p> <p><b>Proposed change:</b> Secondary and/or composite endpoints should also be included.</p>	Secondary endpoints to be added.
Question 1.1	3	<p><b>Comments:</b> Is the term “formulation of the research questions” equivalent to “Objectives of the study”? Why then not use the more common terminology?</p> <p>It seems that 1.1 contains two questions, which should be asked separately, as below.</p> <p><b>Proposed changes:</b> Are the objectives of the study clearly formulated? Is it clearly explained why the study is being conducted?</p>	Agreed. To be amended, but it is proposed that questions 1 and 2 will be inverted.
Question 1.1	4	<p><b>Comments:</b> Is the general term “formulation of the research questions” equivalent to “Objectives of the study”. Why then not use the more common terminology?</p> <p>The research question is usually explained in the background and introduction question, whereas the objectives of the study are at the end of the introduction section in a special section. It appears that 1.1 contains two questions. We would pose</p>	Agreed. To be amended, but it is proposed that questions 1 and 2 will be inverted. See above

Section/Question number	Stakeholder number	Comment and rationale; proposed changes	Outcome
		<p>them as two separate questions 1.1</p> <p><b>Proposed change:</b> Are the objectives of the study clearly formulated? Is it clearly explained why the study is conducted?</p>	
Question 1.2	3	<p><b>Comment:</b> We prefer “study objective” instead of the more general term “research question”.</p>	Agreed. To be amended, but it is proposed that questions 1 and 2 will be inversed. See above
Question 1.2	4	<p><b>Comments:</b> Would prefer “study objective” instead of the more general term “research question”. Some of the information I would seek in the Methods section (1.2.4, &amp; 1.2.5).</p>	Agreed. To be amended, but it is proposed that questions 1 and 2 will be inversed. See above
Question 1.2.1	3	<p><b>Comment:</b> Suggest the term “Target population” be clarified as “Population /subgroup to whom the study results are intended to be generalised”.</p>	Agreed. Checklist amended in line with comment.
Question 1.2.2	3	<p><b>Comment:</b> There should be a clear relationship between the hypothesis and the power and sample size calculation, i.e. the hypotheses are informed by the power of the study.</p> <p><b>Proposed change:</b> Mention the dependency of the study hypotheses/objectives and the power to detect afforded by the sample size.</p>	Not agreed. The Checklist is not a guideline.
Questions 1.2.3; 1.2.4; and 1.2.5	5	<p><b>Comment:</b> The specific points 1.2.3, 1.2.4, and, 1.2.5 do not belong to the research question, they seem to belong to study design characteristics and shall be moved to the relevant sections</p> <p><b>Proposed change:</b> move 1.2.3, 1.2.4 and 1.2.5 to the</p>	Agreed. Checklist amended in line with comment.

Section/Question number	Stakeholder number	Comment and rationale; proposed changes	Outcome
		section "study design"	
Question 1.2.5	3	<b>Comment:</b> Suggest rewording the question as follows: "Main measures of association and/or frequency (e.g. relative risk, odds ratio, incidence rate, prevalence, etc.)"	Agreed. Checklist amended in line with comment.
Question 1.3	3	<b>Comment:</b> Suggest specifying "... <u>potential</u> implications of the study <u>results</u> ...".	Agreed. Checklist amended in line with comment.
<b>Section 2. Study Population</b>			
Section 2	6	<b>Comment:</b> Diseases/indication is simply too general, it needs to be specified. In contemporary studies, instruments used to define and levels of disease severity are mandatory. <b>Proposed change:</b> For Diseases/indication at least ICD codes should be included.	Partly agreed. Heading of sub-section to be changed to "Is the study population <u>defined</u> ..."
Question 2.1	3	<b>Comment:</b> Suggest re-wording "source population" to "target population" for consistency with question 1.2.1.	Not agreed. Source population and target population are different concepts.
Question 2.2	3	<b>Comment:</b> We would rather use "considered" instead of "described" (describing is not possible at the planning stage).	Not agreed. The protocol should define the study population (subjects intended for recruitment).
Question 2.2	4	<b>Comment:</b> We would rather write "is the following information considered" instead of "described" (describing is not possible at the planning stage)	See above
Question 2.2.3	3	<b>Comment:</b> In case of a database study, operational definition	See above ("define"). Definition would include

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		of the study population should be provided (e.g. at least 2 ICD-9 coded claims in a 1-year period).	coding system.
Question 3.1	3	<b>Comment:</b> Usually the choice or rationale to employ a study design is not always explained. <b>Proposed change:</b> Amend to: "Is the study design clearly explained?"	Agreed. Study design should be explained, not only the choice. Checklist amended to include a question 'Is the study design explained'.
Question 3.1	4	<b>Comment:</b> Usually the choice or rational to employ a study design is not always explained. <b>Proposed change:</b> Is the study design clearly explained?	See above
<b>Section 4. Data sources</b>			
Question 4.2.2	3	<b>Comments:</b> Suggest changing "Events" to "Endpoints" for consistency with question 4.1.2.	Agreed. Checklist amended in line with comment.
Question 4.3	3	<b>Comments:</b> Suggested syntax change. <b>Proposed change:</b> 4.3 Is the coding system described for diseases, events and exposure? (e.g. ICD-10, MedDRA, WHO DD ATC).	Agreed. Checklist amended in line with comment.
<b>Section 5. Exposure measurement</b>			
Section 5	3	<b>Comment:</b> Section 5 deals not just with exposure measurement, but exposure definition as well. Suggest changing the section title to "Exposure <u>definition</u> and measurement".	Agreed. Checklist amended in line with comment.
Question 5.1	3	<b>Comment:</b> Suggest adding an item: "Does the protocol	Partially agreed. Explanatory note added to

Section/Question number	Stakeholder number	Comment and rationale; proposed changes	Outcome
		discuss exposure definition and categories (e.g. operational details for defining and categorizing exposure from databases)?"	existing question.
Question 5.1	3 and 4	<b>Comment:</b> Somehow redundant with section 4.1.1 & 4.2.1. <b>Proposed change:</b> Rephrase to a simpler wording: "Does the protocol describe how exposure is measured?"	Agreed. Checklist amended in line with comment.
<b>Section 6. Endpoint definition and measurement</b>			
Question 6.1	3, 4	<b>Comment:</b> Most of the time, the direct endpoint of interest (i.e. MI) is included and not a surrogate marker. Therefore most of the time, there is no description necessary.	Not agreed. If needed, 'N/A' will be checked.
Section 6.1	7	<b>Comment:</b> It should be specified whether the chosen endpoint is a surrogate endpoint.	Not agreed. Considered as not required as endpoint needs to be described.
Question 6.2	3	<b>Comment:</b> Somehow redundant with section 4.1.1 & 4.2.1 <b>Proposed change:</b> Rephrase to a simpler wording: "Does the protocol describe how the endpoints are measured?"	Agreed. Checklist amended in line with comment.
Question 6.2	4	<b>Comment:</b> Somehow redundant with section 4.1.2 & 4.2.2 <b>Proposed change:</b> "Rephrase to a simpler wording: "Does the protocol describe how the endpoints are measured?"	See above
<b>Section 7. Biases and Effect Modifiers</b>			
Section 7	3	<b>Comment:</b> There are more than the three listed types of biases <b>Proposed change:</b> Have only one global question: "Does the	Not agreed; these are considered important biases to be specifically considered.

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		protocol adequately address biases”?	
Section 7	5	<p><b>Comment:</b> Why have those three types of biases been specifically selected from the many known biases?</p> <p><b>Proposed change:</b> As it will be inappropriate to mention every type of bias, it will be more feasible to explain in the study protocol how biases are addressed in the study design, specify which ones and discuss means to minimize them.</p>	See above
Section 7	6	<p><b>Comment:</b> --</p> <p><b>Proposed change:</b> Confounding by indication must be included.</p>	Not agreed. Confounders are addressed in section 8.
Section 7	7	<p><b>Comment:</b> Immortal time bias could be categorised as a type of selection bias (under 7.1.1). Other biases that may be considered under 7.1.2 Information biases would be misclassification bias and reporting bias. It is also felt that attrition bias is a common problem.</p>	ENCePP Working Group 1 (responsible for developing this Checklist) considered immortal time bias should be singled out. Information biases already included.
Question 7.1	1	<p><b>Comment:</b> It is not clear how investigators should address biases. Indeed there some relevant missing biases usually encountered in pharmacoepidemiological studies.</p> <p><b>Proposed change:</b> Replace the question with “Does the protocol address methods for dealing with:” . Add the following biases: channelling bias; confounding by indication. Add in the round brackets: (sensitivity analyses)</p>	Different methods exist to address biases. This will be included in the guideline on methodological standards that is under development by Working Group 1 of ENCePP. Methods on how to address biases are covered in section 8.
Question 7.1	3, 4	<p><b>Comment:</b> --</p>	Not agreed. Aspects to be addressed are specified in parentheses. Relevance is only part

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		<b>Proposed change:</b> "Does the protocol address <u>the potential relevance</u> of: ...?"	of it.
Section 7.1	3	<b>Comment:</b> These are quite broad classes of bias. It would be helpful to add some examples for specific types of selection bias and information bias. Also, please add "statistical techniques" to the last line.	See above. Also, statistical techniques addressed by section 8.
Question 7.1.3	3	<b>Comment:</b> Immortal time bias is a special type of selection bias. <b>Proposed change:</b> Delete and add as an example to 7.1.1	See above.
<b>Section 8. Analysis plan</b>			
Section 8	2	<b>Comment:</b> Missing data may lead to bias and loss of information in epidemiological and clinical research. <b>Proposed change:</b> Add the two following subsections on the current checklist:  - Does the plan include the comparison of distribution of key variables in individuals with and without missing data?  Yes/No/ NA  - Does the plan include the explanation of the imputations?  Yes/No/NA  Reference: Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, Wood AM, Carpenter JR. Multiple imputation for missing data in epidemiological and clinical research:	First question agreed. Second question not agreed. Imputation not always needed.

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		potential and pitfalls. BMJ. 2009; 338.	
Questions 8.1 & 8.2	3	<p><b>Comment:</b> In some retrospective studies that use large automated databases, it may make more sense to calculate the precision of potential results (i.e., width of the Confidence Interval) based on varying assumptions about sample size (which may not be knowable before performing the study) and effect size, rather than formal sample size calculations.</p> <p><b>Proposed change:</b> Suggest adding the following question: "Are the assumptions underlying the sample size calculations provided?"</p>	Not agreed. Question 8.2 is considered sufficiently clear.
Questions 8.1; 8.2.	5	<p><b>Comment:</b> Sample size justification (8.1) and power calculations (8.2) belong to the study planning, not to the analysis plan.</p> <p><b>Proposed change:</b> Move 8.1 and 8.2 to section 3, study design.</p>	Agreed. Checklist amended in line with comment.
Question 8.1	3	<p><b>Comment:</b> In most claims data studies and secondary analyses, sample size calculation is not required.</p> <p><b>Proposed change:</b> No change, one could tick 'NA'</p>	No change needed
Question 8.2	3	<p><b>Comments:</b> In secondary data analyses, this is part of the study results, not the study protocol.</p>	No change needed. If appropriate, 'N/A' will be checked with explanation.
Question 8.3	3, 4	<p><b>Comments:</b> Is it necessary to explain the choice (why?) or the methods. We would prefer only the latter.</p> <p><b>Proposed change:</b> Delete "choice of"</p>	Not agreed. A protocol is not a textbook of epidemiological and statistical methods.



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Question 8.3	3	<p><b>Comment:</b> RR/OR looks like a measure, while instead RR or OR is meant.</p> <p><b>Proposed change:</b> Change 'RR/OR' to 'RR, OR'</p>	Agreed. Checklist amended in line with comment.
Questions 8.1; 8.2; 8.3; and 8.4.	5	<p><b>Comment:</b> Sections 8.1 and 8.2 are addressing the same aspect and shall not be separated from each other.</p> <p><b>Proposed change:</b> 8.3 and 8.4 shall be combined into a single entity.</p>	Not agreed. In some studies, sample size is driven by available data (e.g. database analyses). In such cases, it is important to estimate power.
Question 8.7	3	<p><b>Comment:</b> The analysis plan should contain operational definitions of confounders / effect modifiers for database studies (e.g., ICD-9 codes).</p>	Current wording is sufficiently inclusive.
<b>Section 9. Quality assurance and feasibility.</b>			
Section 9	3, 8	<p><b>Comment:</b> --</p> <p><b>Proposed changes:</b> Have all the sites participating to the study been audited within the last 3 years of the study start and relevant CAPAs being implemented fully? Is documentation available to the Funder and public on the ENCePP website? Public financial disclosure?</p>	Not agreed. Does not refer to the protocol.
<b>Additional proposed changes</b>			
Proposed Section 11	3	<p><b>Comment:</b> Add a new section 11, analogous with Chapter 8 of the Code of Conduct, about the funding contract.</p> <p><b>Proposed change:</b> "Has a contractual arrangement between the (Primary) Lead Investigator or the Coordinating Study Entity and the Funder been signed in a legally binding manner</p>	Redundant with Code of Conduct. There will be a checklist annexed to the Code of Conduct addressing these issues.

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		prior to the first step in the research process subject to the assignment?" "Are the different aspects of the ENCePP Code of Conduct addressed in the funding contract?"	