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European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Overview of comments received on 'The ENCePP Code of Conduct – Draft for public consultation' (Doc.Ref. EMEA/489873/2008)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Bayer Schering Pharma
2	European Federation of Pharmaceutical Industries and Associations (EFPIA)
3	European Parkinson's Disease Association (EPDA)
4	Fundació Institut Català de Farmacologia
5	Centre for Pharmacoepidemiology, Karolinska Institutet, Sweden
6	MHRA Pharmacoepidemiology Research Unit
7	National Institute of Statistical sciences
8	Anonymous
9	Glaxo-SmithKline (GSK)
10	German Pharmaceutical Industry Association (BPI)
11	International Society for Pharmacoepidaemiology(ISPE)
12	Roche
13	The European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
14	Food and Drug Administration (FDA)

The terms of the ENCePP Code of Conduct 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 Code.

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1. Overview of comments

The lines and chapters indicated for the comments refer to the location in the version of the Code of Conduct published for public consultation. However, the location might be different in the revised final version due to changes in the text and restructuring. Comments are presented under the following 11 topics:

1. Scope, rationale and general principles
2. ENCePP membership
3. Compliance monitoring
4. Research contract and study funding
5. Role of investigator – including conflicts of interest
6. Role of study funder – including protocol agreement, study conduct and conflict of interest
7. Study registration and availability of study information and data
8. Study protocol – including statistical analysis
9. Communication & publication/reporting
10. Miscellaneous
11. Annexes

Disclaimer:
Please note that in some instances, notably for topic 6 (Role of study funder- including protocol agreement, study conduct and conflict of interest), several comments were received related to the same concept. To avoid duplication, the verbatim text from individual senders may not always be represented exactly, and the comment may be an amalgamation of the general concept.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
1. Scope, rationale and general principles			
66	2	**Comment/Proposed change:** The term "scientific independence" is not defined – please clarify what this term means. In addition, please consider using the term 'scientific rigour' to 'scientific independence' throughout the document as the quality of the studies will be determined largely by their scientific quality, not their 'independence'.	Not agreed. Further clarification is not required.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
1. Scope, rationale and general principles			
72	11	**Comment:** In terms of scope, it states any kind of observational research - does it include all methods or tools - i.e. chart reviews, prospective data collection and even database analyses? Scope seems very broad, is that the intent?	The scope of the Code is inclusive (see above).
77	2	**Comment:** Observational research includes activities other than Pharmacoepidemiology and Pharmacovigilance studies which appear to be the broad focus of this Code of Conduct document. **Proposed change:** Delete "...and any other type of observational research"	Partly accepted. The wording has been amended from *observational research* to *observational methodology*.
77-79	2	**Comment:** Lines 77-79 indicate that the definition of Pharmacoepidemiology and Pharmacovigilance studies may also include Clinical Trials. However, line 121 appears to contradict this statement, indicating that the Clinical Trials Directive (Directive 2001/20/EC) applies in the case of interventional research. The need for the reference to Clinical Trials at this place is not understood. Also this reference might create an ambiguity as to whether or not the Code applies to a specific clinical trial (i.e. it creates a doubt as to the scope of this Code). Clinical trials should be excluded from the scope of this document, as they are governed by other regulated standards, including Directive 2001/20/EC. Adding a second set of standards opens the door to inconsistencies. **Proposed change:** Delete the following: "However, the definition of Pharmacoepidemiology and Pharmacovigilance studies may also include clinical trials (see Annex 1)." OR amend to: "Although the definition of Pharmacoepidemiology and Pharmacovigilance studies may also include clinical trials, this Code of Conduct does not cover studies within the scope of the Clinical Trials Directive 2001/20/EC"	Proposed change not agreed. The scope of the Code is inclusive. The Code does not replace, affect or is in conflict with any existing legislation that applies, e.g. Directive 2001/20/EC in case of clinical trials. It should rather be considered as being complementary to existing guidelines and rules as applicable. Notably, adherence to the Code is voluntary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
1. Scope, rationale and general principles			
90	2	**Comment:** What is the difference between 'academic' and 'commercial' investigators, given that both types work for the same objective described in the purpose of studies and receive attribution due to their expertise and work? **Proposed change:** Delete "...both academic and commercial...".	Agreed.
174	2	**Comment:** It does not seem appropriate that an investigator can choose to change the status of a study – this could potentially lead to selective disclosure, i.e., "transparency when convenient". If a researcher chooses to withdraw the ENCePP status for a given study, should they then be removed from the ENCePP Inventory of qualified investigators? It is not clear whether investigators can choose to be 'ENCePP-approved' or not when it comes to conducting particular studies – this could lead to situations where an investigator simply doesn't want to reveal details about compensation or intellectual property, etc.	It is at the discretion of the investigators and study funders whether or not to follow the provisions of the Code and to seek the 'ENCePP study seal' for their studies. There are conditions to be met before, during and after the study in order to qualify for the seal. Due to the voluntary nature of the study seal, investigators can withdraw at any point in time, however, the ENCePP Secretariat may identify the respective studies in the annual reports. Of note, the seal refers to studies only, not to investigators.
178-179	2	**Comment:** Regarding the statement "In case of either a voluntary withdrawal or a deprivation for breach, the ENCePP Secretariat may identify the respective studies in the annual reports and on the ENCePP website.". Because of the significant impact this may have on a studied product, this should only happen in exceptional cases and only after having consulted with the relevant Funder/Marketing Authorisation Holder. Add: "The cause for such change in status, either voluntary withdrawal or deprivation for breach, will be given in the annual report and on the website, in the interest of ENCePP transparency."	Agreed. The text concerned has been amended accordingly.
185-186	2	**Comment:** Regarding "The primary purpose of a study shall [not] be [...] to promote the sale of a medicinal product", we do not disagree with this but how is it decided that a study proposal is promotional in nature?	Not agreed. This is a guiding principle for studies to be planned and conducted in line with the Code. If information is confidential it shouldn't be disseminated.

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1. Scope, rationale and general principles			
		This can be very subjective: guidance should be provided on the criteria to differentiate a promoting-type of research and a scientific research, recognising that any scientific study leading to an increase in the knowledge of a product may eventually lead to sales promotion! In addition, since the primary purpose of the study is to generate data of potential scientific or public health importance, we recommend adding that the ENCePP study's purpose is not to disseminate confidential information of a medicinal product. **Proposed change:** Amend to: "The primary purpose of a study shall be to generate data of potential scientific or public health importance and not to promote sales or to disseminate confidential information of a medicinal product."	What constitutes confidential information should be agreed upfront, however it needs to be in line with the Code's definition of confidential information.
187	2, 8	**Comment:** This sentence seems to be polemic pointing too much in the direction of prejudices. We suggest to include a positive aspect as below. **Proposed change:** Amend to: "The design of the research shall aim to result in valid and scientifically integral results and not be aimed…"	Not agreed. The statement represents one of the Code's general principles.
199-200	2	**Comment/Proposed change:** Amend to: "A maximum level of transparency with regard to information necessary to evaluate the conduct of the research and to evaluate its' conclusions …."	Partly agreed. The text has been reworded to improve readability.
210-212	2	**Comment:** It is unclear what is considered under "detailed documentation of all steps throughout the research process". Please clarify accordingly. Any (substantial) changes and deviations should be notified to the ENCePP secretariat.	More detailed information on the requirements of documenting and making available information is provided in the specific chapters as well as the Checklist (new Annex 2) of the Code.
243	2	**Comment:** Regarding "...the ENCePP Secretariat may request to see the funding contract to verify it is not in breach of the Code.", the	In case of complaints regarding the compliance of a particular ENCePP study with the Code, the ENCePP

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1. Scope, rationale and general principles			
		contract may contain confidential or financially sensitive information and the right must be granted to delete any such information from the documents that are made available.	Secretariat may request to see the research contract. However actual figures may be redacted. The research contract will be treated confidentially.
273	2	**Comment:** Reference should not only be made to the Checklist, but also more clearly to the other guidance documents listed in Chapter 4 (lines 129-138). **Proposed change:** Amend to: "…into account the elements of the Checklist of Methodological Research Standards as well as be written in accordance with the other relevant guidance documents in the field (see chapter 4)."	Not agreed. The application of other relevant guidance is self-evident and does not need to be stated again.
297	2	**Comment:** The phrase "…information on the degree of the Funder's involvement…" is ambiguous. How would this be quantified? In addition, is the degree of involvement relevant if the investigator is in agreement with scientific principles developed by qualified scientific staff of Funder? Please clarify this requirement.	The text has been amended as follows: *(…) Involvement of the funder in the design of the protocol shall be specified in the research contract. (…)*
524	2	**Comment:** It appears but is not entirely clear that a study becomes an 'ENCePP study' if the organization initiating the study wishes to take advantage of the 'ENCePP Study' mark of quality, and comply with the Code of Conduct. However, earlier in 2009, EMEA speakers seemingly suggested that all post-authorisation safety studies will need to be conducted in accordance with ENCePP transparency guidances for protocols and study results. Hence, it is not clear whether all post-authorisation studies funded by EU Marketing Authorisation Holders will have to be conducted as ENCePP studies - can an MAH conduct a post-authorisation safety study (PASS) outside of the ENCePP framework?	The ENCePP study seal can be sought on a voluntary basis. Use of the ENCePP network and/or seal is optional. A statement has been added to the text to emphasise this fact.
524	2	**Comment:** The Code of Conduct should be clarified so that explicitly	Agreed as regards the voluntary nature of the Code

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1. Scope, rationale and general principles			
		indicates that not all post authorisation studies are required to become 'ENCePP studies', only those that the study initiator elects to have considered for the 'ENCePP Study' mark of quality. Clinical trials should be excluded from the scope of the Code of Conduct, as they are governed by other regulated standards - adding a second set of standards opens the door to inconsistencies and confusion.	and the ENCePP study seal. Not agreed as regards the exclusion of clinical trial from the scope of the Code. As stated in chapter 2, the Code does not replace or overrule any existing legislation or guidance, but rather complements them. It is at the discretion of the investigators (and funders) to agree to also follow the rules of the Code.
General	2	**Comment:** Does the Code of Conduct apply to post-marketing interventional clinical trials that the initiator wishes to be considered as 'ENCePP studies'?	see above
General	2	**Comment:** The Code of Conduct should be clarified whether it applies only to pharmacoepidemiology studies or if the scope includes other types of studies/registries e.g. disease registries where the aim is not to study effects of the drug but focused on the disease aspects or management.	Agreed. The scope of the Code is inclusive. Relevant parts of the Code have been amended to reflect the inclusion of all kinds of studies; however, the primary focus is pharmacovigilance and pharmacoepidemiology studies.
General	2	**Comment:** Will it be necessary to conduct a study designated as 'ENCePP' to be recognized by the EMEA, or is this only to guarantee independence and adequate scientific input? Will it be necessary to apply the Code of Conduct to studies included in the pharmacovigilance plan of an EU-RMP? What is the anticipated impact for a study not being designated as an 'ENCePP Study'? If adherence to the Code of Conduct is voluntary, how will it be encouraged?	The ENCePP study seal can be sought by investigators and study funders on a voluntary basis, thereby openly committing themselves to a maximum level of transparency with regard to relevant study information.
General	2	**Comment:** Can studies conducted outside of Europe qualify as 'ENCePP studies'? Is the 'ENCePP' designation required for studies funded by the EU MAH but conducted by non-EU parties?	In order to obtain the ENCePP study seal the (primary) lead investigator needs to belong to an entity that is included in the ENCePP Inventory of Centres and Networks. This requires that the researcher is located

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1. Scope, rationale and general principles			
			in one of the EEA/EFTA member states. There are no other geographical restrictions e.g. the data may be collected outside Europe.
General	2	**Comment:** How would the Code of Conduct apply to ongoing pharmacoepidemiological and pharmacovigilance studies?	Researchers are free to make use of the Code at any point in time for their study. However, in order to obtain the ENCePP seal, registration of the study and submission of required documentation is to be done before the study starts. For details see www.encepp.eu.
General	3	**Comment:** We wonder though if there will be a document which clarifies the protocol for dealing with the subjects of these studies as we feel that there is a role for patients and patient organisations in the facilitation of the studies.	The comment is noted. However, this is not part of the scope of the Code.
General	10 (13)	**Comment:** 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 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. BPI therefore would like	Accepted – however, no need for amendments. The study scope is inclusive though it underlines that the emphasis lies on non-interventional post-authorisation studies (see definition of post-authorisation studies and pharmacoepidemiology).

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1. Scope, rationale and general principles			
		to recommend to extent the scope of the ENCePP Code of Conduct and to include effectiveness as well as economic evaluations.	
General	9	**Comment:** Currently, Pharmacovigilance and Pharmacoepidemiological studies with a specific need in terms of clarifying drug safety concerns may be performed as post authorization safety studies (PASS). PASS are designed, performed and analysed based on agreement between the regulatory agencies and the manufacturer of the medicinal product and thus this study type seems to fulfil all requirements made in this Code of Conduct. Studies performed under the ENCePP Code would then form a second class of non-interventional studies and all other pharmacovigilance or pharmacoepidemiological studies would fall in a third class of non-interventional studies. We strongly recommend to re-consider whether three different classes of non-interventional studies are really needed (the former two are not much apart from each other in terms of transparency and scientific independence). If, apart from PASS, a standard Code of conduct for all other non-interventional studies is looked for, we strongly recommend to implement a better compromise between the natural interest and role of a funder and the other key roles including independent scientific input into it and peer review of essential documents.	Not agreed. ENCePP studies do not represent another type of non-interventional studies. However, the ENCePP study seal will identify studies conducted according to high standards in transparency and scientific independence irrespective of whether they were initially requested by regulators or not. Of note, adherence to the Code is voluntary.
General	9	**Comment:** Clinical trials do belong to the scope of this Code of Conduct (cf. lines 77 till 79). In general, no conflict between the definition of roles and their responsibilities between the Directive 2001/20/EC and this Code shall be introduced via the Code of Conduct discussed here. Specifically, the roles of the 'sponsor' and the 'investigator' are clearly defined in the Directive 2001/20/EC. Similar ('funder') or even identical terms are used in this Code of Conduct but the definitions, roles,	The Code does not replace, affect or is in conflict with any existing legislation that applies, e.g. Directive 2001/20/EC in case of clinical trials. A different terminology as in Directive 2001/20/EC is used reflecting the fact that the Code is primarily directed at non-interventional studies.

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1. Scope, rationale and general principles			
		responsibilities and duties are different. Clarification with regard to these roles for clinical trials falling in the scope of the Code of Conduct shall be provided.	
General	7	**Comment:** This document speaks only to the uniform reporting of results; it does not speak to data quality or to the analysis plan. In particular, it does not speak to the soundness of the statistical analysis. For example, observational studies often consider multiple possible claims. STROBE does not require that the number of potential claims be stated. Nor does STROBE require any adjustment of the statistical analysis to reflect multiple testing. STROBE is also largely silent on how to deal with bias and how to adjust for multiple model selection.	The aim of the Code is to provide rules and principles to maximise transparency and to promote scientific independence. Methodological aspects or scientific standards are only covered with the requirement for ENCePP studies to complete the *Checklist of Methodological Standards for ENCePP Study Protocols*. There will be separate methodological guidance, currently under development by ENCePP.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
2. ENCePP membership			
General	9	**Comment:** What is the “ENCePP Inventory of resources” and how can an applicant become a member of it?	More information on and access to the database of research resources is available at http://www.encepp.eu/encepp/resourcesDatabase.jsp. A link is provided in the Code.
101	11	**Comment:** “inventory of resources" - Does this mean that the academic investigator (lead investigator?) needs to come from an established list? Does the same principle apply if one is working in very rare disease areas?	see above
101	2	**Comment:** It is unclear what is meant by the ‘ENCePP Inventory of resources’ i.e., how the Inventory is defined, what the eligibility criteria	Agreed. A link to the ENCePP Database of Resources is provided.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
2. ENCePP membership			
		are for inclusion in the Inventory, what the criteria are for maintaining eligibility once included, etc. **Proposed change:** We suggest defining 'ENCePP Inventory of resources' and specifying the criteria for initial and continued inclusion of a particular entity/investigator in the Inventory.	
General	2	**Comment:** It appears that ENCePP members are mostly academic research groups, with a number of clinical research organisations (CROs) also selected. While these groups are known for the high quality of their pharmacepidemiological research, some drug or vaccine manufacturers also have strong research expertise in this field, with many good pharmacoepidemiologists who could qualify as ENCePP investigators. It seems that the ENCePP Code of Conduct allows 'commercial' CROs to conduct studies that qualify as 'ENCePP studies' provided that the defined criteria are met. If so, is it possible for pharmaceutical industry parties to conduct an 'ENCePP study' if adhering to the Code or can such studies only be conducted by academic centres and CRO's that are on the ENCePP list? In addition, the exclusion of organisations (e.g. pharmaceutical companies) from membership of ENCePP, which may nevertheless follow the very same principles as outlined in the Code of Conduct, appears to render them as 'non-experts'.	In order to obtain the ENCePP study seal the (primary) lead investigator needs to belong to an entity that is included in the ENCePP Inventory of Centres and Networks. This is possible for public and not-for-profit organisations, but also for-profit organisations may qualify for participation in the network provided that they perform studies commissioned by third parties and their main focus is pharmacoepidemiology and pharmacovigilance research. The Code promotes a research concept based on the principles of transparency and scientific independence. This does not mean that non-ENCePP studies automatically produce less valuable or less accurate results. It is appreciated if pharmaceutical companies decide to follow or already follow the rules of the Code.
General	2	**Comment:** What are the qualifications for the investigators to be listed in the ENCePP Inventory of Resources?	see above.
General	2	**Comment:** Is ENCePP a large network or will Funders be restricted to a short list from which they have to choose primary investigators? Will investigators/entities from non-European countries be eligible for	The funder is free to choose the investigator to conduct a particular study. However, in order to obtain the ENCePP study seal the (primary) lead investigator needs to belong to an entity that is included in the

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2. ENCePP membership			
		inclusion in the ENCePP Inventory of resources?	ENCePP Inventory of Centres and Networks (as part of the Database of Resources). The ENCePP Database of Resources is accessible at http://www.encepp.eu/encepp/resourcesDatabase.jsp. ENCePP aims at maximum coverage of the available resources in the EEA/EFTA member states. Registration in the database can be done at any time, provided that the centre meets the criteria for joining ENCePP, i.e. location in one of the EEA/EFTA member states and being a public or not-for-profit organisation; for-profit organisations might also qualify for participation in the network provided that they perform studies commissioned by third parties and their main focus is pharmacoepidemiology and pharmacovigilance research.
General	2	**Comment/Proposed change:** In order to be clear as to the non-binding legal nature of this document, it would be preferable to avoid the term "rules" and use the terms "guidance" or "recommendation" instead.	A statement has been added to chapter 2 of the Code highlighting the voluntary nature of the Code. However, in case of an ENCePP study, adherence to the provisions of the Code is mandatory.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
3. Compliance monitoring			
157-159	2	**Comment:** Please be more precise about the procedures that should be followed for monitoring of adherence and re-certification of adherence in	The ENCePP Steering Group has recognised the need to further develop approaches for compliance monitoring

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
3. Compliance monitoring			
		the case of a study of significant duration (e.g. longer than 6 months).	as one of the priority topics for future ENCePP developments. Of note, the Code will be reviewed in terms of feasibility, acceptability and compliance with its provisions after 1 year's experience or 15 ENCePP studies, whichever event comes first.
166-167	2	**Comments:** Regarding the statement "In case the (Primary) Lead Investigator decides to deviate and/or no longer follow the rules of the Code...", are there situations where this could happen without breaching the underlying contract with and/or without the agreement of the Funder?	It is agreed that this wording could create misunderstandings. The text has therefore been revised as follows: *(…) The (primary) lead investigator should inform the ENCePP Secretariat without delay if the study deviates from and/or no longer follows the rules of the Code. (…)*
166, 176, 178-179, 241-245	2	**Comment:** References are made throughout the document that the ENCePP Secretariat will arbitrate. However, there are no statements on the membership of the Secretariat and a process for arbitration; self-regulation by investigators (e.g. line 166) is insufficient. Please state more explicitly the process for arbitration of disputes on breaches of the code.	Arbitration and decisions concerning breaches will be made on a case-by-case basis and will normally be referred to the ENCePP Steering Group, whose composition is publicly available.
General	2	**Comment:** To meet requirements for ENCePP may be difficult within timelines. Also auditing and publication of independent assessment of how ENCePP network is monitored is essential.	The ENCePP Steering Group has recognised the need to further develop approaches for compliance monitoring as one of the priority topics for future ENCePP developments. Furthermore, the Code will be reviewed in terms of feasibility, acceptability and compliance with its provisions after 1 year's experience or 15 ENCePP studies, whichever event comes first.
General	2	**Comment:** Despite the obvious credentials of the ENCePP membership,	Partly accepted. At this current state, the study

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3. Compliance monitoring			
		it is open to question whether it is ethical for the same organizations and individuals who receive financial compensation for the conduct of post-approval studies to decide what are sound study methods and ethical principles in addition to deciding which organizations and individuals meet these standards. It would be helpful if the inventory of ENCePP-approved members were awarded this status by a group which is external to ENCePP. The same logic would apply to the review of protocols. Instead of signing a statement declaring that a protocol meets the standards, this evaluation would be better left to an external group of experts whose membership precludes compensation for ENCePP endorsed studies. Measures like this would lend greater legitimacy to the phrase "in compliance with ENCePP standards". Otherwise, in one sense, it is simply a form of self-accreditation.	protocol will not be evaluated by an expert group other than foreseen by the study team themselves. The qualification of a study for the ENCePP study seal is based on the researchers' declaration to comply with the provisions of the Code, especially the registration of the study before its start, and the provision of certain documentation (see http://www.encepp.eu/encepp_studies/index.html for details). However, the ENCePP Secretariat has recognised the need to further develop approaches for compliance monitoring as one of the priority topics for future ENCePP developments.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
4. Research contract and study funding			
General	2	**Comment:** What are the potential legal ramifications of having the content of the funding contract available publicly?	The research contract does not need to be made publicly available.
96	2	**Comment:** The 'Main Principles' should acknowledge that investigators will receive financial compensation.	Partly agreed. Chapter 5 and 6 include relevant related provisions.
105-113	2	**Comment:** Funding arrangements and details should be included in the CoRe requirements.	The Code already includes some provisions related to remuneration and the research contract.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
4. Research contract and study funding			
154	2	**Comment:** Financial details relating to the study should be made available on the website.	Information on the funding sources and the proportion of the total study funding is to be provided in the ENCePP Register of Studies.
181, 196, 214	9	**Comments:** Three types of contracts are mentioned in the Code: “contract” (Line 188), “research contract” (Line 196) and “funding contract” (line 214 and chapter 8). **Proposed change (if any):** Clarify whether research contracts and contracts are different entities and the relationship between them and the funding contract.	Agreed. The terminology has been harmonised to ‘research contract’ only.
188	2, 8	**Comment:** Regarding “A contract shall be concluded between the investigator and the Funder…”, in general contracts are established between two institutions, one being the institution to which the investigator belongs and the other the study Funder. Also, in line with the terms used further down in the document, the ‘Investigator’ should be changed by ‘(Primary) Lead Investigator’ or the ‘Coordinating Study Entity’. **Proposed change:** Amend to: “A contract shall be concluded between the (Primary) Lead Investigator or the Coordinating Study Entity and the study Funder…”.	Agreed.
196	14	**Comment:** What is the "relevant information" on the research contract? Will this include fees paid?	More detailed information is provided in chapter 7 and 8. The full content of the research contract should be made available on request but actual figures may be redacted.
234	2, 8	**Comment:** Usually a payment schedule is linked to a timetable of milestones/deliverables and deadlines, and inclusion in contract is a standard. An additional bullet concerning this should be added prior to	Not agreed. However, the inclusion of the payment schedule is not excluded.

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4. Research contract and study funding			
		the payment scheme.	
237	2	**Comment:** Depending on the study design, there may be no “interim results”. Amend to: “A communication strategy for final results and for interim results (if applicable).”	Agreed.
240	2	**Comment:** Financial details should be specified. Add a bullet: “The detailed description of all charges and costs”.	Not agreed. However, information on the funding sources and the proportion of the total study funding is to be provided in the ENCePP Register of Studies.
292-294	2	**Comment:** Regarding "The funding contract between (Primary) Lead Investigator or Coordinating Study Entity and the Study Funder shall specify the negotiation procedure to achieve agreement on the Study Protocol.", it is preferable to replace "specify" by "outline" as it is otherwise not clear how specific this must be. Also, please delete "negotiation" (which sounds quite awkward in this context) and only keep "procedure". **Proposed change:** Amend to: "The funding contract between (Primary) Lead Investigator or Coordinating Study Entity and the Study Funder shall outline the procedure to achieve agreement on the Study Protocol."	Agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
5. Role of investigator - including conflicts of interest			
142-143	2, 12	**Comment:** In publications, the section ‘conflicts of interests’ should make reference to the Code – the meaning of this sentence is unclear.	Partly accepted. The statement has been amended and

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
5. Role of investigator - including conflicts of interest			
		Is adhering to the code a conflict of interest or is it a 'mitigating' factor? **Proposed change:** Add to end of sentence: "….should make reference to the Code as it regards the requirements around scientific independence."	moved in the chapter on publication.
198 - 218	2	**Comment:** There is ample mention of transparency - it is at the foundation of this effort - with respect to the centres of excellence who conduct these approved studies, and the design and conduct of studies. An element which is perhaps under-emphasized is explicit provisions for disclosure of financial compensation details. While it may be considered important to provide public access to protocols and study methods, it is equally important in the spirit of transparency for full and upfront disclosure of compensation for these studies. Even the appearance of a financial conflict of interest should warrant complete transparency with respect to the details of compensation, both to the individual investigator(s), and to their respective organizations.	Not accepted. In the interest of transparency, the Code requires all parties involved in the conduct of the study to declare all existing direct or indirect interests of a commercial, financial or personal nature that might impact their impartiality in relation to the study. While it is appropriate to ask for the source of funding of a study, it is unreasonable to require details of the compensation, i.e. actual financial figures. To avoid misunderstandings, the wording of the Code has been revised and a new chapter on declaration of interest has been introduced.
198 -218	2	**Comment:** Failure to fully disclose financial arrangements publicly would only serve to erode public trust in this regard and therefore undermine one of the main objectives of the Code. A solution to the issue of transparency of compensation would be to post publicly the amount of compensation for services rendered: both overhead costs received by the organization as well as direct compensation to the principal investigator(s). Are there other forms of support other than direct financial funding that need to be considered as something to be disclosed?	Not accepted. In addition to the Code's requirement for the researchers to declare all potential conflicts of interest, registration of the study in the ENCePP Register of Studies requires entering information on the source(s) of the funding and the respective proportion of the total funding.
198 - 218	2	**Comment:** Investigators should list all past and present consultancy agreements with industry parties.	Not accepted. The Code requires all parties involved in the conduct of the study to declare all interests that

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			might impact their impartiality in relation to the study.
251	2	**Comment:** Regarding the statement "Any Conflict of Interest among the Investigators should be declared and be made publicly available", there will always be a conflict of interest whenever an investigator performs a study for compensation. In many instances, the members of ENCePP are not charitable organizations, but act as business consultants.	Partly accepted. The rules as regards conflicts of interest have been amended and clarified. In addition to the requirement for all parties involved in the conduct of the study to declare all existing direct or indirect interests of a commercial, financial or personal nature that might impact their impartiality in relation to the study, the new chapter on declaration of interest lays down the conditions for (non)participation in the study as follows: *(…) Once the protocol has been finalised, no person with a financial interest in a particular outcome of the study shall take part in any study activity that could influence the results or interpretation thereof. (…)*
General	7	**Comment:** The most commonly discussed shield against bias in scientific practice is disclosure of financial conflicts of interest (COI). Such disclosure is necessary because the public wants it. Yet, a growing cadre of scientists question the value of disclosure policies. These dissenters note that such policies may actually increase biased behaviour among some persons judging scientists' credibility by their associations is tantamount to McCarthyism financial interests are neither the sole nor necessarily the most compelling motives for CoIs and judging credibility of scientific conclusions based on characteristics of the scientist offering them is antithetical to the essence of science, which should rely on data and deductive reasoning alone. I add to this list that disclosure does nothing to buttress the validity of the scientific information and conclusions produced. Given this, how can we ensure	The Code lays down a set of transparency measures, one of which is to declare potential conflict of interest. However, adherence to the rules of the Code alone does not automatically guarantee high quality research and validity of the results. Nevertheless, for ENCePP studies it will be easier to assess whether or not a study has been conducted in a methodologically sound way as more information (registration of the study, Checklist of Methodological Standards, etc) will be available early on.

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		the validity of scientific information and conclusions in the face of the potentially biasing influences such as personal predilection, financial interests, philosophical leanings, and the search for personal aggrandizement? The answer lies in the methods of science itself.	
322	14	**Comment:** It should be made clearer just what constitutes a "financial interest." Does 1 Euro constitute a financial interest?	The Code only requires the declaration of interests and sets out conditions for (non)involvement of people with a conflict of interest. It is true that in order to confirm a conflict of interest it is necessary to evaluate the declared interest. It will be discussed whether ENCePP can provide further guidance.
327	2	**Comment:** It is not clear whether this means the (Primary) Lead investigator or every investigator participating in the study. Is the 'Investigator' here the same person who is usually referred to in this document as the '(Primary) Lead Investigator'?	The statement refers to every investigator as regards his assignment in the study.
327	2	**Comment:** Please clarify the meaning of "responsible" (e.g., vs. acceptable).	No clarification is required.
328	2, 8	**Comment:** The assignment of the investigator should include also the preparation of study reports and particularly the final study reports. **Proposed change (if any):** "… the interpretation of the study results, and the preparation of study reports and publication of the study outcome."	Agreed.
331-332 and 332-334	2	**Comment:** Where shall the declaration of interests be done (compare also 251-252)?	When registering the study in the ENCePP Register of Studies, researchers have the opportunity to also make available the declaration of interests.
332	2	**Comment:** It is not clear what may be 'financial interest in the results	Partly agreed. The wording has been revised and a new

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		of the study' but clearly this could go beyond the Funder and potentially could include the Lead Investigator. This meaning should be clearly specified or the sentence should be deleted. Of course, all conflicts of interests and roles during the research process should be declared in a transparent manner. This is generally provided for by disclosure of interest and/or affiliations. If pharmaceutical companies can conduct clinical trials, it is not clear why they could not be involved in the conduct of observational research. Again, if the document is intended to describe the specific process where the funder wishes to have a researcher answer a very specific question independently, this clause may be valid for the Funder (by definition), but the broad statement here is mainly unclear. Arguably the Principal Investigator has both intellectual and financial interest in the results of the study - how does the Code propose this is regulated?	chapter on declaration of interests is introduced. Of note, adherence to the Code is voluntary and the decision to apply for the ENCePP study seal is at the discretion of the researcher and funder.
333	2	**Comment:** It is not clear what "...actively participate in the conduct of the study..." means and which phase between the definition of the study protocol and the publication of the final study results this refers to. This requires clarification in order to avoid an ambiguity, in particular for the Funder(s) of the study who will normally have a financial interest in the results of the study.	Accepted. (See new chapter on declaration of interest)
347-350	2	**Comment:** Steering Committee members should reveal any potential conflicts of interest. However, to require exclusion from the Committee if any conflict of interest exists may exclude the most qualified experts. The extent and significance of such a conflict should be evaluated by Funder and Investigator on an individual case basis. Otherwise, will it be possible to find enough suitable experts in this instance? **Proposed change:** Amend to*: "If a steering group or a scientific*	Partly agreed. Indeed all Steering Group members are required to declare their interests. Whether or not the declared interests would impact their impartiality towards the study requires an evaluation process. The Code does not specify the process for appointing the Steering Group members.

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		oversight committee is foreseen for the purpose of providing scientific advice and guidance and/or to oversee the conduct of the study, the members of this steering group shall declare existing direct or indirect interests of a commercial, financial or personal nature. Selection of the most qualified individuals to sit on a steering group or scientific oversight committee shall be by collaborative agreement between the investigator and the Study Sponsor. Input from regulatory authorities may be helpful in selecting qualified individuals."	
349	2	**Comment:** As written, it sounds as if all investigators would have conflict as they would demand payment to conduct a study, which would mean that no epidemiology study could be conducted under ENCePP rules. **Proposed change:** Amend to" "...declare pre-existing direct or indirect interest..."	Agreed. The wording has been revised and a new chapter on declaration of interests is introduced.
350	2, 8	**Comment:** Especially in Study Steering Committees, it is difficult to appoint individuals with no conflict of interests, especially as in some areas (i.e. epidemiology or orphan diseases) experts are rare and hard to get and mostly a previous collaboration had been established which would already pose a conflict of interest. **Proposed change:** Add after last sentence: "If this is not possible any actual or potential conflicts of interest should be disclosed".	Not agreed. Members of the Steering Group that take part in the decision making should not have conflicts of interests.
350	8	**Comment:** Conflicts of interest may have several different origins and may be difficult to determine. It should be enough that members of the steering group declare any potential conflicts of interest in a transparent manner consistent with practice in all scientific research. The role of 'observer' in a steering group may be somewhat unclear vis a vis the	Partly accepted as text has been revised. It is possible for observers to the Steering Group to become authors of publications of the study as long as the ICMJE Uniform Requirements for authorship are met.

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		role in the performance of the study. Thus, expert representatives of the Funder may provide substantial important information for the design as well as the interpretation of the results in the role as 'observer'. This may be essential to the study and may warrant co-authorship according to the Vancouver rules (cf. line 399-402). It would be better to have this transparently stated rather than this role labelled as 'observer'. **Proposed change:** Delete: "...and should only be appointed if no Conflict of Interest exists" and "Other parties and stakeholders..... in the absence of observers", or revise the definition and role of the 'observer'.	
General	7	**Comment:** Anyone doing this work will have an interest. If they take proper time, they will be compensated in some way, either financially or by other considerations. It is the responsibility of the person reading the report to make due consideration of their compensations. In theory, anyone with the proper intellectual qualifications is eligible to be on a steering committee.	A new chapter on declaration of interests has been introduced and the provision on (non)participation of people in relation to their interests has been revised.
General	2	**Comment:** In the broader context, the potential for conflicts of interest touches many stakeholders beyond the biopharmaceutical industry. For example, a potential investigator's desire to obtain support (financial or otherwise) for a study could create a conflict if that investigator exaggerates concerns regarding a particular risk or the ability of a particular data source to address a particular risk. Would there be a situation in which a PASS requirement for a particular product could arise from the direct interaction of such an investigator with a regulator, independent of the MAH? This could divert scarce resources from more impactful work. In the spirit of transparency and to avoid the perception of possible conflicts of interest, perhaps a representative of the	Regulatory procedures generally imply interaction with the MAH in advance of the request for a post-authorisation safety study (PASS).

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		interested MAH should be invited to participate in all relevant discussions between regulators and potential investigators.	
General	2	**Comment:** In guidelines concerning studies before approval of medicinal products in Europe and worldwide, it is good practice to make sure that people with sufficient training and experience from all relevant scientific fields are involved (e.g. Biostatisticians, compare ICH E9). It seems to be advisable to explicitely mention in the given field of applications the mandatory minimum involvement of Epidemiologists, Pharmacoepidemiologists/Drug Safety Specialists and Biostatisticians. Currently only the general training requirements of the Lead Investigator are mentioned (see Annex 1).	The Code requires the involvement of individuals with appropriate scientific background. Given the wide scope of ENCePP studies, it is not found useful to further specify the type of expertise.

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6. Role of study funder – protocol agreement, study conduct and conflict of interest			
246-249	1, 2, 9,12	**Comment:** To exclude the Study Funder as an equal partner in the study design is contrary to the concept of open scientific dialog and transparency. Usually all co-authors are responsible for the research. Similarly in this case, the PI, any intended co-authors from the ENCePP centre, the Funder, other interested parties or other collaborators should carry a joint responsibility. This will also imply that all participants intending to co-author and present the results should have participation in the research process. **Proposed change:** The content of the assigned research project, the design of the protocol, including the analysis plan, shall be established	Accepted.

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		by agreement between the Study Funder and the investigator.	
252-255	2	**Comment:** The investigator's knowledge of any "preliminary results" could lead to investigator bias, and this issue should be thoroughly addressed in the study protocol. In some cases, an external DMC not involved with the study conduct should be employed to review interim and preliminary results as needed so as to avoid investigator bias. In cases in which the investigator does have knowledge of "preliminary results", there is no justifiable basis whatsoever for keeping that information from the Study Funder.	The respective text has been amended and provides for sharing of 'final or scheduled interim results'.
255	14	**Comment:** Provision that the researchers should not communicate preliminary findings to the Funder may be problematic: if the Funder has regulatory obligations, it is in everyone's best interest to know findings as early as possible.	Accepted. The following text has been added to chapter "Rights and Obligations of the Investigator and the Study Funder": *(…) In the event of a potential serious public health issue, relevant regulatory authorities and the funder should be informed without delay. (…)*
270-308	1	**Comments:** Protocol development should be a collaboration between investigator, funder and health authorities.	Partly accepted. The principles of protocol agreement are explained in chapter 10. The Code does not exclude the funder's involvement. However, the wording has been adjusted to avoid misperception. In addition, the interaction with competent authorities has been addressed.
270-308	2,12	**Comment:** The Funder will in general contribute scientifically/medically in a very significant way to the protocol, hence may be considered as co-author of the protocol.	Accepted. The Code is not in conflict with this statement.
270-308	2	**Comments:** Written agreement from study funder should be required before investigator deviates from protocol.	Partly accepted. Except for changes to protect the safety of study subjects, changes to the protocol should

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			be agreed in writing with the Funder before taking effect.
300-302	1,2	**Comments:** If the investigator has final responsibility for the content of the study protocol, the funder may find him being compelled to fund a study which they believe to be suboptimal, flawed or does not meet the objectives of the health authorities.	Partly accepted. The scope of the study (main objectives and a brief description of the intended methods of the research) should be addressed in the research contract (chapter 8). However, the following text was included to complement the rules for protocol development with the involvement of competent authorities: *(…) If the study has been requested by a particular competent authority, all parties involved in the development of the protocol are responsible for ensuring that the study meets the requirements of the competent authority. In these circumstances, the competent authority might be involved in the development of the protocol according to its regulatory practices. (…)*
309-323	2,12	**Comments:** Data shall belong to both investigator and funder for purposes of future meta analyses.	Accepted. The Code specifies that data ownership should be defined in the research contract. This requirement has been complemented by the statement that, in principle, data shall belong to both the investigator(s) and the funder.
331-334	9	**Comment:** For all other pharmacovigilance or pharmacoepidemiological studies, even when following this new code of conduct, the peer review and the involvement of an independent scientific primary lead investigator shall be sufficient. Complete exclusion of the funder from the content of such a study seems to be not a balanced requirement in	Partly accepted as there is no full exclusion of the funder from the conduct of the study. The Code lays down the rights and obligations of researchers and funders of studies including conditions for the (non)participation in the conduct of studies in relations

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		the context of the existing regulations. Re-consider the role of the funder in relation to all the other roles defined in this version of the code of conduct and try to find a better balance between them, still keeping scientific independence and transparency in mind. As long as the independent role of the primary lead investigator and a peer review of relevant documents of an ENCePP study are maintained, the full exclusion of the funder from the conduct of the study can and shall be avoided.	to conflicts of interest.
331–334	2	**Comment:** It should be clarified that qualified representatives of the Study Funder may provide unsolicited expert advice when there is no financial interest in the study outcome, i.e., no tie between the study result and any financial remuneration. **Proposed change:** All parties to be involved in the conduct of a study shall declare existing direct or indirect interests of a commercial, financial or personal nature. Any party with a financial interest in the results of a study should not actively participate in the conduct of the study. Qualified individuals representing the Study Funder (employees or consultants to the Study Funder) may provide expert advice, provided that it is documented that there is no relationship between the study outcome and any remuneration to that individual.	Partly accepted. A new chapter on declaration of interest was introduced to clarify the conditions for (non)involvement of individuals in light of any existing interests. The Code does not exclude the funder from providing advice or comments.
332-334	9	**Comments:** This is a very strong statement about the participation of parties with financial interests in the results of the study. This seems to be much more exclusive than e.g. the definition of the coordinating study entity (lines 520 till 525) and the statements about the protocol agreement (lines 291 till 302). Moreover, we do not see a need to handle it like this in every ENCePP study. If there is a strong need, a pharmacovigilance or pharmacoepidemiological study shall be performed	Partly accepted. A new chapter on declaration of interest has been introduced clarifying the conditions for involvement of individuals in the conduct of a study.

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		in a way the study funder has no solely influence on the design, conduct and analysis of it, this can already be achieved via a post authorization safety study (PASS) where the regulatory bodies have the possibility to strongly influence all those aspects. For all other pharmacovigilance or pharmacoepidemiological studies, even when following this new code of conduct, the peer review and the involvement of an independent scientific primary lead investigator shall be sufficient. Complete exclusion of the funder from the content of such a study seems to be not a balanced requirement in the context of the existing regulations. **Proposed change:** Re-consider the role of the funder in relation to all the other roles defined in this version of the code of conduct and try to find a better balance between them, still keeping scientific independence and transparency in mind. As long as the independent role of the primary lead investigator and a peer review of relevant documents of an ENCePP study are maintained, the full exclusion of the funder from the conduct of the study can and shall be avoided.	
332-334, 347-350 & 352-355	2	**Comment:** Any party with a financial interest needs to be defined clearly. It may be too restrictive to require an investigator to own no stocks of an entity that the study results may have a direct or indirect impact upon. In addition, Funder representatives with proven expertise and scientific knowledge in the area of the research (e.g., Lead Epidemiologists) should be full partners in protocol design and should not be precluded from actively participating in the conduct of the study. Therefore, given that the Code requires declaration of all potential direct or indirect interests of a commercial, financial, or personal nature, we suggest that such Funder representatives should have a right to participate in the Study Steering Group meetings as equal members rather than invited observers, and should be involved in the decision-	Not accepted. Please refer to the new chapter on declaration of interest in which it is stated that once the protocol has been finalised, no person with a financial interest in a particular outcome of the study shall take part in any study activity that could influence the results or interpretation thereof. Of note, particular attention to the definition of direct and indirect interests will be given at the time of the first revision of the Code.

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		making. We suggest changing the Study Steering Group membership requirement from “no Conflict of Interest exists” to “any potential Conflict of Interest is declared”.	
335-360	2, 12	**Comment:** Maximum transparency should include the scientists of the Funder. Data analysis plan should only be changed after discussion and approval with the scientific oversight committee and justification be provided in the final study report and publication. The scientists from the Funder should be entitled to participate to the scientific steering committee as full members.	Partly accepted. The data analysis plan should be integrated or annexed to the study protocol. The Code has been amended to provide for consultation of the funder in case of changes to the protocol.
346-360	2, 12	**Comments:** The funder should be allowed to participate in the study steering group provided there are no conflicts of interest and they should be limited to 1 or 2 representatives but not assume the role of chair.	Partly accepted. The steering group should be an independent body to guide on the conduct of the study. The Code does not exclude the funders’ participation in discussions of the steering group, but like other individuals with a conflict of interest, may only participate as invited observer and cannot be involved in any decision-making steps.
352-355	7	**Comment:** The protocol stands on its own once determined and should be the result of deliberations of all interested parties. The study funder should be a party to all deliberations and decisions on the protocol.	The Code does not exclude participation of the funder in the development of the protocol.
355-357	2	**Comment:** Please clarify this sentence with the suggestion below. **Proposed change:** “The Study Funder may only be represented by a person with proven expertise and scientific knowledge in the area and/or methods of the research.”	Accepted.
355-357	7	**Comment:** It is up to the Study Funder to select their representative. All representatives should provide a CV as part of the study protocol. The consumer of the report should judge the qualifications of the	Not accepted. Like the members of the Steering Group who will be appointed for their expertise in one or another area, the representative of the funder should

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		individuals.	as well be a person with proven expertise and scientific knowledge in the area and/or methods of the research even if he/she may only participate as observer.
388	11	**Comment:** Does this exclude to have both academic authors and authors from the study funder?	Authorship should be determined in line with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors. At the same time, the Code provides the basis for independent publications by the investigator, but this does not exclude the funder from being an author if he/she meets the criteria.
521-525	9	**Comments:** We don't know whether this was planned like this, as in lines 524 till 525 the possibility that the primary lead investigator may be the person representing the Coordinating Study Entity and (line 521 till 523) says that the Coordinating Study Entity can even be identical to the funder. As a consequence, one could assume that the primary lead investigator could be a person representing the funder. In this case we do not have major objections as this keeps the funder more or less in the role of planning and conducting the study. However, this is in sharp contrast to lines 331 till 334 of chapter 12, where it is stated that any party with direct or indirect interest in the result of the study shall not play an active role in an ENCePP study. **Proposed change (if any):** Clarify how the three sections shall be interpreted and consider to maintain a more central role of the study funder while establishing the primary lead investigator as an independent peer review role.	Accepted as regards the need for clarification. A new chapter on declaration of interest was introduced to clarify the conditions for (non)involvement of individuals in light of any existing interests. The reference to the study funder in the definition of coordinating study entity was deleted to avoid confusion.
General	2	**Comments:** For certain types of studies eg de novo data collection multi centre, there may not be a lead investigator and the funder bears	Not accepted. If the study is conducted by the funder, i.e. the funder and the investigator being the same

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		all the responsibility.	person, it cannot fulfil the criteria of the Code regarding (non)involvement of people with a financial interest (see new chapter on declaration of interest).

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7. Study registration and availability of study information and data			
111	2	**Comment:** It is unclear why all ENCePP studies should be registered into an e-Register with the name "ENCePP Register of Post-Authorization Studies". Given the broad definition ("any other type of observational research" and "Clinical Trials"), ENCePP studies may also include pre-authorisation activities.	The respective chapter has been revised. Registration remains mandatory. Studies for which the status 'ENCePP study' is applied for must be registered in the ENCePP Register of Studies.
114-138	2	**Comment:** Do any ENCePP centres have non-EU data? If so, do EU regulations apply to these data?	The Code applies regardless of the origin of the data.
151, 154 and 157	9	**Comment:** What is the timeframe between submission of documentation to the ENCePP Secretariat and confirmation of the eligibility of the study to the Code of Conduct? Within which period will the study material be made publicly available by the Secretariat from the moment study eligibility status is granted? As e.g. the protocol development is part of the duties of the Primary Lead Investigator, the funding contract needs to be finished and signed before submission of the study protocol to the ENCePP Secretariat. Any outcome of the submission process can thus not be anticipated in the funding contract.	Not agreed. The ENCePP label is independent from the timing of the study start as long as the study has been registered before start of data collection. Likewise, the intention of the investigator and funder to follow the rules of the Code can be seen as independent of granting the ENCePP status; therefore 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*" can be

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		So the order of these steps needs to be looked at more carefully.	included in the contract independent of the evaluation of the ENCePP study status.
153-155, 108-109, 149, 196-197, 206-209, 304	2	**Comment:** Some study protocols might contain confidential information and details on new techniques, questionnaires under development and/or new statistical analysis that are intellectual property of the investigator. If all ENCePP study protocols need to be published, we suggest that there exemptions should be allowed when they contain innovations in methodology which may be considered propriety – these protocols could be published after study closure rather than before study initiation, so that new ideas, techniques or methods are kept confidential until the end of the study and the investigators can then publish the complete information in scientific journals. Overall, we prefer that you publish a high level summary of the study protocol, or a study synopsis, and not the full study protocol. In addition, clarification is required as to when the study protocol will be made public. **Proposed change:** Amend to: "The declaration, the checklist and an abstract of the study protocol will be made publicly available on the ENCePP webpage."	Accepted. The provision for availability of the study protocol has been revised. Whilst the version of the study protocol at the time of study registration still needs to be uploaded in the register, it will not be available to the general public unless the investigator chooses so to do. However, after the final study report becomes available, the last version of the protocol needs to be provided and both the initial and last version will be made publicly available.
198-218	2, 12	**Comment**: There is no added value to make systematically public all exchanges and comments on draft documents: they should be available only if requested (e.g. under 'Freedom of Information').	Open access should be provided as specified in the Code; there is no request to make systematically public all exchanges and comments, but on request.
208	2	**Comment:** If protocol information is to be made public, then the data fields of the ENCePP registry should be consistent with other regulatory requirements and the WHO 'core' information. This harmonisation will engender better understanding by public if it is to utilise public registries. Disclosure of the full study protocol may contain highly sensitive/confidential proprietary information (as commented above). It	The ENCePP Register of Studies has been conceived taking into account the WHO Trial Registration Data Set but with a view to capturing primarily post-authorisation non-interventional studies. However in addition to the registration, for ENCePP studies, in line with the principle of maximum transparency, also the

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		should be sufficient to disclose protocol information consistent with EudraCT and WHO requirements.	protocol needs to be provided. Both the version at the time of study start and the final version will need to be made public after the final study report.
210	2	**Comment:** It is important that once registered, the information must be kept accurate & updated. However, to disclose the justification for the change may be highly sensitive or confidential. It should be sufficient to ensure accuracy of the record of changes, and to require disclosure of the justification for changes only when the final results are presented.	Agreed. The provisions of the Code have been revised.
213	8	**Comment:** It should be clear who and under what conditions can request this information. Will conducting additional/re-analyses by external parties possible/encouraged?	More details on access to study information and study data is provided in the specific chapters of the Code. See also the recently published “Implementing Rules on Access to Data” on the ENCePP website at http://www.encepp.eu/code_of_conduct/index.html.
213-215	5	**Comment:** This para may be interpreted as all study documentation and data should be available to anybody at anytime. It is not described whether the documentation should include raw data and preliminary analyses and it is unclear what “non-identifiable study data” means. An important question is whether all interim study findings are to be public, even when the analysis is in progress.	The provision has been revised. Access should be provided on request and as further specified in the following chapters of the Code. It has been clarified that access should be provided to scheduled interim findings and the data set used for analysis only.
213-216	2	**Comment:** Is it appropriate to make unpublished data and interim results available to the public? Misinterpretation and misuse of data (for personal gain or to advance a position of special interest erroneously based on premature findings) could flourish in this setting, potentially becoming a liability. Furthermore, the phrase "...all interim and final study findings.." should apply only to those interim findings that will have been expressly defined in the study protocol. Please clarify this	Accepted.

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		sentence with the suggestion below. **Proposed change:** Amend to: "...all scheduled interim…"	
213-216	2	**Comment:** The Code includes “Agreement to make available on request any information including the content of the funding contract, reports from independent reviewers, non-identifiable study data, all interim and final study findings irrespective of positive or negative results”. This seemingly fails to take into account that the contract may contain confidential or financially sensitive information. The Code of Conduct should allow for the right to delete any such information from the documents that are made publicly available. Does this statement mean that such information should be made available ‘upon request’ by the ENCePP Secretariat or by any other party, e.g. EU and non-EU regulators, health care professionals, competing companies, the press, the general public, etc? Does the standard to share such information also apply to research funded by government or charitable foundations? If not, why not?	Agreed. The provision concerning access to the research contract has been amended to allow for redaction of actual financial figures. It applies to any kind of agreements between investigators and funders. A definition of ‘research contract’ has been introduced to avoid misunderstandings as regards publicly funded research. Access should be provided upon request in line with the provisions of the specific chapters of the Code.
213-216	6	**Comment:** Please clarify which parties can request the information described in lines 213-216, and under what conditions they can request this information. In addition, please clarify what is meant by ‘all interim and final study findings’. Providing study data to any interested party appears potentially onerous if done on multiple occasions for requests from different parties. In addition, such requests may be in conflict if the data is considered proprietary. If additional analysis on the data is desired, we suggest an additional provision for specified analysis by a third party.	It is agreed that the conditions and purposes for providing access to data need clarification. To this end, the chapter on access to data has been revised and a separate document “Implementing Rules on Access to Data”, available at http://www.encepp.eu/code_of_conduct/index.html, has been prepared.
213-216	6	**Comment:** The guidance is very clear with regards to the publication of results, i.e. all data have to be made available to anybody anytime. It is	It is agreed that the conditions and purposes for providing access to data need clarification. To this end,

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		felt that this may in some instances work against the valued tradition of peer-reviewed journal publishing. A clause on disclosure of data might be purposeful in these cases. Additionally the situation regarding data obtained under licence from a third party for the purposes of conducting the study should be clarified.	the chapter on access to data has been revised and a separate document "Implementation Rules on Access to Data", available at http://www.encepp.eu/code_of_conduct/index.html, has been prepared.
214	14	**Comment:** Making non-identifiable study data available to anyone who asks for it may be problematic, depending on the data source. Data owners may not agree to this.	The provision has been amended and its implementation is addressed in more detail in a separate document (see above).
269	2	**Comment:** This sentence is ambiguous. What changes need to be made to the Register? All of them, or only significant changes? What time frame for notification is acceptable. **Proposed change:** We suggest that a reasonable time frame for notification of significant changes is stipulated, and some examples given of significant changes.	Not agreed. More details on when and how the entry in the register should be amended are provided in the specific sections of the Code.
309	14	**Comment:** Data ownership is overly simplified. For example, for company-sponsored clinical trials, the company typically owns the data. However, for a study using GPRD data, GPRD owns the data, even if the study is designed and conducted by independent researchers.	This provision refers to data generated under the study, i.e. not pre-owned by a data provider.
316	14	**Comment:** It should be clearer just what data could be available to independent parties on request. This is especially true for observational studies using electronic health care data, where the starting point is a massive database that is not feasible to make publicly available.	Agreed. The respective provision has been amended and its implementation is addressed in more detail in a separate document (see above).
321	2	**Comment:** For how long does this responsibility exist? How can the PI have this responsibility if the Funder owns the data?	This is to be decided on a case by case basis taking into account applicable regulations and guidelines.

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321-323	9	**Comment:** This sentence is not completely clear, specifically what is meant by "…all data collected and generated in a study" and how the primary lead investigator shall and can "ensure" that they "are recorded in an accurate way…". Explain exactly the meaning of "data generated". What are the means to ensure the "recording in an accurate way" for the "purpose of verifying the published results …" and how a primary lead investigator can be put into a position to do this.	The respective text has been amended.
359-360	2	**Comment:** Regarding the statement "The composition of the steering group including observers participating in its meetings should be made publicly available.", Is this compatible with applicable data privacy rules? How will it be made publicly available?	There is no conflict with data privacy. One possibility to make this information public will be provided by means of the ENCePP Register of Studies.
384	7	**Comment:** Electronic data sets should be publicly available so additional analysis is to be expected by any interested party. Any analysis not specified in the protocol should be clearly labelled as a secondary analysis.	The revised Code requires providing access to the analytical data set as well as a description of the transformation of raw data needs to be provided upon request. The chapter on access to data has been revised and a separate document "Implementing Rules on Access to Study Data", available at http://www.encepp.eu/code_of_conduct/index.html, has been prepared, defining in more detail the conditions for access to data.
416	7	**Comment:** Referee or scientific committee reports should be made to the Lead Investigator and Funder and be considered confidential. The final report is considered the public statement of the results. The detailed protocol, the electronic data and the analysis code should be public in addition to the final report.	Partly agreed. Access to scientific comments and/or reports should be possible for transparency reasons. Access to data should only be provided upon request and under certain conditions – see <link>.
427	2, 5	**Comment:** Regarding the statement "...any data produced during the study shall not be regarded as Confidential Information", is this meant	The provision concerned has been amended for the sake of clarity as follows:

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		to apply also to any raw data?	*(…) Data and results derived from a study shall be regarded as confidential only in relation to relevant data privacy law. (…)*
General	7	**Comment:** Publicly sharing data offers one examplative countermeasure. When data are public, no one need take analyses on faith. Anyone with the skills can conduct their own analyses, draw their own conclusions, and share those conclusions with others. This is more constructive than simply casting doubt on the analyses' integrity because of the analyst's affiliations. The movement toward open data has begun. NIH, Science, the Nature journals, and other journals all have policies encouraging or mandating it. Still, compliance with data sharing is challenging.	The Code requires researchers to grant access to the study data upon request. The conditions and purposes for providing access to data are further clarified in the "Implementing Rules on Access to Study Data" which is available on the ENCePP website at http://www.encepp.eu/code_of_conduct/index.html.
General	7	**Comment:** Funder, lead investigator, the statistician and 3rd party payers all need access to an electronic copy of the data. Oversight is best provided by public data access.	Not agreed. However, it was decided that the conditions and purposes for providing access to data need clarification. To this end, the chapter on access to data has been revised and a separate document "Implementation Rules on Access to Data", available at http://www.encepp.eu/code_of_conduct/index.html, has been prepared.
General	5	**Comment:** We have no major concerns regarding the code draft since it proposes a set of study formalities, most of which are already applied in research contracts. However, we do question the proposals to make the study protocols fully public and the suggestion to document all changes in the analytical approach during the progression of a study. As epidemiological research, particularly the arrangement of data and analyses, is an explorative and iterative process it is very difficult to detail each expected step in the analysis in advance since very much	Partly accepted. The study protocol should be submitted with the application for an 'ENCePP study', however it will not be published until after the final study report. Changes to the protocol should be documented and those changes that might affect the interpretation of the study shall be identified and reported in publications and the register of studies and the checklist of methodological standards should be

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		depends on preliminary findings. The preliminary findings will often result in changes in the analytical approach. We are in favor of transparency but to demand open access to all details and steps in the study process might have the opposite effect of what was intended. There is a risk that such transparent study protocols from the very beginning would be less detailed and even ambiguously written. **Proposed change:** We therefore suggest that only the synopsis of a study protocol should be public and that documentation of changes is limited to major ones such as an extension of the study or a completely new design.	amended as necessary. Once the final study report is available, both the versions of the study protocol before study start and the final version should be published in the register of studies, thus providing for full transparency.
General	2	**Comment:** The document should clarify that after the primary research question has been answered and reported, as intended per protocol, the data will remain in existence and are of potential use for answering further questions and/or exploratory research as dictated by the evolving scientific evidence, whether related to the initial research question or not. Indeed, data should be co-owned by the ENCePP entity and the Funder to contribute to the full data pool hosted by the Funder e.g. for future meta-analyses.	Agreed. The respective provision provides for recording of the study data in a way that allows verification of the published results. As regards ownership, the text has been amended to add that, in principle, data shall belong to both investigator and funder.
General	2, 9	**Comment:** In section 3 and elsewhere the “electronic ENCePP Register” is mentioned as a new register to be set-up for all ENCePP-studies. Our question here is whether a new and separate register for this specific study type is needed and whether the existence of an additional register really will better support transparency compared with using existing and well known registers for that purpose, too (e.g. EudraCT; Clinicaltrials.gov). Registration needs (or possibilities) in multiple registries and potential redundancy of making study results available in different registries as a consequence of the former shall be avoided to	In the amended version of the Code, it is required to register the study. For ENCePP studies it is mandatory to register within the ENCePP Register of Studies which has been tailored towards the needs of the studies covered by the Code and, specifically, the transparency requirements applying to ENCePP studies.

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		better support the aim of transparency.	

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8. Study protocol - including statistical analysis			
274-275, 304-308	5	**Comment:** The feasibility and usefulness of a continuous on-line update of any amendment of the study plan needs to be clarified. Though transparency is important, it might not be scientifically appropriate to open up for any person to influence an ongoing data analysis.	Not agreed. It is at the discretion of the researcher to decide if comments provided from third parties should be taken into account or not.
147-155	2	**Comment:** There appears to be a provision for archiving the study protocol before study start, but no provision for archiving the statistical analysis plan before the analysis. Modern statistical methods (e.g., propensity score methodology) require refinement to the statistical analysis plan after data collection (without access to the outcome data) and before analysis of the outcomes. **Proposed change:** Add: "This section should indicate that the statistical analysis plan should be archived prior to analysis of the outcome data."	The Code has been revised in response to another comment and now requires that the analysis plan is either a part of the protocol or annexed to the protocol. Therefore, it should be provided with the protocol.
187	14	**Comment:** It may be hard to insure that a study design is not purposefully aimed at producing a pre-specified result. Independent, unbiased protocol review can help in this regard, though this does not appear to be a required part of the Code. Posting the protocol should help by making the methods transparent - however, our experience is that investigators are hesitant to share full protocols. Has there been	The Code requires studies to be registered in a publicly accessible register and to provide a synopsis of the study therein (see chapter 10 of the Code).

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8. Study protocol - including statistical analysis			
		thought about sharing protocol summaries instead?	
207	14	**Comment:** How does ENCePP define "the study start" for observational studies using already collected healthcare data?	A definition of 'study start' was included in the revised Code. It refers to the start of data collection *'as defined in the study protocol'*.
250	2	**Comment:** Please clarify what is meant by the phrase "...and their roles in doing so...".	The text has been reworded and moved to a new chapter 'Declaration of Interest'.
266	7	**Comment / Proposed change:** Any modification of protocol should be agreed to by all that wrote the protocol. There should be no "preliminary results". The lead investigator should faithfully execute the analysis specified in the protocol. The analysis strategy should not be "guided" by the ongoing analysis results.	Partly agreed. The provision regarding changes to the protocol has been revised. The term '*preliminary results*' is no longer used and is replaced by '*scheduled interim results*' where appropriate.
267	7	**Comment / Proposed change:** The lead investigator should be blind to outcomes under analysis until the protocol specific analysis plan is executed for all to see. Once the protocol specified analysis is executed by the Independent Statistician and its results distributed to the interested parties, an electronic copy of the analysis data set should be made available to the interested parties (specified in the protocol).	Not agreed. This would not be reasonable and feasible in all research settings.
270	2, 12	**Comment:** Should there be any reference that the protocols should be sent on or reviewed by the member states where the study will take place?	Not agreed. The Code does not replace or affect any existing legislation that applies. Established regulatory practice should be followed.
271-274	2	**Comment:** The draft Code states "The protocol shall be developed before the study commences by individuals with appropriate scientific background and experience. The funding contract should refer to a clear protocol taking into account the elements of the Checklist of Methodological Research Standards (also see Chapter 4)."	Not agreed. The Code does not exclude involvement of the funder in the writing of the protocol (see chapters on '*declaration of interest'* and '*development of study protocol'*).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
8. Study protocol - including statistical analysis			
		Proposed change: Please clarify with the suggested wording. Amend to: “The protocol shall be developed by collaboration of the investigator and the Study Funder by individuals with appropriate scientific background and experience. Such individuals can be staff at Funder and investigator institutions. The funding contract should refer to a clear protocol taking into account, as a minimum standard, the elements of the Checklist of Methodological Research Standards (also see Chapter 4).”	
271-274	5	**Comment:** The text gives no guidance as to who will formulate the research questions and which level of detail which is needed for a larger audience. It needs to be clarified who has the privilege to define the research questions (the MAH, the PI or the EMA).	The originator of the research question may be any party participating in the study. The Code does not provide for restrictions in this regard.
271-308	2	**Comment:** Since pharmaceutical companies may like to meet their post-approval commitments by running ENCePP studies, the Funder must have the right to provide some minimum requests of the protocols. Although it is may not be intentional, the current wording in the Code may be interpreted as meaning that the Funder might invest in a study which ultimately may not meet the objectives of the post-approval commitment it is designed to address.	Agreed. The following statement was included: *(…) If the study has been requested by a particular competent authority, all parties involved in the development of the protocol are responsible for ensuring that the study meets the requirements of the competent authority. In these circumstances, the competent authority might be involved in the development of the protocol according to its regulatory practices. (…)*
275-276	2	**Comment:** The statement "Changes for reasons such as marketing and/or advertising strategies shall not be acceptable." is ambiguous and may not be entirely warranted. There may be good ‘marketing reasons’ for changing the course of an observational study, e.g. stopping the study because the drug is withdrawn from the market making the exposure of a population no longer possible. Limits of any advertising	Not agreed. The respective provision is not considered to be ambiguous.

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8. Study protocol - including statistical analysis			
		are defined by the SmPC, so there is no reason to point to this here. Amend to: "Changes for non-scientific reasons that are exclusively driven by drug promotion strategies shall not be acceptable."	
285-288	2	**Comment:** The draft Code states: “Any deviation from the initial protocol should be duly justified and documented including the date of the change. Particularly, any changes after the start of data collection, especially after the first results have become available, shall be identifiable and reported as such in publications and the ENCePP Register of Post-Authorisation Studies.” The above text appears to disregard the fact that modern methods may require examination of some of the data before a final statistical analysis plan can be documented. For example, propensity score methodology requires examination of baseline covariates and treatment assignment, hiding the outcome data. In general, these considerations will be noted a priori in the study protocol. **Proposed change:** Amend to: “Any deviation by the investigator from the initial protocol shall be documented with scientific justification, and shall occur only with the written agreement, as soon as practical, of the Study Funder, and informing (where applicable) regulatory authorities, and Ethics Review Boards. Such changes to the protocol shall be identifiable and reported as such in publications and study registries, as applicable. This deviation should be considered for the purpose of the interpretation of the findings.”	Partly agreed. Changes to the protocol are possible but should be documented and reported. The respective provision on changes to protocols has been revised and the requirement to agree changes with the study funder was included.
288	7	**Comment:** The primary way to ensure valid results is to have a sound analysis plan given in the protocol and making the data set public. The financial interest of the funder is not the only competing interest. The LI seeks the prestige of publication. Third parties want low negotiated	Agreed as regards the analysis plan and the involvement of the study entities in the agreement of the protocol. As regards access to data, the chapter on access to data has been revised and a separate

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		prices. Government entities are risk adverse. Etc. The protocol should be negotiated prior to the study so all interests are balanced.	document “Implementing Rules on Access to Data”, available at http://www.encepp.eu/code_of_conduct/index.html, has been prepared.
291	14	**Comment:** In the section on Study Protocol, it is implied that the researcher will largely develop the protocol independently or perhaps with some input from the Funder. For observational studies, this could easily be the case. For clinical trials, which are within the scope for this document, this is not the usual case. The usual case is that the company (i.e., the Funder) develops the protocol, and the research sites execute it. The company may also collect, manage, and analyze the data. The document should address this situation. Under what situations could such studies not be ENCePP studies?	The respective provision has been clarified. The Code does not exclude the involvement of the funder in the development of the study protocol. However, as specified in the new chapter on declaration of interest, once the protocol has been finalised, no person with a financial interest in a particular outcome of the study shall take part in any study activity that could influence the results or interpretation thereof.
291-302	5	**Comment:** The request of continuously reporting preliminary analyses and changes of initial analysis plans are new to the scientific process. A clarification is needed.	Agreed as regards the clarification. The respective provision has been revised. However, the Code still requires documentation of all changes to the protocol.
291-302	2	**Comment:** It is unclear if these rules are applicable only to study protocols or to pilot studies. Please clarify if these rules are applicable to pilot studies.	The provision applies to study protocols including those of pilot studies.
294	2	**Comment:** Regarding "If the development of the Protocol is part of the assignment...", is this compatible with line 248 where it appears to be said that the protocol design must always be part of the assignment?	The respective provisions have been reworded and clarified.
294-295	2	**Comment:** Regarding "...the Investigator shall write the Protocol within the remits of the assignment.", what does this mean and why is this specification needed?	The respective provision has been reworded and clarified.

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8. Study protocol - including statistical analysis			
301-302	5	**Comment:** The recommendation of an impartial review of the study protocol before adoption is also novel. Since the availability of unbiased expertise is very limited, this proposal may compete with the possibility to recruit an unbiased scientific oversight committee or study steering group proposed in section 12 (line 347-350).	Agreed. The respective text was deleted to avoid confusion.
301-302	2	**Comment:** It is recommended to subject the Protocol to an 'impartial peer-review' before its final adoption. Who should conduct the peer-review? How should the peer-reviewers be appointed? Please provide more details on this peer-review process. It is not clear what "...recommended..." means, since it is not part of the checklist. Please clarify accordingly. If protocols/reports are done by well qualified researchers, reviewed by regulators, and posted on the website, why should the protocols/reports be subjected to another 'impartial' peer-review before its final adoption? This process will add an unnecessary step of delay for the study conduct and report. **Proposed change:** Delete the sentence "It is recommended to subject the protocol to an impartial peer-review before its final adoption."	Agreed as regards the deletion of the text referring to a peer-review of the protocol.
303	2	**Comment / Proposed change:** The phrase "...should be replaced without delay..." should be quantified to a realistic timeline so that all stakeholders operate to same timeline.	The provision for availability of the study protocol has been revised. Only the initial and the final version of the protocol are required.
304-308	2	**Comment:** Posting of any changes to the protocol should be the responsibility of the investigator and include scientific justification. **Proposed change:** Amend to: "The full Study Protocol shall be made publicly available. In case of amendments to the Protocol, the former version or the information on the concerned elements should be	The provisions for availability of the study protocol and handling of changes to the protocol have been revised in response to other comments received. Of note, a justification of the changes is only required upon request once the results of the study have been

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8. Study protocol - including statistical analysis			
		replaced by the investigator without delay by the new version/information including the date of the amendment, a summary of the main changes, and the scientific justification for the changes."	published.
336	11	**Comment:** Should it be possible to have a protocol with a brief statistical section if the intent is to develop a more detailed SAP at a later stage?	Agreed. This is in line with the Code which requires that *'a statistical analysis plan shall be described in, or annexed to, the study protocol.'*
336	2	**Comment:** The data analysis plan can be detailed in the protocol, but in many instances the details are in a separate document (Statistical Analysis Plan). A choice should be given in this regard. We suggest it should be "sufficiently detailed". We also suggest to explicitly acknowledge that an observational study will often require steps where subsequent analysis will depend on preliminary results (simple example - comparing smokers of 20+ cigarettes with those smoking less will be useless scientifically if it turns out when the data are collected and initially analysed that too few smoke 20+ to give sufficient statistical power). It should be recognized that it is often not possible to prepare a detailed statistical analysis plan with the Study Protocol. **Proposed change:** Amend to: "A detailed statistical analysis plan shall be prepared and documented prior to analysis of the study outcomes. Any deviations from the analysis plan should be clearly documented with a rigorous scientific justification".	Agreed. The revised Code requires that the analysis plan is either a part of the protocol or annexed to the protocol.
336	7	**Comment:** The statistical analysis plan should be jointly developed by the interested parties, the funder, the LI, the IS and interested 3rd parties.	The Code does not specify involvement in the writing of the analysis plan.

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8. Study protocol - including statistical analysis			
340-344	2	**Comment:** The statement above seems to imply that researchers, regulators and the industry should turn a blind eye to results that may have high relevance depending on the situation and available scientific evidence, which may very well have changed since the conception of the study. Probably this sentence should be changed to indicate that ex-protocol analyses will require strong arguments or external evidence to have any strong bearing on the initial research question. Also, this section could cross-reference to the statement about subsequent research using the same data. It should be clarified that changes to the analysis plan must be justified if this occurs after knowledge of outcome data. **Proposed change:** Amend to: "Study results reported on the basis of changes to the analysis plan after analysis of the outcomes has begun, e.g. formation of new sub-groups based on knowledge of outcome data may not be used for the purpose of verifying or rejecting a hypothesis of a causal association. In any case, all changes need to be documented and shall also be indicated in communications on the study results."	Partly agreed. A caveat has been added as follows: *(…) A caveat regarding this view is that important safety concerns, even if based purely on subgroup analyses, should be documented and evaluated appropriately. (…)*
340-344	5	**Comment:** This para should be rewritten. The intention by including the remarks of additional sub-group analyses is not clear and the para needs to be modified to also accommodate the research process of retrospective register studies.	Not agreed. The reference to the formation of sub-groups based on the knowledge of study findings is part of an example only.
340-344	2	**Comment:** The Code states "Outcomes resulting from changes to the analysis plan after data analysis has begun, e.g. formation of new sub-groups based on knowledge of (initial) study results may not be used for the purpose of verifying or rejecting a hypothesis of a causal association." While it is important to be transparent and any post-hoc modifications to the study protocol should be documented (along with	Not agreed. The possibility to change data analysis and reasons for doing so, if at all, should be written into the protocol.

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		the rationale), changes to the analysis plan post-hoc should not invalidate/lessen the strength of the results. In fact, the strength of the study may be improved by improvements in the model/study design driven by findings after the data analysis has begun. For example, if you discover that your statistical model violates a key assumption (e.g, non-proportional hazards in a Cox regression model) and you need to modify the analysis based on this finding (e.g., including a time-dependent variable in the Cox model) a more robust/valid result is obtained.	
342	2	**Comment/Proposed change:** Please clarify this sentence with the suggestion below. Add: "… of a causal association without review and prior authorisation by an external scientific advisory board (e.g. a scientific oversight committee)."	Not agreed. The statement applies regardless of the review by an advisory board.
362	7	**Comment:** The study should be executed by the lead investigator and the analysis by the independent statistician. ANY changes to the analysis plan must be agreed to by the interested parties, funder, lead investigator and interested 3rd parties. Data analysis plan should give specific strategies to address multiple testing, bias, and multiple model building.	The Code only specifies that, ultimately, the investigator shall be responsible for the conduct of the study. Apart from the conditions for (non)participation in the study conduct given in the chapter on declaration of interest, there is no further specification as regards the execution of the analysis plan. Guidance on methodological standards is provided by means of the *Checklist of Methodological Standards for ENCePP Study Protocols*. Researchers of ENCePP studies are required to provide here information on the methodologies applied.
General	2	**Comment:** Some provisions in the draft Code appear to disregard modern statistical methods that are applied in observational studies e.g. no change to the protocol after beginning data collection. Propensity	Agreed. There is no conflict with the provisions of the Code. However, the Code requires documentation of all changes and being transparent about them.

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		score methods require knowledge of baseline covariates and treatment assignment (while hiding the outcomes of interest) in developing the propensity estimation. Thus, modifications to the protocol or, more specifically, to the statistical analysis plan, after data collection are required in this instance, and entirely appropriate.	
General	4	**Comment/proposed change:** The section on statistical analysis requires a detailed statistical analysis before starting the study. Given the comments we heard at the Plenary meeting on the difficulties of making public a full study protocol, I am afraid we will have to withdraw the word "detailed" from the Statistical analysis section of the Code of Conduct.	Agreed.
General	7	**Comment:** Everyone interested should have access to the study protocol including the detailed statistical analysis plan. The analysis plan should be complete and specific before anyone has access to the data. An Independent Statistician should execute the statistical analysis.	Partly agreed. The Code requires making publicly available the study protocol once the final study report is available.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
9. Communication & publication/reporting			
193	14	**Comment:** How will results be "made available to public scrutiny" if they are not published? Will they have to be on a website somewhere?	The requirement to make the results available to public scrutiny is not in contrast to publication. Preferably, this would be done in peer-reviewed journals; however, other means would also be acceptable, e.g. placing a summary of the results online.
193-195	2	**Comment:** Regarding "The results of a study shall always be published	Agreed. No disagreement with the provisions of the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
9. Communication & publication / reporting			
		or made available to public scrutiny within an acceptable time frame, regardless of the (positive or negative) results and the statistical significance", the publication of the results regardless of their statistical significance can be quite misleading if this is done without further explanation. Therefore, the opportunity must be granted to the MAH to publish, together with the results, comments on their statistical relevance.	Code.
193-195	6	**Comment / proposed change:** The guidance could be more specific (e.g. 'within x months of …') with regards to what would account for an 'acceptable timeframe'.	Agreed. However, no change is required as more detailed information is provided in chapter 14 (Publication/Reporting of Study Results).
194, 374	2	**Comment:** These lines indicate that a full report with assessment of public health impact should be available in 'an acceptable time frame' (line 194) and 'without unjustifiable delay' (line 374). Please clarify this otherwise ambiguous wording. **Proposed change:** We suggest that the timeframes for availability to ENCePP and for publication are the same as for clinical trials, and stipulated as "….not longer than x months/years after study completion".	Partly agreed. Chapter 14 provides more detail on the timelines for publishing the study results..
237	2	**Comment:** What is defined as a 'publication'? Peer-reviewed journals may not be interested in accepting certain types of studies. Does the term 'publication plan' include a publication plan in the ENCePP website? Any plans for publication, e.g. publication in ENCePP Register, should be stated.	As a principle, the study results should always be published, preferably in a peer-reviewed journal, or made available for public scrutiny within an acceptable time frame. To avoid misunderstandings the chapter concerned has been revised and the reference to a plan, for publications has been deleted.
254	2	**Comment:** Preliminary results could be communicated to the Funder if specified in the protocol as scheduled interim analyses and/or reports.	Partly agreed (see amendments). The ENCePP Register of Studies requires the provision of milestones.

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		Otherwise, it will be difficult to determine the exact meaning of 'preliminary results' in this context. A better approach would be to specify milestones where certain communication is provided and forms for this (e.g. database finalised (lock), data quality check, interim report, final report) Amend to: ".....and the reasons for it, and at appropriate study milestones (e.g. database finalised (lock), data quality check, interim report, final report)".	
256	14	**Comment:** The implicit assumption here is that the main output of a research endeavour is a publication. For public health and regulatory work, this is not always the case. Public health (see lines 185-186 for research purposes) and regulatory actions often precede publication. The document should address this issue.	Partly accepted. It is clearly stated that the Code does not replace or affect any existing legislation that applies. However, in the revised version of the Code, the interaction with regulators has been more clearly addressed to avoid misunderstandings.
213-216, 254-255	2	**Comment:** The statement "The (Primary) Lead Investigator.....should not communicate preliminary results" seems to contradict the statement in lines 213-216 regarding making 'interim results' available to the public upon request. Is the distinction between 'preliminary' and 'interim' results clear? Please clarify whether this is applicable to 'interim study reports' as well as 'preliminary results'.	The terminology has been amended and harmonised throughout the Code. The relevant text in chapter 9 read now as follows: *(…) The (primary) lead investigator (…) should not communicate results other than final or scheduled interim results. (…)*
362	7	**Comment:** The web offers opportunities of speed and thoroughness of reporting largely unavailable with journal publication. Also, journals often expect a "statistically significant" result and authors often feel obliged to find/create such a result. There should be no publication pressure on authors to find statistical significance. The official report should be publicly published on the ENCePP web sites. Any journal should sign an agreement with the SI prior to submission of a manuscript that "statistical significance" is not a condition of publication.	Agreed as regards publication of results on ENCePP website – this is in line with the provisions of the Code.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
9. Communication & publication / reporting			
368	2	**Comment:** Results of studies should complete the peer review process prior to being made available to the public on the ENCePP website.	It is agreed (and indicated in the Code) that it is good practice to invite review of the study results and any publications and/or communications thereof by independent experts.
369	2	**Comment:** Many journals will publish original results only - results already found in abstract form on an internet webpage may appear to be no longer original. Therefore, the early publication of the abstract on the ENCePP website might block subsequent full publication and thereby counteract rather than promote transparency.	To a limited extent, this is already incorporated in the Code. While the Code requires the timely publication of the results of the study - including publication of an abstract within 3 months after the final study report, a delay can be requested pending peer-review comments.
370	2, 8	**Comment:** It should be made clear that the publication of any results can sometimes not be done because of the embargo policy of scientific journals. **Proposed change:** Amend to: "....to delay the publication of this abstract for a limited period. In case the publication is intended in a peer-reviewed scientific journal the period has to consider the publication policy of the potential target journals and to be in line with the embargo strategy of the journal that accepted the work for publication."	Not accepted. However, the ENCePP Steering Group has recognised the need to review this provision in the light of practical experience gained with its application. Extended publication timelines for a limited period pending response to peer-review comments.can be requested on a case-by-case basis
370	2	**Comment:** As many of the ENCePP studies will likely be published in peer-reviewed journals, the ENCePP Secretariat should allow more lead-time (i.e., greater than 3 months after final study report) in posting the abstract of study findings on the ENCePP webpage, especially when the publication review process can be a lengthy process in obtaining final approval. In addition, several major peer-reviewed journals require their publications to be the first presentation. Also, "3 months from final study report" presents ambiguous timelines, since delivery of the final report is not defined, and delay due to patent considerations should be	Not accepted. However, the ENCePP Steering Group has recognised the need to review this provision in the light of practical experience gained with its application. Extended publication timelines for a limited period pending response to peer-review comments can be requested on a case-by-case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
9. Communication & publication / reporting			
		mentioned.	
373	14	**Comment:** A full report of results will be made available (assume this is via a public website) - will the draft report be peer reviewed or available for public comment before finalizing the report and publishing the final report, which will include findings and a conclusion based on these findings? (It is stated that it is recommended that the protocol will be peer reviewed, but what about the report?) For example, AHRQ's Effective Health Care program now makes all draft reports of technical briefs, systematic reviews, and original research reports (including reports on observational research studies) open to public comment for a period of 4 weeks. Also, if the recommendation with respect to ensuring that the protocol is peer-reviewed is not followed, can you be sure the protocol development is scientifically valid? How do you compare findings from ENCePP studies with peer reviewed protocols vs. ones that are not?	The recommendation of peer-review refers to study results and any publication thereof, i.e. this would also include the final study report. The draft Code included a recommendation for a peer-review of the protocol. However, for the sake of clarity, this recommendation has been deleted.
373	2	**Comment:** The phrase “without unjustified delay” is ambiguous, and should be quantified, otherwise it obfuscates for all stakeholders rather than provide transparency. Other regulators do not consider seeking or pending publication as justifiable delay.	Not agreed. To be decided on a case-by-case basis.
373	2	**Comment:** The Code should further define and provide greater clarity for what is meant by ‘public health impact’. For example, this may include a criterion for determining whether study findings have an impact on the public health. If, specifically, (urgent) safety issues are included in such definition, a recommendation to inform the Competent Authorities in an expedited way (and not just “in advance of publication”) should be added.	Not agreed. The Code clearly states that relevant legislation needs to be followed (chapter 4). This includes reporting (urgent) safety issues to regulatory authorities.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
9. Communication & publication / reporting			
375	2	**Comment:** It should be sufficient to say "...relevant legal provisions shall be followed". The additional stipulation "...and the respective regulatory authority(ies) shall be informed forthwith and in advance of publication." is already covered by that first part of the sentence and should be deleted. **Proposed change:** Delete "...and the respective regulatory authority(ies) shall be informed forthwith and in advance of publication."	Not agreed as it is important to highlight the need to inform regulatory authorities.
378	7	**Comment:** Process should govern. Any potential problems here should be resolved in designing the protocol. If the analysis plan addresses multiple testing, bias, and multiple modeling, then reporting should be straightforward. Analysis summary tables and figures should be described in the study protocol.	This is addressed in a separate chapter (Study conduct, data analysis).
385	2	**Comment:** Please clarify this sentence with the suggestion below. **Proposed change:** Add: "… for the update. In the case of results with a scientific or public health impact, presentations to a limited….".	Not agreed. All results should be made available to the general public.
388	5	**Comment:** The right of the primary lead investigator to prepare publications needs to be harmonized with the tradition of most medical journals to accept only new research findings, not published elsewhere. This may be in conflict with the availability of the summary and final study report (line 365-371).	As a principle, the study results should always be published, preferably in a peer-reviewed journal, but not necessarily.
388	7	**Comment / proposed change:** An alternative publication strategy would be as follows. The final report is posted on the web. The Lead Investigator and the Funder are then free to either jointly or separately seek publication. It should be recognized by all that peer review is no guarantee of the validity of claims or quality of the work.	Not accepted. The respective provision intends to increase the independence of the researcher as regard the interpretation of the study findings.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
9. Communication & publication / reporting			
388	2	**Comment:** The Funder should be given the right to independently publish, to safeguard publication if the Principal Investigator fails in this respect and to recognize the right to re-analysis of the same data by another party that is a common ground-rule in science today. The process of joint publication should be described, where scientific staff of the funder (who often have much of the inside scientific knowledge of the research question) are involved in the manuscript preparation. A final round of official comment can be included, but should apply equally to all co-authors and the funder and not only the comments, but the response to them and motivation of the lead author for implementing them or not should be followed. Otherwise it will be impossible for an interested party to understand why certain comments were followed and others not.	The involvement of the funder in the writing of publications is not excluded. However, the Code provides for the right of the investigator to independently prepare publications. Further detail for this case is provided in the paragraph concerned.
388	2, 8	**Comment:** It should be made clear that in the further preparation process of the manuscript the other individuals shall be included that had made substantial intellectual contributions. **Proposed change:** Add after end of sentence in line 389: “Other individuals shall be included that had made substantial intellectual contributions and all included co-authors should agree with the content of the final version.”	Not agreed. For authorship, the provisions of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* by the International Committee of Medical Journal Editors should be followed.
388	2	**Comment:** The chapter states that the (Primary) Lead Investigator should have the right to independently prepare publications of the study results irrespective of data ownership. Ideally it should be clearly specified in the contract what publications are planned. In case of unplanned publications, the (Primary) Lead Investigator should give an adequate notice to the Funder. The chapter states that “the Funder may only require that the presentation of the results be changed to delete	Partly agreed. Indeed a communication strategy should be agreed upfront (see chapter 8). The provision concerned in the chapter *Publication/Reporting on Study Results* has been amended taking into account the comment made. A peer review of the results is part of good research practice.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
9. Communication & publication / reporting			
		Confidential Information". There may be other legitimate modifications requested / recommended by the Funder based on sound scientific reasons. The chapter states that the study results and any publications and/or communications thereof should be peer-reviewed by independent experts. Who should the experts be and how should they be appointed? Is it the expectation that the results/communications/publications be peer-reviewed prior to submission for publication? Please provide more details on the peer-review process of the study results.	
388	2	**Proposed change:** Amend to: "The Study Funder shall be entitled to view the final results prior to submission for publication and to comment on the results and interpretations of the findings in advance of submission for publication within a reasonable time limit, e.g. one month, as agreed in the funding contract and without unjustifiably delaying the publication."	Agreed.
392	2	**Proposed change:** Please delete "(...) e.g. one month, (...)" as the contract will stipulate the terms.	Not agreed. The deadline is indicative only.
396	9	**Comment:** The need to make comments from the funder to any planned publication publicly available is not clear to us.	This requirement is in line with the principle of transparency.
396	2	**Comment:** The Code should provide greater clarity on whether Funder's comments will be made publically available for the publication and/or final study report. The EMEA should also consider the value of making these comments publically available before committing to this policy, especially considering the different types of comments which can range from editorial to scientific comments with extensive dialogue between the Principal Investigator(s) and the Funder. **Proposed change:** Delete "Any comments of the Funder should be	The provision concerned refers to publications of study results. In addition to the publication itself, it is sufficient to make available the comments of the funder.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
9. Communication & publication / reporting			
		made publicly available." Otherwise, add: "Any Investigator responses to comments from Study Funder(s) should also be made publicly available."	
361-407	2	**Comment:** As regards the proposed publication of comments to draft reports, it is not helpful to disclose the process of report writing with errors and corrections, whereas comments by either the Funder or the investigator to the final published report should be published together with the final report.	Not agreed. In line with the principle of transparency, all comments made by the funder should be made publicly available.
361-407	2	**Comment:** This chapter of the Code should also provide guidance on co-authorship for publications, including such topics as who and how co-authorship eligibility should be defined.	Not agreed. No further guidance on authorship than currently available is required. For authorship, the provisions of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* by the International Committee of Medical Journal Editors should be followed.
394-396	2	**Comment:** The Code states "The Investigator is free not to take the comments of the Funder into account and the Funder may only require that the presentation of the results be changed to delete Confidential Information". If the comments of the Funder are scientifically valid, the Investigator should be expected to take the comments into account. Further, the Funder should have the opportunity to have scientific discussions with the Investigator to appropriately change the presentation of results if the comments are scientifically valid. **Proposed change:** Add: "If the Investigator does not take comments of the Funder into account and the omission of such comments, in the opinion of the Funder, results in a material scientific deficiency of the publication, then the Funder will provide a written comment on the publication to be provided to the ENCePP Secretariat for publication on the ENCePP webpage when the publication is made available."	Not agreed. The current provision provides for comments by the funder for scientific reasons and the publication of the comments of the funder regardless of whether they have been taken into account or not.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
9. Communication & publication / reporting			
394-396	2	**Comment:** It is not clear what is meant by "...and the Funder may only require that the presentation of the results be changed to delete Confidential Information". What is this meant to refer to? **Proposed change:** Amend to: "The Investigator is free not to take the comments of the Funder into account and, in case of such a refusal to take his comments into account, the Funder may only require that the presentation of the results be changed to delete Confidential Information"?	Agreed. The wording has been amended accordingly.
409	2	**Comment:** If protocols/reports are done by well qualified researchers, reviewed by regulators, and posted on the website, why should the protocols/reports be subjected to another impartial peer-review before its final adoption? This process will add an unnecessary step of delay for the study conduct and report.	Independent peer-review of study results is good research practice. The draft Code included a recommendation for a peer-review of the protocol. However, for the sake of clarity, this recommendation has been deleted.
409	2	**Comment:** The Code should provide greater clarity in defining 'independent reviewers'. It currently states that the independent reviewers are responsible for providing a peer-review of study publications and/or communication. The Code should clarify if this includes review by external consultants (or Advisory Boards) that are independently used by the Funder.	The term 'independent' in this context should be understood as free from conflicts of interest.
408-417	2	**Comment:** We do not see a need to review all the work again by "independent experts". Usually the manuscript in its final version should be the product of experts and mirror the objective of this Code of Conduct (be thereafter a integer and valid result). Also, if published in a peer review journal, the manuscript usually has undergone a peer-review process, that in open-access journals is even transparent. Also, it is not clear why review by "independent experts" is required if the	The provision concerned has been amended for the sake of clarity. Independent peer-review is good research practice.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
9. Communication & publication / reporting			
		steering/scientific committee is constituted as outlined in the document. So why have this extra round of review? We recommend to make this optional or to indicate that the peer-review process of scientific journal can be considered also an adequate review process that should serve the same purpose.	
408-417	9	**Comment:** Given the current role of the primary lead investigator and the complete exclusion of the funder, the need for an additional peer-review of every study detail seems not necessary. Re-consider the various roles and their real role in achieving the aims of the code of conduct in comparison to the efforts to establish and maintain them during the conduct of an ENCePP study.	The provision concerned has been amended for the sake of clarity. Independent peer-review is good research practice. As regards the feasibility and applicability of the provisions of the Code, these will be reviewed on a regular basis.
409-417	2	**Comment:** This section on "scientific review" is not clear. Who are the peer-reviewers? Does this refer to the journal peer-review process? If so, is it intended that the journal reviewers' comments be documented along with authors' responses and made available on request? Journals generally require that reviewer comments are kept confidential. If this section in the draft Code refers to a peer-review process separate from peer review by the journal, how are these reviewers selected? The draft Code states that the comments by these reviewers should be made available upon request. Made available to whom on request?	The wording has been amended. Independent peer-review is good research practice. However, the exact form of the review and the selection of the experts should be appropriate for the level and purpose of the communication.
Chapter 13	2, 12	**Comment:** The final study report should be finalized within a predefined timeline, an executive summary should be published on the public website within predetermined timelines.	Partly agreed. While the full final study report should be provided without delay, an abstract of the study findings is required within 3 months following the final report.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
10. Miscellaneous			
151	2	**Comment:** Please define the phrase "termination of the study".	The Code has been revised for the sake of clarity and now only includes reference to the availability of the final study report where appropriate.
356	2	**Comment:** Please clarify how expertise will be “proven”.	This is at the discretion of the (principle lead) investigators, e.g. curriculum vitae.
General	2	**Comment:** The Code of Conduct (as well as the Checklist of Methodological Research Standards) does not presently cover the Funder’s responsibilities on Adverse Reaction reporting according to Volume 9A of the Rules Governing medicinal Products in the European Union. Please consider adding a section that describes expectations regarding Adverse Event/Reaction reporting for ENCePP studies. In case the study is a regulatory post-approval commitment or requirement for the Funder, there is often the need to await communication/approval from regulatory authorities before a study protocol can be considered final. This needs to be taken into account as regards any timelines for submitting the protocol to ENCePP and making it publicly available.	Not agreed. The Code does not replace existing legislation nor does it aim to clarify/expand or repeat existing guidance, e.g. it does not affect the funders’ obligations as regards adverse event reporting. It should rather be considered as being complementary to existing guidelines and rules applying to studies.
General	2	**Comment:** The vision and expectations for the peer-review process should be clarified for both the protocol and results/communication aspects. The Code of Conduct recommends that the protocol should be subject to impartial peer-review before its final adoption, and that study results and any publications and/or relevant communications are peer-reviewed by independent experts. • Who should the peer-reviewers be and how will they be selected and appointed? • What criteria are contemplated to define an ‘independent’ reviewer? • Is a fixed number of peer-reviewers contemplated and should they	Peer-review is a normal part of study development and reporting and highly recommended. The peer-review process is a responsibility of the lead investigator. However, for the sake of clarity the recommendation for a peer-review of the protocol has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
10. Miscellaneous			
		be retained for the duration of the study, i.e., should the same reviewers evaluate both the protocol and the results/reports/manuscripts/communications?	
General	12	**Comment:** Should there be a chapter on how to request an ENCePP study?	Chapter 3 includes information on the criteria for the ENCePP study label. A link to the ENCePP website is provided where further information on the application process is available.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
11. Annexes			
Annex 1	2	**Comment:** The definitions provided in the ENCePP Code of Conduct should be consistent with those provided by European post-marketing regulations, e.g. Volume 9A of the Rules Governing Medicinal Products in the European Union. For example, the definition provided for Post-Authorisation Study ("Any study conducted with an authorised medicinal product") is not correct since it is also necessary that the study is conducted in the approved conditions of use (as per the definition provided in Volume 9A, page 198). It would be appropriate to add the definition of 'Post Authorisation Safety Study' (PASS) as many of the ENCePP studies will be PASS.	The scope of the Code is different and wider than the scope of Volume 9A. Therefore, a wider definition is used.
Annex 1	2	**Comment/Proposed change:** For the ease of reference, please to change the order of the definitions into an alphabetic sequence.	Agreed.
Annex 1	2	**Comment:** As written, the definition of 'Post authorization studies'	The scope is inclusive and does not exclude

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
11. Annexes			
		covers phase IV interventional clinical trials as well as observational product studies. The definition needs to be clarified as to the scope of studies covered by it.	interventional studies. Therefore, a wider definition is used.
Annex 1, line 501	2	**Comment:** What exactly means “authorised” here?	The definition has been amended as follows: *Any study conducted with a medicinal product authorised in the European Economic Area (EEA).*
Annex 1	2	**Comment/Proposed change:** Please amend the definition of ‘Non-interventional study’, as suggested below. Based on Directive 2001/20/EC, in a non-interventional study the assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data. Or, add the following from Volume 9A: “In this context it is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice.”	The definition has been replaced by a reference to Volume 9A.
Annex 1, line 510	2	**Comment/Proposed change:** Under study protocol definition, please add ethical considerations. Amend to “A document that describes the objective (s), design, methodology, statistical and ethical considerations, as well as organization of the study.”	Agreed.
Annex 1, line 515	9	**Comment:** Is the term “lead” as an attribute to investigator omitted intentionally here or is this distinction meaningful?	The definition has been amended to ‘lead investigator’.
Annex 1, line 517	9	**Comment:** From the body of text of the Code the role of the primary lead investigator seems to be much broader then given here. Please	Not agreed. The specific components of the role of the principle lead investigator are discussed in the Code.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
11. Annexes			
		give a comprehensive definition of this key role as outlined in the current draft of the Code.	
Annex 1	9	**Comment:** The Role of the Lead Investigator, as a representative of the Study Funder, needs to be clarified.	See amended definition of 'Coordinating Study Entity'.
Annex 1	2	**Comment:** Need to specify that the 'Study Funder' may designate a group of legal persons.	Agreed.
Annex 1, line 533	2, 8	**Comment:** The world 'science' would be more appropriate here than 'study'.	The definition of 'Pharmacoepidemiology' is in line with the definition by the International Society of Pharmacoepidemiology (ISPE).
Annex 1	2	**Comment:** It is not clear if the definition of clinical trial noted here is intended to refer to an "interventional" study or not? In what case can a "trial" be considered a Pharmacoepidemiology and Pharmacovigilance study?	The definition of 'Clinical Trial' is in line with Directive 2001/20/EC.