



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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EMA/641434/2010  
Patient Health Protection

## Overview of comments received on the 'ENCePP Guide on Methodological Standards in Pharmacoepidemiology' (EMA/95098/2010)

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

Stakeholder no.	Name of organisation or individual
1.	Loreto Carmona, Sociedad Española de Reumatología
2.	Nawab Qizilbash, Oxon Epidemiology Limited
3.	FDA/CDER
4.	International Society for Pharmacoepidemiology (ISPE)
5.	Novartis Pharmaceuticals
6.	GSK Biologicals
7.	Gabriel Schnetzler
8.	F. Hoffmann La Roche Ltd
9.	Novo Nordisk A/S
10.	Bayer Schering Pharma
11.	BPI – German Pharmaceutical Industry Association
12.	European Confederation of Pharmaceutical Entrepreneurs (EUCOPE)
13.	European Federation of Pharmaceutical Industries and Associations (EFPIA)
14.	Stefanie Prilla, European Medicines Agency
15.	Peter Arlett, European Medicines Agency



# 1. Overview of comments

The comments received are presented as 'General comments' and 'Specific comments on the text'. The latter are presented under the following topics in line with the Sections of the Guide:

1. Introduction
2. General aspects of study protocol
3. Research question
4. Governance
5. Study Design and Methods
6. Data Sources
7. Statistical Analysis Plan
8. Quality Control and Quality Assurance
9. Safety reporting (Adverse Events)
10. Communication
11. Update of the Guide

The lines and chapters indicated for the comments refer to the location in the version published for public consultation. However, the location might be different in the revised final version due to changes in the text and restructuring.

## 2. General comments

Stakeholder no.	Comment and rationale; proposed changes	Outcome
1	<p>A very good working document. At EULAR (European League Against Rheumatism), a taskforce on biologics registries has issued recommendations: Dixon WG, Carmona L, Finckh A, Hetland ML, Kvien TK, Landewe R, Listing J, Nicola PJ, Tarp U, Zink A, Askling J. EULAR points to consider when establishing, analysing and reporting safety data of biologics registers in rheumatology. <i>Ann Rheum Dis.</i> 2010 Sep; 69(9):1596-602. Most are in line with what you recommend. Others are even more practical, especially for registries, both for undertaking as well as for reporting. In January we will have a workshop in Zurich to help countries with developing safety registries in rheumatology to understand the methodology.</p>	No change required to the text
2	<p>An important component of ENCEPP should be the potential for meta-analysis. Otherwise, though ENCePP is an important advance, it may remain limited to being a database to identify individual databases for individual studies and register individual studies. The potential for meta-analysis should be developed, as this will enhance the benefit of the ENCEPP network, similar but not identical to the Sentinel system being developed in the USA. This development requires guidance on the steps that need to be taken in the issues for meta-analysis, planning, methodology, statistical and discussion sections of your draft Guide on Methodological Standards in Pharmacoepidemiology document to maximise the information gathered for an issue addressed in different databases. This will allow: (1) more precise risk estimates; (2) address heterogeneity; (3) explore subgroups; (4) more robust meta-regression to be performed; and (5) research of factors and methods for optimising meta-analysis of health care databases.</p> <p>Meta-analysis will allow the maximum use of all the relevant data in the ENCEPP centres to address issues where one database is likely to possess insufficient statistical power and where differences between</p>	Partially agree. The distinction between multi-centre/data base studies and meta-analysis of studies, both in terms of methods and required governance structures for sharing crude data is acknowledged and there are separate sections within the Guide relating to both (6.4 Research networks and 5.4 Integrating and pooling studies, respectively). In addition, the text of section 6.4 has been amended to reflect that ENCePP has the potential to do individual patient based meta-analysis and that the application of relatively common standards and use of similar populations by accessing data across ENCePP centres could be useful to increase precision and to maximise the use of all relevant data.

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	countries may play an important role in modulating risks and benefits.	
3	FDA's draft guidance on pharmacoepidemiologic safety studies using electronic healthcare data sets, when available, may serve as another resource to cite in this guide.	Agree. Await availability of final FDA guidance (draft issued for two-month public consultation 16/02/2011). May be used in an update of the Guide.
3	We agree with the obligation to publish findings but have concerns about study registration without knowing more about how this would be done, who has access to the content of what has been registered, and other operational aspects. Registration of a study being undertaken by investigators from a regulatory agency could create problems in a variety of ways (e.g., public alarm, industry interference, violation of pre-decisional confidentiality (potential advantage for market competitors)).	Outside the scope of the present document – issue to be referred to ENCePP Task Force on access to data in terms of interpretation of Code of Conduct etc.
4	We find that the document represents highly qualified work and that it has the potential to become a very useful tool for the researchers within the field. It may also find some use in teaching.	No change to text required.
5	Inclusion of a comprehensive list of abbreviations and acronyms would be useful to the reader.	Agree. A list of abbreviations has been added.
5	The objective is a collection of relevant references, guidelines and articles for study protocols, research areas, study designs, data sources, statistical & epidemiological methods, QC/ QA, AEs and Signal detection, ethics, etc. The document nicely has achieved the objectives for <u>some</u> areas and is most valuable as checklist/ advice/ reference for Clinical teams, DRA, Statistics, DSE, HE, External affair, etc.	No change to text required
5	We note the following areas for improvement: (a) Greater explanation of expectations for Safety Risk Management Plans (RMPs); (b) Reference to expectations for Investigator brochure (IB) and IB updates is missing; (c)	Not agreed. These are regulatory requirements detailed in the relevant guidance that are referred to in the

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	Structured identification of Adverse Drug Reactions (ADR) became a new requirement. More detail on this topic would be beneficial; and (d) Reference to expectations for SAE reporting and Investigator notifications (Ins) is missing.	document. These requirements may change over time.
5	ENCePP working group could further comment on a strategy for regular updates or replacements (necessary because important to keep this document emerging with latest references). In general, we find the structure of the document would benefit from following a clear progression of activities. While it mentions many instruments available for designing and conducting an epi study, the commentary is not always adequate. Inexperienced readers may benefit from a more in depth commentary, while experienced ones may do with a list of publications upon which to rely for updates. We would favour the latter approach, provided that all topics are covered and updates are frequent.	Agree. In line with the scope of the present document, to make the updates as dynamic as possible, an open access, interactive platform (e.g. a wiki or Google document) is being considered.
5	It would be useful to add a caution note that different referenced sources may express conflicting messages.	No change required. Although it is agreed that different sources may provide conflicting messages, the Guide pinpoints the relevant references (including sections of guidance where relevant) to support the conclusions drawn.
6	Extremely useful reference document	No change to text required
7	This guide on methodological standards in pharmacoepidemiology is very comprehensive and an invaluable tool supporting anyone planning and conducting studies in this field.	No change to text required
7	The guide could be further enhanced by providing a short overview of the different approaches used (randomised clinical trials, large simple trials, cohort studies (including registries) and surveys), their strengths and limitations as well as other considerations regarding. Eudralex Volume 9A	Not agreed. The approach of the authors was not to repeat well known concepts verbatim in the present document but to refer to relevant source documents of information. This is explained in the first paragraph of the

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	could serve as a baseline. This would help to put section 5 (study design and methods) into context.	introduction.
7	<p>The ENCePP Guide on Methodological Standards in Pharmacoepidemiology would benefit of a detailed interpretation of what can be defined as a non-interventional trial, further building on the exclusion criteria for the European Clinical Trial Directive and the Eudralex Volume 9A. A possible interpretation of non-interventional could include:</p> <p>A non-interventional trial is a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. 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 (Article 2c, DIRECTIVE 2001/20/EC). In this context it is considered important to clarify that interview, questionnaires and blood samples may be considered as normal clinical practice (Chapter 1.7 Section 1 of Volume 9A of the Rules governing Medicinal Products in the European Union).</p> <p>Specific diagnostic, treatment or monitoring measures can be defined as normal clinical practice, if they fulfill the criteria of evidence based medicine principles, are defined by guidelines issued by relevant bodies or are mandated by regulatory and medical authorities (<i>proposed addition</i>).</p>	Not agreed. The concept of what defines a 'non-interventional trial' is currently under review in the light of the new pharmacovigilance legislation. The Guide will be updated accordingly.
7	A general recommendation should be given on the form and duration of archiving the raw data and any other relevant documents which are study related. Such guidance is warranted given the requirement for data access	Not agreed. The concept of access to data is under review by an ENCePP Task Force and the Guide will be updated. A reference to the GPP is made throughout the Guide

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	outlined in section 12 of the ENCePP Code of Conduct. Some considerations of the Guidelines for Good Pharmacoepidemiology Practice (Epstein M, et al, Pharmacoepidemiol Drug Saf. 2005 Aug;14(8):589-95) could be adopted.	currently.
8	Overall, the document does an excellent job of compiling the latest guidelines from learned society and from European regulators. This approach of allowing the learned societies to provide guidance seems entirely appropriate.	No change to text required.
8	However, the document also attempts to highlight some of the pitfalls of observational research (Section 5.2) which ends up detracting the reader from the purpose of the document (i.e., to serve as a “guide” to methodological standards). We suggest deleting the section to bring the focus back to the list of guidances from learned societies.	Disagree. A specific aim of document is to provide guidance on ‘Challenges and lessons learned’ and not just to replicate or list existing guidance documents. However, text of section 5.1 amended to serve as a more specific introduction to the issues in section 5.2.
8	There is no acknowledgement that the statistical methodologies which deal with confounding are themselves imperfect (and rather complex) and carry with them strong model assumptions and difficulty in interpretation. Moreover, they all have trouble dealing with unmeasured confounding, including IV methods, the results of which are entirely reliant on the validity of the instrument. Instead of focusing on statistical methodologies available to deal with confounding, the focus should be brought back to building a robust study design (through appropriate patient selection, avoidance of misclassification, etc), as well as setting limits on the extent to which conclusions can be drawn given the study limitations (due to confounding, selection bias, etc.).	Not agreed. The two approaches (robust study design and statistical methods) are considered complementary and both are covered in the Guide. Reference is specifically made in Section 5.1 to a series of textbooks covering standards to assure validity and robustness of study results.
8	There are inconsistencies between the methodology document and the Checklist of Methodological Standards; some items listed on the Checklist are not covered in the methodology document and vice versa. In particular, the statistical analysis section only contains some of the elements on the Checklist and seems to lack consistency as written.	Partially agree. The two documents have different purposes so that they need not be completely aligned but the Checklist is to be reviewed for any inconsistencies.

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8	<p>The document seems to call for pre-specified statistical analysis plans (as required in a RCT). However, the investigator often lacks information about the content of the data if they are working with existing data. Many of the pre-planned analysis may not be possible simply because of lack of available information, and the investigator often has to modify the analysis strategy to suit the availability of data. The document gives the impression that anything short of a priori analysis is invalid; however, in the context of existing data studies, post-hoc analysis becomes a pragmatic solution to arriving at interpretable results.</p>	<p>Disagree. Even in RCTs a lot of work goes into specifying what will be done if the data are not collected as hoped and this is no different in observational studies. Thus it is usual to pre-specify preferences and fall-back options rather a unique analysis. This is good practice in any study. To clarify, however, the following statement has been added to the section:</p> <p><i>'The statistical analysis plan should be sufficiently detailed so that it can be followed in the same way by any competent analyst. Thus it should provide clear and complete templates for each analysis. <b>Pre-specified statistical analyses can be challenging for data that are not collected specifically to answer the study questions. This is usually the case in retrospective observational studies. However, thoughtful specification of the way missing values will be handled or the use of a small part of the data as a pilot set to guide analysis can be useful techniques to overcome such problems.</b> A feature common to most studies is that some not pre-specified analyses will be performed in response to chance observations in the data. It is important to distinguish between such data-driven analyses and the pre-specified findings. <b>Post-hoc modifications to the analysis strategy should be noted and explained.</b> The statistical analysis plan provides a confirmation of this process.'</i></p>
8	<p>It is unclear how pilot studies will be handled by ENCePP which could be needed to better understand the dataset prior to performing the full analysis.</p>	<p>Agree but issue is still under discussion within ENCePP and the document may be updated at a later stage in line with the outcome of discussions. In the meantime, an</p>



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		acknowledgement that feasibility/pilot studies may be an important part of a study as long as they do not impact on the outcomes planned in the study protocol has been added to the section on statistical analysis.
9	This is a very well written and comprehensive document giving the foundation for pharmacoepidemiological studies. It is very valuable especially due to the large number of references for further reading within the different presented subjects.	No change to text required
10	This draft guide constitutes a very important document for a large epidemiology and pharmacoepidemiology audience. Similar methodological standards should be present in all pharmacoepidemiology protocols, reports and related documents, whether they apply to academic, industry, regulatory or public health organizations. The draft guide addresses some of those very nicely but, at times, tends to lose focus, on aspects that are critical on Pharmacoepidemiology studies such as AEs safety reporting details or discussion on specific protocol design and methodological questions. A bit more of balance could be established in the draft guide by reducing some sections and expanding others a bit more (see other comments below).	No change to text required.
10	The draft guide takes note of the increasing application of modern statistical methods, such as propensity score methodology and instrumental variable analysis, to problems in epidemiology. However, the document does not cite definitive references by recognized experts. For example, the paper by Angrist JD, Imbens GW, and Rubin DB. Identification of Causal Effects Using Instrumental Variables. Journal of the American Statistical Association 91: 444-472, 1996; and the paper by Rubin DB. "Estimating Causal Effects from Large Data Sets Using Propensity Scores". Annals of Internal Medicine 127; (8): 757-763, 1997. Consequently, the draft guide does not provide sufficient guidance as to the underlying assumptions that are requisite to	Not agreed. The articles published by Angrist and by Rubin are good; however, the more recent articles cited in the Guide further develop the method with more practical applications that may be more useful to the readers. The article by Angrist is cited in the references of currently cited articles and may be consulted for further reading.

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	the correct application of these methods.	
10	Another general comment is that the draft guide has very little mention to biological products and vaccines. This could be addressed and expanded.	Not agreed. The present document does not address requirements for specific classes of products. These aspects might be considered at a later stage as an update.
11	BPI welcomes the ENCePP Guide on Methodological Standards in Pharmacoepidemiology in order to assure high quality pharmacoepidemiological "ENCEPP Studies". The Guide has been well received and generally accepted by BPI Members to be a valuable and important step forward to promote transparency regarding methodologies and design used in pharmacoepidemiological studies performed in the EU. However, there is one aspect to be considered concerning the data sources (see 'specific comments on text').	No change in text required other than that relating to specific comment.
12	EUCOPE welcomes the approach taken in the ENCePP Guide on Methodological Standards in Pharmacoepidemiology to identify in a dynamic process reliable sources regarding methodologies and design used in pharmacoepidemiological studies performed in the EU. Guidance in this regard is an important basis for coherent approaches which are increasingly important in a European environment. Transparency and coherence are key to assure high quality pharmacoepidemiological "ENCEPP Studies". Thus, the Guide has been well received and generally accepted by EUCOPE Members. We have only one aspect that needs to be clarified (see 'specific comments on text').	No change in text required other than that relating to specific comment.
13	Overall the document has been praised by EFPIA companies as well written, very comprehensive, an excellent information resource document, detailing much of the necessary information that researchers should adhere to.	No change to text required
13	The document is generally considered up-to-date, despite use of older, but well-known examples. Many of the references, however, are quite old or from older texts. As the stated goal is 'to provide a structured architecture	Not agreed. References are provided and these are considered as access documents supporting key concepts

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	for thinking and learning', it would be useful to <u>provide relevant search terms/MESH terms</u> for the key concepts throughout the document. This would allow the reader to go to the literature for a deeper dive on a particular topic or to update the content as they see fit. If ENCePP has used particular search strategies to identify the literature in a particular area, it could be very useful for further updates.	and providing MESH terms.
13	The tone and language should make clearer that <u>this is a reference document, not a regulatory guidance.</u> For example, in most places it would be appropriate to replace the word "should" with "could". The word "Overview" instead of "Guide" in the title would more accurately describe the purpose of the document.	Not agreed. Decision is to keep "should" where this is intended. From the outset, the intention was to do something more than compile an inventory of existing guidelines, and the aim was to provide a guidance on what ENCePP considers as good practice, for example in terms of study protocols, what confounders to consider etc. A statement that this is a scientific guidance rather than a regulatory one has been added in the 'Introduction'.
13	The objectives of the document are fairly stated but actual <u>standards in epidemiology</u> seem to be obscured in the style of the writing of the document. The document has the ambition to cover an incredibly broad, evolving and sometime controversial area yet it could be improved so as not seeming to be a patchwork of thoughts and consideration around a loose framework of key topics. The 'vocabulary' is a bit peculiar in places (e.g., the use of "occurrence relation" in the Study Design section as well as the term 'cohort' which alternates between population of people and the study design).	Agreed. The text has been screened for clarity. For example, "occurrence relation" is a well known concept in epidemiology introduced by Miettinen although it may not be used across the range of epidemiologists. The text has been clarified with the addition of the definition of the term 'occurrence relation' and a reference:  <i>..(1) the design of the 'occurrence relation' as defined in Theoretical Epidemiology (Miettinen O.S. John Wiley &amp; Sons, 1985) as the relation of a parameter of occurrence to a determinant or a set of determinants e.g. the incidence rate ratio of GI bleeds among users and non-users of NSAIDs),</i> <del>(theoretical design, for instance use of NSAIDs resulting</del>

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		<del>in GI bleeds),...</del>
13	The <u>document structure</u> could be improved to provide a logical flow of the document, re- arranging some sections as follows: moving “Section 4. Governance” after “Section 9. Safety Reporting” and “Section 6. Data Sources” after “Section 3. Research Question”.	Partially agree. Section 4 ‘Governance’ moved to after Section 1 ‘Introduction’ because principles are important and then the subsequent sections follow more the flow of a study protocol. Otherwise to remain as is.
13	There is some <u>lack of consistency in the level of detail</u> achieved in various sections: section 5.2 “challenges and lessons learned” could be less detailed as this information changes rapidly and should be obtained from up to date texts. There is a lot of territory given to some bias issues (e.g., immortal time bias) that seems disproportionate to its level of discussion in the pharmacoepidemiology literature.	Not agreed. The topics included in this section have been identified as gaps in the guidance that is currently provided and in the pharmacoepidemiological literature and the level of discussion reflects this appropriately.
13	<u>Discussion of ‘data quality’</u> not the quality assurance process is difficult to find in this document. Underlying data quality, particularly in US claims databases, is particularly problematic---there is some discussion and a couple of references (lines 349 to 384) but given the territory afforded confounding, this issue deserves a bit stronger section. We would suggest that the authors look to substantive studies from Duke University and elsewhere that have attempted to systematically compare what is in the database to the actual clinical reality (Duke did this for major cardiovascular issues---see Jollis et al., Ann Intern Med. 1993;119: 844-850). Similarly, consistency and totality of data capture (does the database reliably capture all of the patient’s health care interactions or are there known gaps in coverage, capture, longitudinality, eligibility). Similarly, validity of the data and the definitions used. This is not simply about source record validation of a particular endpoint---there are many possible ways to define endpoints and researchers that do validate, only seek to validate their choice. We would strongly recommend that the authors also look at what the Observational Medical Outcomes Partnership (OMOP <a href="http://omop.fnih.org">http://omop.fnih.org</a> )	Agree. Text amended to cite Observational Medical Outcomes Partnership website and articles by Jollis et al. and Stang et al. referred to.

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	are doing in several of these areas: methods, data quality, databases, definition of events of interest, networks (see Stang et al., Annals of Internal Medicine 2010; 153:600-606). As with EU-ADR and other similar efforts, the website contains a lot of relevant information and findings that may be helpful. Similarly, the mini-Sentinel effort may be informative.	
13	There is little, if any discussion of <u>adaptive designs</u> .	Agreed. Adaptive designs are designs for clinical trials that are still under development. They may be included in an update.
13	Some of the methods literature cites <u>spontaneous adverse event reporting database</u> analyses, in particular in Section 5.3 “Signal detection and methodology and application”. Little else in the document really focuses on this data source which has a long and rich history in this field. This data source should be cited in section 6.	Agreed section 5.3 has been relocated among “Data sources” available for pharmacoepidemiology research in Section 6.
13	We recommend clarifying in the document (e.g. in Section 10. Communication, when referencing to the <u>ENCePP Code of Conduct</u> ) that only ENCePP conducted studies should be registered and results posted on the ENCePP website. Studies conducted by MAH as a regulatory commitment with the EMA will become available via the EPARs after regulatory assessment.	See outcome of previous similar comment – refer to ENCePP Task Force on access to data.
13	The format and content for the posting of <u>epidemiology study results</u> should be discussed with all stakeholders to ensure it is adequate and user friendly.	See outcome of previous similar comment – refer to ENCePP Task Force on access to data.
13	The <u>hyperlinks</u> cited throughout the document are a valuable resource. We suggest including a table in the appendix for all hyperlinks organized by topic.	Not agreed. Hyperlinks are embedded in the text in the relevant sections and compiled alphabetically – a table by topic would lead to multiple repetitions.
13	It would be useful to add a <u>list of abbreviations</u> at the beginning of the document.	Agree. A list of abbreviations has been added following the Table of Contents.

### 3. Specific comments on text

(new text in **bold**, deletions in ~~double strikethrough~~)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>1. Introduction</b>			
Lines 54 – 56	3	It might be helpful to mention early in the document that other EMA documents should be consulted for more detailed information on study design and methods considerations in the context of conduct and evaluation of pharmacoepidemiologic and pharmacovigilance studies (e.g., ENCePP methods checklist).	Not agreed. Already covered in the 'Introduction' and the section on 'Governance' has been moved to just after the 'Introduction' to refer to ENCePP documents.
Lines 59 - 60	5	Comment: .... "to fuel learned regulatory decision making" ... Please clarify the meaning of this statement.	Agreed. Text amended to read ....'to <b>inform regulatory decision making</b> '.
Lines 77 – 80	14	Comment: Reference should be made to the list of recommended guidances that were reviewed and that have been published on the ENCePP website.	Agreed. Link to ENCePP website provided.

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<b>2. General aspects of study protocol</b>			
Lines 94 – 100	10	Comment: The draft guide could emphasize a bit more the importance to minimize the number of protocol amendments and updates. It is not good practice to have too many amendments in a protocol since they often create inconsistencies in definitions, interpretation of data etc. and can result in exclusion of data from final analysis.  Proposed change (if any): "The study protocol is the core document	Agree. Text amended to read as follows:  <i>'The study protocol is the core document of a study. A protocol should be drafted as one of the first steps in any research project, and should be amended and updated as needed throughout its course. <b>Amendments should be justified.</b>'</i>

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<b>2. General aspects of study protocol</b>			
		of a study. A protocol should be drafted as one of the first steps in any research project, and should be amended and updated as needed throughout its course. <b>Amendments should be justified and minimized, as much as possible”....</b>	
Lines 94 – 100	13	<p>Comment: Protocol should be reviewed, discussed, revised, agreed, and approved. Any later changes have to be made through an agreed amendment process</p> <p>Proposed change: A protocol should be drafted as one of the first steps in any research project, and should be <del>amended and updated as needed throughout its course</del> <b>reviewed, discussed, revised, agreed, and approved. Any later changes have to be made through an agreed amendment process.</b></p>	Agree. See previous comment for amended text.
Line 96	15	Comment: Rephrase as ‘It must precisely describe everything that...’	Agree. Text amended as suggested.
Lines 96 – 97	13	<p>Comment: it is not possible to achieve exact reproduction without the complete program code. Presumably this will require updates to the protocol once submitted, but this should be clarified.</p> <p>Proposed change: No change proposed.</p>	Agree. The term ‘ <i>exactly</i> ’ deleted
Lines 101 – 114	10	<p>Comment: A sentence could be added indicating that laboratory tests should be validate or a validation plan should be proposed in the protocol.</p> <p>Proposed change (if any): “As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included, <b>as well as validation steps taken or considered to standardize laboratory methods proposed.</b>”</p>	Agree. Text amended as proposed.

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<b>2. General aspects of study protocol</b>			
Line 102	13	<p>Comment: Please add “pharmacoepidemiology” prior to “protocol” to avoid any confusion with interventional study protocols.</p> <p>Proposed change: ...guidance on what is expected of a <b>pharmacoepidemiology</b> study protocol.</p>	Agree. Text amended as proposed.
Line 115	3	Suggest mentioning that this is not an all inclusive list of key aspects of a study protocol, as the statement that the protocol should cover all of the following aspects may lead people to believe that it is a comprehensive listing versus a high level overview.	<p>Agree. The text has been amended to read as follows:</p> <p><i>‘The protocol should cover <del>all of</del> at least the following aspects’</i></p>
Line 115	13	<p>Comment: Use less authoritative wording regarding protocol content.</p> <p>Proposed change: <del>The protocol should cover all of the following aspects.</del> <b>Factors that should be considered; if applicable:</b></p>	<p>Agree. The text has been amended to read as follows:</p> <p><i>‘The protocol should cover <del>all of</del> at least the following aspects’</i></p>
Lines 115 – 155	13	<p>Comment: It is stated that the study protocol should cover a number of aspects that are not traditionally included in a study protocol, or within large de novo studies are typically supplemental documents referred to in the study protocol. For example, in a large de novo study protocol it would be typical to have a separate Monitoring Plan document and Endpoint Manual covering the definition of endpoints and the processes used to adjudicate endpoints. Even in claims or medical records databases, the codes used to define an endpoint could be supplemental documents. The guide should consider more flexibility in that it is important to document/address these elements but they do not need to be included in the study protocol itself. Further, these extremely detailed elements are likely not relevant to most ethical review boards or investigators and a streamlined</p>	Disagree. The text provides high level recommendations without specifying the format of the protocol documentation.



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<b>2. General aspects of study protocol</b>			
		<p>protocol would better serve their needs.</p> <p>Proposed change: Consider language that provides more flexibility, such as the possibility to refer to appendices for elements of the protocol that would be too voluminous.</p>	
Lines 117 – 119	13	<p>Comment: Use less authoritative wording regarding protocol content.</p> <p>Proposed change (if any): The protocol <del>will</del> <b>should</b> include a background description that expounds the origin (scientific, regulatory, etc.) and the state of present knowledge of the research question.</p>	Agree. Text amended as suggested
Line 128	5	<p>Proposed change (if any): Please consider: “The source and study populations to be used to answer the research question...” Otherwise it sounds as if one would derive the study population from the research question.</p>	<p>Agree. Text amended as suggested to read:</p> <p><i>‘The source and study populations to be <del>derived from</del> <b>used to answer</b> the research question. <del>and the specific study objectives.</del></i></p>
Lines 128 – 129	5	<p>Proposed change (if any): Delete “and the specific study objectives.” (this is already mentioned in Lines 124-127).</p>	Agree. Text amended as suggested.
Lines 128 – 133	10	<p>Comment: A sentence could be added indicating the importance to address representativeness of the data (strengths and limitations) to the general population.</p>	Disagree. The study population is derived from the research question and representativeness is not necessarily relevant
Lines 129 – 130	13	<p>Comment: Alternate wording proposed.</p> <p>Proposed change: The protocol should describe whether this population is already <del>included</del> <b>available (such as, in a database)</b> or whether it needs to be recruited <i>de novo</i>.</p>	Agree. Text amended as suggested

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<b>2. General aspects of study protocol</b>			
Lines 141 – 144	13	<p>Comment: suggestion for better organisation.</p> <p>Proposed change: The paragraphs on covariates, statistical analysis, and identification of biases... could be grouped into a single section called “Methods of data analysis” (or similar).</p>	Disagree. Each bullet point addresses specific issues.
Line 143	5	<p>Comment: ... “and how the results are going to be addressed.” Please clarify the meaning of this statement.</p>	Agree text amended to replace ‘addressed’ with ‘presented’
Line 147	14	<p>Comment: replace ‘the ENCePP Code of Conduct’ with ‘Section 4 of the current guidance document’.</p>	Agree. Text amended as suggested
Lines 148 – 149	13	<p>Comment: The EMA recommends that the contract be a part of the protocol or that the protocol be part of the contract. The contract between the investigator and the sponsor should exist separately, not as part of the protocol. The contract contains proprietary/competitive information about vendors (i.e. pay per hour, cost of specific deliverables) that would be inappropriate to include as part of a protocol. Certainly, it would not be appropriate to include this information in a protocol filed to numerous regulatory bodies/Ethical Review Boards, effectively making the contract publically available through its wide distribution (i.e. in large de novo epidemiology studies hundreds of Ethical Review Boards might review a protocol).</p> <p>Proposed change: This would be better stated as recommending that the contract reference the study protocol and associated obligations of each investigator.</p>	Agree. Sentence deleted as outside scope of the present guidance.
Lines 150 – 155	5	<p>Comment: Please clarify if this is specifically if one wants to register the study with ENCePP or in general? Often the CRF per se is not part of the protocol.</p>	Agree. See comment below. Text amended to read <i>‘Other forms might be included as needed, such as patient information and patient-oriented summaries,</i>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>2. General aspects of study protocol</b>			
			<i>etc. <del>copies of submissions (e.g. to ClinicalTrials.gov, ENCePP or other repositories), publications etc.</del></i>
Lines 150 – 155	10	<p>Comment: It is not uncommon for CRFs to be amended as study is the being implemented. This is not good practice (see also comment above). One way to address this is by proposing a piloting of the CRF (and / or study) as part of the protocol with a specific short section defining how the piloting will take place and at what point the CRF will be considered as final.</p> <p>Proposed change (if any): "The various data collection forms including the Case Report Form (CRF) or descriptions of the data elements to be appended to the protocol, allowing having an exact representation of the data collection. <b>The study protocols could include a section specifying ways in which the CRF will be piloted, tested and finalized. Amendments of final CRFs should be avoided as much as possible.</b> For field studies, physician or patient forms would be included depending on data collection methodology. Other forms might be included as needed, such as patient information, patient-oriented summaries, copies of submissions (e.g. to ClinicalTrials.gov, ENCePP or other repositories), publications etc."</p>	Partially agree. Text amended with addition of ' <b>The study protocols could include a section specifying ways in which the CRF will be piloted, tested and finalized.</b> ' The second proposed additional statement that ' <b>Amendments of final CRFs should be avoided as much as possible.</b> ' has not been included in the text as it is considered that amendments may be appropriate, if justified. See also previous comment relating to this point.
Lines 153 – 155	14	<p>Comment: The rationale behind the request to include copies of submissions (for example to ClinicalTrials.gov, ENCePP or other repositories) and publications with the protocol is unclear.</p> <p>Proposed change: Rephrase statement as follows:</p>	<p>Agree. Text amended as follows:</p> <p><i>'Other forms might be included as needed, such as patient information and patient-oriented summaries, etc. <del>copies of submissions (e.g. to ClinicalTrials.gov, ENCePP or other repositories), publications etc.</del></i></p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>2. General aspects of study protocol</b>			
		"Other forms might be included as needed, such as patient information, patient-oriented summaries, <del>copies of submissions (e.g. to ClinicalTrials.gov, ENCePP or other repositories), publications</del> etc."	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>3. Research question</b>			
Lines 163 -166	15	Comment: Add 'health outcomes or benefit/risk profile' as a reason for conducting a pharmacoepidemiology study.	Agree. Text amended as suggested.
Lines 166 - 167	13	Comment: The current document reads "a-priori hypotheses or data driven research." In fact most a-priori hypotheses are data driven, and this wording is unclear.  Proposed change: "a-priori hypotheses <b>or hypothesis generating research</b> ".	Partially agree. The term ' <i>data driven research</i> ' replaced with ' <i>exploratory analyses</i> '.
Line 169 – 170	5	Comment: Please clarify if main statistical measures really be part of the objectives?	Agree. Text amended to replace the term ' <i>statistical</i> ' with ' <i>outcome</i> '
Lines 171 -173	10	Comment: The statement below is unclear.  "A critical and thorough review of the literature usually forms the basis for the background description of the research question and a description of the theoretical framework of the study should be included in a protocol."	Agree. Text amended as suggested.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>3. Research question</b>			
		Proposed change (if any): "A critical and thorough review of the literature usually forms the basis for the background description <b>and theoretical</b> framework of the research question and <del>a description of the theoretical framework of the study</del> should be included in a protocol."	
Lines 188 – 196	13	<p>Comment: It is unusual for a background section to comprise a formal meta-analysis which is a research work in itself and should be the subject of a separate protocol and a separate study. The background section should reference to and a summary of available systematic reviews and meta-analyses.</p> <p>Proposed change: Delete the sentence in line 192-194.</p>	<p>Agree. Meta-analysis is addressed elsewhere in the Guide. The following text has been deleted:</p> <p><del>In some circumstances systematic review and meta-analysis are appropriate (see Section 5.4) and guidance is available in the Cochrane Handbook for Systematic Reviews of Interventions. The key source for identifying systematic reviews is via the Cochrane Collaboration, an international network of researchers working on systematic reviews.</del></p>
Lines 188 – 196	13	<p>Comment: Lines 188-196 provide the first mention of systematic reviews. There is a reference to the Cochrane Handbook. It might be helpful to get more specific and mention sections on non-randomized studies, which are not a major focus of Cochrane, in general.</p>	<p>Disagree. Meta-analysis is addressed elsewhere in the Guide. The following text has been deleted (see previous comment):</p> <p><del>In some circumstances systematic review and meta-analysis are appropriate (see Section 5.4) and guidance is available in the Cochrane Handbook for Systematic Reviews of Interventions. The key source for identifying systematic reviews is via the Cochrane Collaboration, an international network of researchers working on systematic reviews.</del></p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>3. Research question</b>			

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>4. Governance</b>			
Line 197	13	<p>Comment: Use more descriptive section heading.</p> <p>Proposed change: <u>Data Source Permissions and Governance</u></p>	Disagree. See comment below.
Line 197	14	<p>Comment: Replace heading 'Governance' with 'General principles'.</p>	Disagree. Leave as 'Governance'.
Lines 200 – 203	13	<p>Comment: Alternate wording proposed below.</p> <p>Proposed change: Regarding the requirements of differing data custodians across EU, the <u>maximum</u> requirement (rather than minimum) should naturally fit within the overall need to meet all applicable EU and national laws and guidelines for the actual study</p>	<p>Partially agree. The text has been amended as follows:</p> <p><i>'While differing data custodians currently have differing requirements related to what approvals are needed before data can be released, the <del>minimum</del> requirements will naturally fit within the overall need to meet all applicable EU and national laws and guidelines for the actual study,...'</i></p>
Lines 208 – 210	14	<p>Comment: The requirements of various approval systems are outside the scope of the current document and these lines repeat what is already said in lines 205 – 207.</p> <p>Proposed change: <del>"Of note, some approval systems only want to see a summary or shortened form of the protocol, but at least one of the approvals generally needs to be based upon the full protocol."</del></p>	<p>Agree. Text amended as follows:</p> <p><del>'Of note, some approval systems only want to see a summary or shortened form of the protocol, but at least one of the approvals generally needs to be based upon the full protocol.'</del></p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>4. Governance</b>			
Lines 210 – 211	13	<p>Comment: 'In addition, ethics approval does not cover science approval and within the concept'. We believe that this sentence is confusing as many ethics committees do in fact cover scientific approval. Please clarify the exact intent of the sentence here.</p> <p>Proposed change: Please expand on what is seen as 'scientific approval' in the context of an epidemiological study.</p>	<p>Agree. Text amended as follows:</p> <p><del>"In addition, ethics approval does not cover science approval and within the concept of ENCePP both need to be fully satisfied."</del></p>
Lines 210 – 211	14	<p>Comment: The ENCePP Code of Conduct does not provide rules or guidance on methodological aspects or scientific standards to be used for specific studies or study types. Adherence to the Code will not guarantee validity or accuracy of study data. Science approval is, therefore, outside the concept of ENCePP.</p> <p>Proposed change: <del>"In addition, ethics approval does not cover science approval and within the concept of ENCePP both need to be fully satisfied."</del></p>	<p>Agree. See previous comment. Text amended as follows:</p> <p><del>"In addition, ethics approval does not cover science approval and within the concept of ENCePP both need to be fully satisfied."</del></p>
Line 212	14	<p>Comment: Suggest replacing the section heading '4.1. General principles' with '4.1. Best practice of ENCePP Studies' as the section text relates entirely to the ENCePP Code of Conduct and its relevance to the ENCePP Study concept.</p>	<p>Agree. Heading replaced.</p>
Lines 221 – 223	13	<p>Comment: It is reminded that the ENCePP Code of Conduct requires an "obligation to publish all study findings irrespective of positive or negative results." Is the intention to mean obligation to submit to a journal for publication? Study authors do not have influence over Journal Editors decision to publish nor their preferences which are demonstrated in numerous studies to be toward publishing positive, as opposed to negative, results. It should be reminded that the</p>	<p>Partially agree. The relevant section heading has been changed from '4.1 General principles' to '4.1 General principles of ENCePP Studies' to clarify the section relates to implementation of the ENCePP Code of Conduct in the context of ENCePP studies. Further aspects of research communication including submission to journals are already highlighted in the</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>4. Governance</b>			
		obligation is for publishing in the registry.  Proposed change underlined: "... obligation to publish all study findings irrespective of positive or negative results <u>in the ENCePP e-register of studies</u> ".	section of the Guide on 'Communication'.
Lines 231 – 237	10	Comment: First sentence does not read well.  Proposed change (if any): "Many research organisations <b>(including those owning or hosting/holding databases)</b> have scientific review boards that ensure scientific standards are met".	Agree. Text amended as suggested.
Lines 234 – 236	13	Comment: The lines 'independent experts to review the study results as well as the protocol and any publications and/or communications thereof, regardless of whether a study steering group has been established' may need to be further explained as steering groups are often set up to assure 'independence' from sponsors and institutions. This could lead to many separate groups having to be set up to govern pharmacoepidemiology studies and lead to unnecessary complexity.	Disagree. Text amended as follows:  <i>'In addition, it is good practice to invite <del>independent</del> experts to review the study results as well as the protocol and any publications and/or communications thereof. <del>regardless of whether a study steering group has been established.</del></i>
Lines 238 – 280	3	One comment on Section 4.3: Ethical conduct, patient and data protection. Some aspects of ENCePP appear to be similar to FDA's Sentinel project. FDA has worked hard to identify and protect patient privacy and related interests in the Sentinel project, and has concluded that certain human subject protections applicable to clinical studies would not apply to certain kinds of medical record review and/or research – although privacy protection is critical. Section 4.3 of this document identifies a wide range of human subject protection documents, leading with the Declaration of	Agree: the following statement has been added to the section to highlight that ethical requirements differ between studies:  <b><i>'From the examples provided above, it may be seen that there is a wide range of human subject protection documents. The applicability of ethical requirements, however, varies based on the nature of the inquiry and the studies to be conducted. Certain human subject</i></b>



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<b>4. Governance</b>			
		Helsinki, without stating that the applicability of these may vary based on the nature of the inquiry. This could be understood to imply that the full range of protections applicable to clinical research would always apply. If that is the case (full informed consent even for review of data from de-identified medical records?) it may be very difficult to conduct certain studies under this program.	<b><i>protections applicable to clinical studies (e.g. full informed consent) would not apply to certain kinds of research (e.g. review of data from de-identified medical records).</i></b>
Lines 239 – 243	13	<p>Comment: It is important to create conscience on the rights of patients, including health data protection, not only in clinical trials, but also in non-interventional studies.</p> <p>Proposed change underlined: The Declaration of Helsinki and the provisions on processing of personal data and the protection of privacy as laid down in Directive 95/46/EC and Regulation 45/2001 of the European Parliament and the Council need to be followed in terms of the ethical conduct of <b>interventional and observational</b> studies. For interventional research, the clinical Trial Directive (Directive 2001/20/EC) applies.</p>	Agree. Addressed in relation to previous comment
Lines 244-249	7	It is worthwhile to mention here, that non-interventional studies are not governed by the European Clinical Trial Directive (and therefore the Guidelines for Good Clinical Practice (Commission Directive 2005/28/EC) is not applicable. This needs to be clarified in this section.	Agree. Text amended in line with proposal in comment below.
Lines 247 - 249	15	Comment: Rephrase as “The guidance in Volume 9A on Pharmacovigilance of the Rules Governing Medicinal Products in the EU and, <b>for clinical trials, the</b> Guidelines for Good Clinical Practice (Commission Directive 2005/28/EC) should also be followed.”	Agree. Text amended as proposed to read:  <i>‘The guidance in Volume 9A on Pharmacovigilance of the Rules Governing Medicinal Products in the EU and, <b>for clinical trials, the</b> Guidelines for Good</i>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>4. Governance</b>			
			<i>Clinical Practice (Commission Directive 2005/28/EC) should also be followed.'</i>
Lines 250 - 258	13	Comment: Lines 250-258 talk only briefly about privacy issues. Is there a summary message here about what usually is or isn't allowable in terms of privacy (for specific types of data, e.g., claims data, EMR, etc.)? It's helpful to have a list of references, but are there any general principles here? The document does provide general principle in other sections.	Agree: A summary statement added referring to the need for privacy as paramount but that there may be situations in which the use of data for secondary analyses has public health benefits:  <b><i>'Furthermore, while protection of privacy is paramount, there may be situations in which the use of data for secondary analyses has public health benefits.'</i></b>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>5. Study Design and Methods</b>			
Lines 333 - 583	13	Comment: Good overview of methodological challenges.	No change to text required
Lines 281 - 667	13	Proposed change: Please carry the example in Section 5.1 throughout the various methods, as applicable.	Agree. Example is provided where relevant.
Line 281	5	Comment: The section mainly focuses on analytical methods. We suggest also a section with the different study designs, pros and cons that could also refer to which analytical methods are best used for which study design.	Disagree (see response to similar general comment i.e. the approach of the authors was not to repeat well known concepts verbatim in the present document but to refer to relevant source documents of information. This is explained in the first paragraph of the introduction).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>5. Study Design and Methods</b>			
Lines 282 - 332	13	<p>Comment: Nothing is said about the main study designs, just providing a list of textbooks. This omission seems strange, considering the great amount of detail provided on other aspects such as bias and confounding.</p> <p>Proposed change: Some considerations on the classical study designs (case-control, cohort....) should be added. Also, the new designs mentioned in 6.3 ("Hybrid studies") could be moved to this section rather than discussing them in section 6 "Data sources".</p>	Disagree see also previous comment and section on 'Hybrid studies' relates directly to data sources
Lines 283 – 287 and beyond	10	<p>Comment: It is fine to use the example of NSAIDs and risk of GI bleedings throughout the text but it should be done with moderation. Some parts of the document go too much into detail on this example.</p>	Disagree. Example is provided where relevant.
Line 288	13	<p>Comment: Line 288 refers to "three keys", but does not explain what is meant.</p> <p>Proposed change: The sentence would suffice as "The research question drives three and sequentially structured phases...."</p> <p>NB: Typographical error "three keys"</p>	<p><i>Partially agree. Text amended to read:</i></p> <p><i>'The research question drives three keys sequentially structured phases....'</i></p>
Line 289 (and also 291, 295, 298)	13	<p>Comment: It is not clear what is meant by "(1) the design of the occurrence relation (theoretical design)..." and the example given in parentheses on line 290 " for instance use of NSAIDs resulting in GI bleeds" does not help to clarify. Does it refer to the study question, hypothesis, design, or something else? Also, The phrase "occurrence relation" is particularly obscure. It appears to refer to what is commonly referred to as the "association of interest" or the "exposure-outcome association".</p>	<p>Disagree on avoiding the use of the term, however, text clarified (see previous similar general comment):</p> <p><i>'..(1) the design of the 'occurrence relation' as defined in Theoretical Epidemiology (Miettinen O.S. John Wiley &amp; Sons, 1985) as the relation of a parameter of occurrence to a determinant or a set of determinants e.g. the incidence rate</i></p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>5. Study Design and Methods</b>			
		Proposed change: Revise and clarify item 1 and avoid the use of "occurrence relation".	<b>ratio of GI bleeds among users and non-users of NSAIDs),</b> <del>(theoretical design, for instance use of NSAIDs resulting in GI bleeds),...</del>
Line 290	3	Selection of appropriate e-health data sources is an important aspect of the "design of data collection." It might be helpful to mention this explicitly.	Agree. Depending on research question you may need to go to other sources of data so text amended accordingly, including a reference to Section 6 and an example:  <b>'Note the selection of appropriate electronic health data sources is an important aspect of the design of data collection and depending on the research question, other sources of data may be needed e.g. some claims databases may not have a 'reason for stopping' a NSAID whereas another may have (see Section 6).'</b>
Line 303	5	Comment: It would be useful to mention the Do's and Don'ts.	Disagree. This is a general expression and the following paragraph expands on the statement.
Lines 333 - 583	8	Comment: The purpose of Section 5.2 is unclear. Good practice guidelines and reference materials for epidemiologic principles have already been cited in earlier sections, so the purpose of providing a listing of potential biases is unclear.  Proposed change (if any): Clarify purpose of Section 5.2.	Previously addressed as a general comment.
Lines 333 - 583	3	Would be helpful to organize the challenges and lessons learned under a few key categories. For example: 1. Study design (drug exposure and outcome definition; validation); 2. Use of automated health data; 3. Bias and confounding (confounding by indication,	Agree. Section amended as suggested.

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<b>5. Study Design and Methods</b>			
		channelling, immortal time bias, unmeasured confounding); and 4. Methods to handle bias and confounding (disease risk scores, propensity scores, IV, MSM).	
Lines 333 - 583	13	<p>Comment: This section is extremely long and detailed, but has also not included some of the most basic methodologies (that could be reminded in 5.1, see above). There needs to be a better structure of the chapter: it would be helpful to have a top-line summary of each method, and a brief explanation of the concept to better understand the difference between the approaches – each method should also have the relevant references listed.</p> <p>The document overall seems to mix various levels of granularity in the description of methods, there is no consistent level of detail.</p> <p>Some additional organization would be helpful, such as grouping the challenges and lessons learned into categories.</p> <p>Proposed changes: (1) Edit the sections on more complex methods and provide references. (2) (Multiple) regression techniques are fundamental to epidemiology and should be included. (3) We also recommend to add a paragraph on Bayesian methods, as per below: Bayesian methods as an approach to the multiple testing problem Pharmacoepidemiology has the potential to study the effect of exposure to each of large number of medicines on each of a large number of outcomes. If all possible significance tests are performed, a large number of false-positive results is expected. This makes decision-taking on the basis of significant test results difficult, which may inhibit researchers from exploring many hypotheses of potential interest.</p>	<p>Partially agree to aspects of this comment and the structure is to be amended in line with previous comment with the aim of getting balance in granularity and a reminder added in the introduction to the section stating:</p> <p><b><i>'It is reminded that these are not basic methodologies that are well covered in the textbooks cited. Furthermore, the granularity in the description of some of the methods is in line with the extent to which the issue is considered covered in existing guidances.'</i></b></p> <p>There are textbooks addressing multiple regression techniques and so this does not need to be explored here. Bayesian techniques are referred to in section 5.3. The proposed text on Bayesian methods is considered too detailed.</p>

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		<p>Corrections for multiple testing, such as the Bonferroni correction, are available. However, the Bonferroni correction has two important drawbacks: - it is strongly dependent on the number of tests for which the correction is made, whereas in practice this number may not be closely specified, and may change as discussion proceeds; - it assumes that the tests are mutually independent, whereas there are typically strong correlations among the tests performed.</p> <p>An alternative approach that avoids these drawbacks is provided by Bayesian methods, such as Bayesian logistic regression. This makes the assumption that most exposures do not affect most outcomes, and hence gives a large prior probability to the hypothesis that the regression coefficient for each exposure-outcome combination is zero. The result is a parsimonious regression model, in which the outcome is explained by just a few exposures, for which there is strong evidence against this hypothesis. Even for these exposures, the regression coefficient is shrunk towards zero. This shrinkage reflects the lack of prior confidence in the association, which is due its being one of a large number of associations considered in a 'fishing expedition'.</p> <p>Bayesian logistic regression presents the evidence of association between an exposure and an outcome in terms of the posterior distribution of a regression parameter, rather than a p values representing the strength of evidence against a null hypothesis. This is not necessarily a disadvantage, but may not be readily accepted by an audience that is more familiar with p values.</p> <p>(4) Separate the section into sub-sections, for example: <u>5.2.1 Data quality</u> (to include Drug exposure/outcome definition and validation,</p>	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>5. Study Design and Methods</b>			
		use of automated databases) – see general comment to develop this part. <u>5.2.2 "Bias and confounding"</u> (to include confounding by indication, immortal time bias, channelling, unmeasured confounding). <u>5.2.3 "Analytic strategies to control for confounding"</u> (to include Multiple regression, Bayesian methods, Disease scores, Propensity scores, IV and MSM). (5) We recommend final editing of a very small writing group, right now there is too much variation in style and level of detail.	
Lines 334-339 and lines 386-391 and beyond	10	Comment: In general, the material dealing with methodology in observational studies, in particular Section 5.2 "Challenges and Lessons Learned" is not easy to read and follow. Some paragraphs in this section (e.g. lines 334-339 and lines 386-391) are not clear or are misleading. Also, too much detail seems to be provided in some sections of this part of the document. Could it be considered rewriting and simplifying this section (5) a bit more?	See response to previous comment. The specific text referred to has also been reviewed and is not considered misleading.
Line 340 - 348	6	Comment: Section on exposure/outcome definition may benefit from further development. First sentence of this section is unclear.	Disagree. Reference given to textbook.
Line 340 - 348	6	Have separate sections for Exposure and Outcome	Disagree. This section relates to definition and validation, which apply to both.
Line 340 - 348	6	For outcome validation: add a reference to the Brighton Collaboration case definitions ( <a href="http://brightoncollaboration.org">brightoncollaboration.org</a> )	Disagree. The Brighton Collaboration is specific to immunisation.
Line 340 - 348	6	Discuss the option of blind, independent case adjudication	Disagree. This section relates to case definition and validation.
Line 340 -	6	Discuss the effect of case ascertainment specificity on risk estimates	Disagree. This aspect is covered in the reference

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348			provided.
Lines 350 - 351	3	Might want to include the following reference on the limitations of pharmacoepidemiology research using e-health data: Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. Journal of Clinical Epidemiology 2005; 58:323-337.	Agreed. The reference has been included in section 6.1.
Lines 350 - 384	3	Would be helpful to first state each limitation followed by the explanation and finally the examples.	Agree. Text amended in line with the comment.
Line 374	13	Comment: Alternate wording proposed below.  Proposed change: The findings <del>included</del> <b>concluded</b> that a number...	Agree. Text amended as suggested.
Line 399	5	Comment: Several analytic methods for controlling of confounding by indication are mentioned and all of them except G-estimation are briefly explained in the guide.  Proposed change (if any): Include a brief explanation of G-estimation with a link to a proper citation if available.	Agree. Brief paragraph added to section 5.2.4 on G-estimation with an appropriate reference.
Line 405	6	Comment: Channelling bias is only one of many type of biases.  Proposed change (if any): Add sections on selection bias, protopathic bias, and so on, or refer to a publication where biases are systematically reviewed.	Disagree. The topics selected were issues that were considered as important to be addressed in the current guidance relating to gaps in existing guidance.
Lines 452 - 466	13	Comment: The discussion on immortal time bias has lots of useful references, and discusses possible solutions, but we are not sure the explanation of the phenomenon is clear enough. A detailed example would be most helpful.	Disagree. Reference may be consulted for additional information



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<b>5. Study Design and Methods</b>			
		Proposed change: We would suggest taking the Shariff example (lines 452-466) and explaining the nature of the potential bias very explicitly in the context of this example. Specifically how would the bias arise in this setting? Presenting this would make it clear why the solutions are solutions.	
Line 460	13	Comment: Alternate wording proposed.  Proposed change: ... is not counted <del>for</del> <b>in</b> either of the groups.	Agree. Text amended as suggested.
Line 513	3	Might want to consider citing publications discussing the emerging high dimension propensity (HDPS) model approach (e.g. Schneeweiss S, Rassen JA, et al. High-dimensional Propensity Score Adjustment in Studies of Treatment Effects Using Health Care Claims Data. Epidemiology July 2009; 20(4):512-522).	Agreed. This article addresses a frequent problem in propensity score adjustment and proposes a practical solution. Reference to the article has been added in section 5.2, Propensity scores.
Line 513	13	Comment: It will be helpful to point out that propensity scores are valid only when predicting exposure in cohort studies. The term has been misused in case-control studies to refer to predictors of outcome.	Disagree. Cohort study is mentioned in line 522.
Lines 530 - 536	7	These lines occur in a different font size.	Font amended.
Lines 584 - 667	13	Comment: Sections 5.3 (Signal detection) and 5.4 (Integrating and pooling studies) do not logically correspond to section 5 "Study design and methods"  Proposed change: These 2 sections should be separated from section 5.	Partially agree. Section 5.3 moved to Section 6 on 'Data sources', however, section on integrating studies considered relevant within 'Study design' and so retained in this section.
Lines 584 -	8	Comment: In Section 5.3 a discussion on the potential usefulness of large observational (claims data) as part of a larger signal detection	Agree. Reference to be made to a number of initiatives with observational data e.g. mini-Senitel,

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
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618		<p>strategy is missing.</p> <p>Proposed change (if any): Section 5.3 should include a discussion on the potential usefulness of large observational (claims data) as part of a larger signal detection strategy.</p>	EU-ADR, Protect. The section was also amended to streamline and to emphasise CIOMS report.
Lines 584 - 618	13	<p>Comment: This section should be either removed from the document or expanded to include rigorous discussion of limitations and predictive value for the identification of safety concerns with reference to publications (similar to epidemiologic study sections 5.1 and 5.2) and including separate considerations for differing data sources (spontaneous/clinical/longitudinal) and application to both passive and active pharmacovigilance surveillance systems. This section may have more relevance to a general pharmacovigilance and/or hypothesis-generation discussion.</p> <p>Proposed change: Remove or expand section.</p>	Agree in terms of expanding the section in line with response to previous comment.
Lines 599 - 603	13	<p>Comment: It is rare that there is sufficient information in spontaneous reports on confounding and risk factors, or sufficient sensitivity to stimulated reporting, consequently the data quality is unlikely to be robust enough for a case-control study, and this should not be encouraged as good practice.</p>	Agreed. Mention of a case-control study has been deleted.
Lines 619 - 667	8	<p>Comment: In Section 5.4 the role of pooled RCT data as part of the post-marketing surveillance strategy is not discussed.</p> <p>Proposed change (if any): Section 5.4 should discuss the role of pooled RCT data as part of the post-marketing surveillance strategy.</p>	Disagree. Section 5.4 addresses challenges and lessons learned on methodological issues not the different potential use of these methods
Lines 621 -	13	<p>Comment: see suggested changes.</p>	Disagree. The proposal is contradictory to what is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>5. Study Design and Methods</b>			
623		Proposed change: In epidemiological studies, <b>especially meta-analyses</b> , the focus of the activity is to obtain an estimate of the effect size, <b>while trying to accommodate the heterogeneity that is inherent in study designs</b> , populations, results, and associated gaps in knowledge.	being said namely that the focus is not only on obtaining a valid point estimate but to also learn from the differences.
Lines 639 - 649	13	<p>Comment: The section on systematic reviews and meta-analyses might be enhanced by expanding on the notion that it will often be of greater interest to investigate sources of (reasons for) heterogeneity than to estimate a common effect. The document cites the Glasziou paper on this point, but could additional examples be added? There is a paper by Hennessy and colleagues* that somewhat debunks the notion that studies comparing 3rd generation to 2nd generation oral contraceptives, when they show an increase in risk of VTE, just reflect depletion of susceptibles (i.e., women who are new users are believed to be at increased risk of VTE, relative to experienced users. When the current document compares 3rd generation users, who were mostly new OC users at the time these studies were done, to 2nd generation OC users, who were mostly experienced users, one compares a population at risk (new users of 3rd generation OCs) with naïve users (experienced users of 2nd generation), thereby generating bias. The paper by Hennessy et al. addresses this point by doing a set of analyses limited to studies, or subgroups, examining new users in their first year of use. Even with this restriction imposed, the risk of VTE was increased among 3rd generation OC users.</p> <p>*Hennessy S, Berlin JA, Kinman JL, Margolis DJ, Marcus SM, Strom BL. Risk of venous thromboembolism from oral contraceptives</p>	Agreed. This paper has been added in the 5 <sup>th</sup> paragraph of section 5.4 as an example of a meta-analysis addressing confounding.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>5. Study Design and Methods</b>			
		containing gestodene and desogestrel versus levonorgestrel: a meta-analysis and formal sensitivity analysis. Contraception, 2001; 64:125-133.	
Lines 648 - 649	13	<p>Comment: alternate wording proposed</p> <p>Proposed change (if any):...when very significant heterogeneity exists, <del>the heterogeneity itself may deserve more emphasis than the pooled summary estimates</del> <b>it may not be appropriate to try and conduct a meta-analysis on such heterogeneous studies.</b></p>	Disagree – a lot can be learned from the heterogeneity of studies.
Lines 652 - 653	3	Suggest mentioning that in addition to the limitations of the sources of information that constitute a meta-analysis, there are also additional limitations pertaining to the actual statistical combination of data via a meta-analytic approach.	<p>Agree. Text amended in line with comment as follows:</p> <p><i>'Any SR and MA will, however, have the same limitations as the sources of information they use. <b>There are also additional limitations pertaining to the actual statistical combination of data via a meta-analytic approach.</b>'</i></p>
Line 655 - 658	5	<p>Comment: We do not believe that the incidence of disease is a good example here. Certainly, RCTs are not a proper method to address it, since it's a subject of a descriptive research and not analytical one, which RCTs are part of.</p> <p>Proposed change (if any): delete a mention of the incidence of disease here.</p>	Disagree – the point is made that RCTs will not address issues of incidence.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>6. Data Sources</b>			
Lines 669 - 672	10	Comment: This section is a very important part of the document. Good to comment more on the strengths and limitations of using existing and de novo data on pharmacoepidemiology studies.	No change to text required
Lines 673 - 751	4	This document presumes to be comprehensive, covering a wide range of study designs appropriate to pharmacoepidemiology, but we could not find a single reference to case-control (CC) studies or, more specifically, case-control surveillance (CCS). We would have expected to see these covered in section 6 (Data Sources), either under 6.1 or 6.2. The latter refers to "prospective patient-based studies", and includes registries and surveys, but does not include mention of CC or CCS approaches. Indeed, a specific chapter on CCS appears in Strom's frequently-cited text (Rosenberg L: Case-control surveillance, Chapter 11 in the Part IIIa "Ad hoc data sources available for Pharmacoepidemiology Studies". I would also cite for consideration: Kaufman DW, Rosenberg L, Mitchell AA: Signal generation and clarification: use of case-control data. Pharmacoepi Drug Safety 2001; 10:197-203.	Agreed. A new paragraph on case-control surveillance has been added in section 6.2, with references to four articles including the cited article published by Kaufman et al.
Line 689	6	Comment: Additional guidelines which could be referred to.  Proposed change (if any): Consider making reference to: Verstraeten T, DeStefano F, Chen RT, Miller E. 2003 Vaccine safety surveillance using large linked databases: opportunities, hazards and proposed guidelines. Expert Rev Vaccines. 2003 Feb; 2(1):21-9.	Agreed. Article mentioned in section 5.2., Use of automated health databases, as an example of hazards using large linked databases and recommendations to increase the reliability of outcomes.
Line 707 - 709	13	Comment: "Some important aspects for pharmacoepidemiological studies are not covered, such as outcome definition and validity, evaluation of biases, sensitivity analyses, ethical issues, data ownership and privacy." Given the significant number of issues	Agree. Clarification made in text to emphasise that this statement relates to deficiencies in ISPOR guideline, only:  <i>'Of note, some important aspects for</i>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
6. Data Sources			
		related to the use of secondary datasets, what is the ENCePP's/EMA's recommendation with respect to using them to answer pharmacovigilance questions as they arise?	<i>pharmacoepidemiological studies <del>are not covered</del>, such as outcome definition and validity, evaluation of biases, sensitivity analyses, ethical issues, data ownership and privacy, <b>are not covered in the ISPOR guideline.</b></i>
Lines 711-751	11	<p>Comment: By offering an overview document and web resource that refers to specific existing guidances, general aspects of study designs already covered by existing legislation in Europe needs to be included. The Notice to Applicants Volume 9A, Part I N° 7 as well as Directive 2001/83/EC in Article 1 (15) are describing many possible design options for post authorisation (safety) studies: "Registries, Comparative Observational Studies, Cross-sectional Study (Survey), Cohort Study, Case-control Study, Clinical Trials, Large Simple Trials, Descriptive Studies"</p> <p>Descriptive Studies are described separately in NtA Vol. 9A Part I N° 7 (PASS) 1.4 "Other Studies": "... are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with exposures to medicinal products. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of medicinal products in specified populations."</p> <p>The detailed description of "large simple trials" in the ENCePP Guide on Methodological Standards in Pharmacoepidemiology without mentioning all other design options could mislead to the impression, that "large simple trials" are the first choice for post authorisation (safety) studies.</p>	Disagree. The purpose of the current guideline is not to replicate existing text books or regulatory recommendations

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
6. Data Sources			
		Proposed change: BPI recommends listing all design options for post authorisation (safety) studies (focussing on non-interventional studies) provided by existing European legislation by including the legislative terms and explanations. This should be added in section 6 (Data Sources), under 6.2 'De novo data collection'.	
Lines 711 -751	12	<p>Comment: By offering an overview document that refers to specific existing guidances, general aspects of study designs already covered by existing legislation in Europe needs to be included. The Volume 9A as well as Directive 2001/83/EC are providing different possible design options for non-interventional post authorisation studies:</p> <p>"Registries, Comparative Observational Studies, Cross-sectional Study (Survey), Cohort Study, Case-control Study, Clinical Trials, Large Simple Trials (Pragmatic Trials), Descriptive Studies"</p> <p>Descriptive Studies are described separately in Volume 9A Part I N° 7 (PASS) 1.4 „Other Studies“: "... are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with exposures to medicinal products. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of medicinal products in specified populations."</p> <p>Proposed change (if any): EUCOPE recommends to including all these design options as regards non-interventional post authorisation studies in section 6 (Data Sources), either under 6.1 or 6.2.</p>	Disagree. The purpose of the current guideline is not to replicate existing text books or regulatory recommendations.
Lines 718 - 720	3	We disagree with the statement that a registry should be considered as an observational study. Registries constitute a form of	Agree. A registry is a structure within which studies can be performed – a data source. The text has been

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
6. Data Sources			
		observational data. Because not all registries are set up with a pre-specified hypothesis, they are not necessarily studies.	amended accordingly:  'A registry should be considered <del>as an observational study</del> <b>a structure within which studies can be performed, i.e. a data source</b> , where entry is defined either by diagnosis of a disease (disease registry) or prescription of a drug (exposure registry).'
Lines 734 - 737	13	Comment: When discussing surveys related to disease epidemiology and risk minimization evaluation efforts, the ENCePP guide refers to survey methodology books. They state that surveys "should be validated based on accepted measures including, if appropriate, construct, criterion and content validity, inter-rater and test-retest reliability, sensitivity and responsiveness." In practice, most of these concepts apply to psychiatric epidemiology or psychology, particularly the development of reliable scale measurements. These measures would typically be feasible, or appropriate, for much survey research in pharmacoepidemiology. It may be more appropriate to recommend pilot testing of surveys, where time permits. Otherwise, important risk evaluation efforts, etc could be delayed significantly in the design & start-up phases.  Proposed change: Consider recommending pilot testing of surveys.	Disagree. Use of validated study instruments is good practice and should be documented in the study protocol. The existing statement includes '..., if appropriate, ...'
Line 760	13	Typographical error: (with a <del>n</del> large expected attrition rate).	Agree – typographical error corrected.
Lines 770 - 771	13	Comment: Another LST to study a safety outcome (ZODIAC) among 18,000 patients was recently completed. This study was a commitment to the Swedish MPA and the US FDA. The reference is: Strom BL et al. Am J Psychiatry 2010; Published online Nov 1, print	Agreed. Paper cited as a second example of a LST.



Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
6. Data Sources			
		<p>edition February 2011.</p> <p>Proposed change: Consider adding in the additional reference.</p>	
Line 775 - 778		<p>The word 'simple' applies to the structure of the data - not the ease of performance - and is certainly correct in comparison to the multi page data collection forms we see in many industry trials. The question is whether ENCePP WG1 is the right forum to change the terminology.</p>	<p>Agree. 'Simple' in the term 'LST' refers to data structure and not data collection and in relation to situations in which a small number of outcomes are measured the term 'Large Simple Trial' is used widely so the text has been amended to remove the recommendation of a change of term to read as follows:</p> <p><i>'Note that the use of the term 'simple' in the expression 'LST' <b>refers to data structure and not data collection. It is used in relation to situations in which a small number of outcomes are measured. The term</b> may not adequately reflect the complexity of the studies undertaken.</i></p> <p><del>Replacement of the term 'simple' with 'streamlined' is considered appropriate in that it better reflects the rationalised and efficient nature of these studies.'</del></p>
Line 798	13	<p>Comment: The section on research networks could refer to the Cochrane Prospective Meta-analysis website and a corresponding section in the Cochrane handbook. The points made in this guidance parallel the points made in the Cochrane prospective meta-analysis material, emphasizing the idea of developing a collaborative effort / consortium by engaging investigators of the primary studies.</p>	<p>Disagree. The Cochrane Collaboration is not a research network per se. It is referred to in other sections of the Guide.</p>
Lines 798	13	<p>Comment: We suggest reducing the emphasis on this section and clarify which components have yet to be set up and/or current</p>	<p>Partially agree. It is not considered appropriate to reduce the emphasis of this section but other</p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>6. Data Sources</b>			
- 879		<p>accessibility to researchers. Also, the section does not mention that the use of networks of databases does not overcome problems of misclassification of exposure / outcome, confounding by indication or other factors, and the other limitations inherent in using any single health care administrative or electronic health record database.</p> <p>While this section is great at highlighting European research networks, the document would be enhanced by considering some US focused research networks such as the FDA's Sentinel Initiative and the HMO Research Network.</p> <p>Proposed change: Include this information in the subsection</p>	proposals have been incorporated into the text including reference to the FDA Mini-Sentinel project and the HMPO Research Network.
Line 819	13	<p>Comment: multinational studies also provide important information to licence holders, who should not be excluded from this section</p> <p>Proposed change: "... which can lead to important information for regulators <b>and sponsors holding drug licences.</b>"</p>	Agree. Text amended to include reference to marketing authorisation holders.
Lines 843 -844	5	<p>Comment: person-level meta-analysis is not mentioned in Section 5.4 describing the technique of meta-analysis.</p> <p>Proposed change (if any): Include a sentence of person-level meta-analysis in Section 5.4. List references with links, if possible.</p>	Disagree. Section 5.4 cross-refers to other methods of pooling data in Section 6.4.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>7. Statistical Analysis Plan</b>			

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>7. Statistical Analysis Plan</b>			
Lines 881 - 934	8	<p>Comment: Section 7 (Statistical analysis) contains several ambiguous phrases which need clarification.</p> <p>Proposed change (if any): Re-write ambiguous phrases so they are clear.</p>	Disagree. Only statements that were specifically highlighted have been amended where considered appropriate.
Lines 881 - 934	10	<p>Comment: A very good initiative to discuss further the need to have strong statistical analysis plans and to define, at the time of study protocol writing, clear statistical methods and considerations. It is not unusual that study protocols “skip” completely this section with the excuse of a later “SAP” (emphasis on this point could be made here or after lines 142-143).</p>	No change to text required
Line 887	13	<p>Comment: Alternate wording proposed.</p> <p>Proposed change: A study is generally designed with the objective of <del>deciding</del> providing information about the answers to a set of research questions.</p>	<p>Partially agree. Text amended as follows:</p> <p><i>‘A study is generally designed with the objective of <del>deciding</del> <b>addressing</b> a set of research questions.’</i></p>
Line 890	9	<p>Comment: The wording “mathematical manipulations” does not sound very well, first of all it is not mathematical operations which is performed, I would rather say it is statistical calculations, secondly I also don’t like to use the term manipulations in this context.</p> <p>Proposed change (if any): Maybe “Statistical calculations” can be used instead?</p>	Agree. Term ‘ <i>manipulation</i> ’ replaced with ‘ <i>transformation</i> ’
Lines 903 - 905	10	<p>Comment: Though not well-stated, this is actually a very insightful provision - particularly if the intended meaning is that correct study design for causal effects cannot depend on knowledge of the observed outcomes (for example, covariates should not be selected based on the outcomes, a very common error in published</p>	Agree. See response to comment below.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>7. Statistical Analysis Plan</b>			
		observational studies).	
Lines 903 - 905	3	Expanding a bit on the content of lines 903-905 might be useful. Feasibility studies can easily be misused to "stack the deck" in favor of a particular outcome. The feasibility study can give a "sneak peek" at the results and influence the decision to proceed.	Agree. The analysis plan should be developed without knowledge of the results of a study but from the outset the analysis must be considered in terms of the outcomes of interest – this, of course, is particularly relevant in terms of feasibility studies that are conducted. The text has been, therefore, amended to clarify that the analysis should be made blinded to any knowledge of the results as follows:  <i>'A particular concern in retrospective studies is that decisions about the analysis should be made blinded to any knowledge of the <del>outcomes</del> results. This should be a consideration in the study design, particularly when feasibility studies are to be performed to inform the design phase.'</i>
Lines 903 - 907	13	Comment: Expand this topic and include common approaches to "blinding" or reword. Is the concern here data dredging?	Agree. See response to previous comment – the following text added:  <b><i>'Feasibility studies should be independent of the main study results'</i></b> .
Line 906	13	Comment: The definition of study population and of valid patient should be included.  Proposed change: The statistical analysis plan is usually structured to reflect the protocol and will address where relevant, the following points ( <u>add the following underlined items</u> ):  (...)- <u>Formal definition of study population, valid patient and</u>	Partially agree. Statement amended to include:  <b><i>'10.1 Description of target population'</i></b>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>7. Statistical Analysis Plan</b>			
		<p><u>departures</u></p> <p>(...)10 - Description of achieved patient population <u>10.1 Description of valid patients</u> <u>10. 2 Departures from targeted population</u></p>	
Line 913	6	Comment: Sample size issues (often encountered in safety studies of rare events) may deserve a larger section in itself, possibly under section 5.	Partially agree. See response to related comments below.
Lines 913 - 914	13	<p>Comment: The Guide is quite clear when acknowledging that pharmacoepidemiological studies can be exploratory and when saying that "if there is no a priori hypothesis, this should be clearly stated" in the protocol. However, this statement has not been followed-up in the Statistical Analysis Plan part (section 7) when addressing the issue of sample size calculation.</p> <p>Proposed change: Advice on sample size calculation (or absence of it) in that case should be provided.</p>	<p>Agree. Text amended as follows:</p> <p><i>'Sample size considerations making <b>explicit</b> the data source <b>from which</b> <del>concerning</del> the expected variation of relevant quantities and the <del>study power</del> <del>explicit</del> <b>clinically relevant differences are derived should be presented. It should be noted that in retrospective observational studies where no additional data can be collected sample size is not a relevant consideration and the ethical injunction against 'underpowered' studies has no obvious force provided the results, in particular the 'absence of effect' and 'insufficient evidence', are properly presented and interpreted.'</b></i></p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>8. Quality Control and Quality Assurance</b>			

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>8. Quality Control and Quality Assurance</b>			
Line 969	5	<p>Comment: The full name of the Agency for Healthcare Research and Quality is used while the abbreviation AHRO was used already earlier.</p> <p>Proposed change (if any): Use the abbreviation.</p>	Agree. Abbreviation used.
Line 935	13	<p>Comment: The document should include the need of monitoring in order to oversee the progress of the study and to ensure that it is conducted, recorded and reported in accordance to the protocol, SOPs, and applicable regulatory requirements. It could also be interesting to mention, in the process, the resolution of queries, as this procedure improves quality.</p>	Disagree. The text sufficiently addresses the issue by providing examples.
Lines 936 - 939	15	<p>Comment: The statement that observational studies should be held to the same standards of quality as randomised clinical trials appears to suggest a requirement for GCP for epidemiological studies. This needs to be clarified.</p>	<p>Agree. Text amended as follows:</p> <p><i>'Although quality assurance is the rule for randomised clinical trials, the practice is less well established for observational studies, which may be used instead of clinical trials to assess the safety and effectiveness of specific pharmacologic interventions. <del>They should, therefore, be held to the same standards of quality.</del> In a randomised clinical trial the vast majority of data is quality assured but it may not be feasible to do the same for large pharmacoepidemiological studies making secondary use of data collected for another purpose. However, use of the results of such studies in outcomes research requires knowledge of the quality and validity of the data and of the studies themselves. In particular, there ideally needs to be some level</i></p>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>8. Quality Control and Quality Assurance</b>			
			<i>of validation of the recording and coding for electronic data sets. It is considered the responsibility of database owners to provide researchers with the minimal level of validity and sensitivity of the coded data. It is also acknowledged that there is a need to move towards better quality control/assurance in terms of data quality assurance and study methodology. Quality should be mentioned in the study protocol in terms of quality assurance but this may, for example, lead to sensitivity analyses.'</i>
Line 947	13	<p>Comment: additional wording proposed.</p> <p>Propose change: "Aspects of research quality control that require close attention include data collection, data recording, numbers <b>and qualification</b> of people making measurements and recording of data..."</p>	Agree. Text amended as proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>9. Safety reporting (Adverse Events)</b>			
Lines 1005 – 11	10	<p>Comment: The "six conditions" mentioned in this paragraph should be further discussed in the document. Safety reporting is a critical element on most pharmacoepidemiology studies assessing safety</p>	Agreed. Text amended as detailed in relation to comment below to mention the 'six conditions' referred to.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>9. Safety reporting (Adverse Events)</b>			
		endpoints.	
Line 1008	9	Comment: this section may describe and address more directly the common issue that safety reporting may not be appropriate/applicable in some retrospective, anonymised database studies.	<p>Line 1008 of the Guide refers to the ISPE Guideline, which addresses adverse event reporting from aggregate analysis of databases. The text has been amended as follows to reflect this aspect and to address the previous comment:</p> <p><i>"Chapter VI of the <u>ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP)</u> provides general recommendations for adverse event reporting from pharmacoepidemiology studies. This text should be consulted by investigators when designing a non-interventional study. It specifies six conditions which, if obtained, generally require expedited individual case reporting: <b><u>1) the study prospectively gathers data on individual patients, 2) the study involves direct contact with patients, 3) study personnel are trained on gathering and reporting adverse events and determining whether events might be considered "expected" for a specific product, 4) a serious event is identified by someone who has direct contact with the patient, 5) the event is considered unexpected, and 6) the reporter believes there is a causal association with the product or that causality cannot be ruled out. The GPP further specify that analyses of database studies can identify an unexpected</u></b></i></p>



Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>9. Safety reporting (Adverse Events)</b>			
			<p><b><u>increase in risk associated with a particular exposure but such studies typically do not require reporting of individual cases.</u></b> These recommendations do not take precedence over the obligations to companies sponsoring a post-authorisation study in the European Union specified in Volume 9A."</p> <p>In addition, Lines 1022 to 1028 of the Guide state that : "However, it is acknowledged that for certain study designs, such as case-control or retrospective cohort studies, it is not feasible or appropriate to make a causality assessment at the individual case level, and therefore expedited reporting is not required. In case of doubt, the reporting requirements for a specific study should be clarified with the competent authority. Marketing Authorisation Holders should check whether additional national requirements apply in countries where the study will be carried-out." It could be considered that retrospective cohort studies also cover retrospective database studies. However, it is preferable not to amend or interpret this text, which is directly derived from Volume 9A.</p>
Lines 1009 - 11	15	Comment: Rephrase as "While these ISPE recommendations are helpful, the EU obligations to companies sponsoring a post-authorisation study are specified in Volume 9A."	Agree. Text amended in line with comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>10. Communication</b>			
Lines 1056 - 69	10	<p>Comment: The paragraph below does not read well and seems unclear. Also, is the purpose of this draft guide to inform audience/readers on the key elements to report AEs or, is it rather to inform clinicians on how to report observation of AEs?</p> <p>Proposed change (if any): "The Guidelines for Submitting Adverse Event Reports for Publication endorsed by ISOP and ISPE aim to introduce <b>clinicians (?)</b> to the key elements that have to be included <b>for the publication of observations about</b> adverse drug events (AEs). The information is clearly and coherently presented in the cited guideline. The required data are divided based on three levels of <b>information</b>: 'required', 'highly desirable' and 'if relevant'. <del>Of note, these requirements only give clinical practitioners the opportunity to report and to publish AE findings, because the majority of these data are at their disposal"</del></p>	<p>Agree. Text amended in line with comment:</p> <p><i>'The Guidelines for Submitting Adverse Event Reports for Publication endorsed by ISOP and ISPE aim to introduce <del>clinicians</del> <b>readers</b> to the key elements that have to be included for the publication of observations about adverse drug events (AEs). The information is clearly and coherently presented in the cited guideline. The required data are divided based on three levels of information: 'required', 'highly desirable' and 'if relevant'. <del>Of note, these requirements only give clinical practitioners the opportunity to report and to publish AE findings, because the majority of these data are at their disposal'</del></i></p>
Lines 1098 - 1104	7	These lines occur in a different font size.	Agree. Font amended accordingly.
Lines 1105 - 07	13	<p>Comment: We recommend clarifying in the document (e.g. in Section 10. Communication, when referencing to the ENCePP Code of conduct) that only EnCePP conducted studies should be registered and results posted on the EnCePP website. Studies conducted by MAH as a regulatory commitment with the EMA will become available via the EPARs after regulatory assessment.</p> <p>Proposed change: new paragraph "As per the EnCePP Code of Conduct", studies for which the status "ENCEPP study" is applied</p>	Previously addressed in the section on 'Governance'.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>10. Communication</b>			
		must be registered in the ENCePP Register of Studies, and communicate the study protocol and results through posting in this e-registry. Other studies are also free to use the ENCePP Register."	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
<b>11. Update of the Guide</b>			
Lines 1129 - 30	4	The Guide is a comprehensive overview of the methodological traditions within pharmacoepidemiology in 2010. It can quickly become dated and irrelevant, if it is not properly maintained. EMA has declared its intentions to do so on page 28 (line 1129-30), but the specifics about how and by whom are virtually absent. We suggest that the maintenance of the document, which is so essential for its usefulness, is described in more detail.	Agree. See previous response to general comment raised on issue of updating the guide.