



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH



European Network of Centres for  
Pharmacoepidemiology and  
Pharmacovigilance

1 13 May 2011  
2 EMA/95098/2010 (amended)

3

4 The European Network of Centres for  
5 Pharmacoepidemiology and Pharmacovigilance (ENCePP)

6

7 Guide on Methodological Standards in  
8 Pharmacoepidemiology

9

10

Steps taken	Date
First draft agreed by ENCePP Working Group 1	4 <sup>th</sup> Oct 2010
Peer Review	4 <sup>th</sup> – 15 <sup>th</sup> October 2010
Draft adopted by ENCePP Steering Group for release for consultation	21 <sup>st</sup> October 2010
Public consultation	5 <sup>th</sup> November 2010 – 3 <sup>rd</sup> January 2011
Adoption of final draft by ENCePP Steering Group	3 <sup>rd</sup> May 2011
<i>Amendment:</i> The wording 'Checklist of Methodological Standards for ENCePP Study Protocols' has been replaced throughout the document with 'ENCePP Checklist for Study Protocols'	23 August 2011

11

<b>KEYWORDS</b>	<i>methodological standards, pharmacoepidemiology, pharmacovigilance, ENCePP, research, guidance</i>
-----------------	--

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom

Telephone +44 (0)20 7418 8400 Facsimile +44 (0)20 7418 8660

E-mail [info@ema.europa.eu](mailto:info@ema.europa.eu) Website [www.ema.europa.eu](http://www.ema.europa.eu)

An agency of the European Union



12 **Table of Contents**

13

14 **List of Acronyms..... 3**

15 **1. Introduction ..... 5**

16 **2. Governance ..... 5**

17 2.1. General Principles for ENCePP studies ..... 6

18 2.2. Scientific standards, review and approval ..... 6

19 2.3. Ethical conduct, patient and data protection ..... 6

20 **3. General aspects of study protocol ..... 7**

21 **4. Research question ..... 9**

22 **5. Study Design and Methods ..... 10**

23 5.1. General considerations ..... 10

24 5.2. Challenges and lessons learned ..... 11

25 5.2.1. Drug exposure/outcome definition and validation ..... 11

26 5.2.2. Use of automated health databases ..... 11

27 5.2.3. Bias and confounding ..... 13

28 5.2.4. Methods to handle bias and confounding ..... 16

29 5.3. Integrating and pooling studies ..... 18

30 **6. Data Sources ..... 19**

31 6.1. Use of available data ..... 19

32 6.2. De novo data collection ..... 20

33 6.3. Signal detection methodology and application ..... 21

34 6.4. Hybrid studies ..... 22

35 6.4.1. Large simple trials ..... 22

36 6.4.2. Randomised database studies ..... 23

37 6.5. Research networks ..... 23

38 **7. Statistical Analysis Plan..... 26**

39 **8. Quality Control and Quality Assurance ..... 27**

40 **9. Safety reporting (Adverse Events) ..... 29**

41 **10. Communication..... 30**

42 **11. Update of the Guide..... 32**

43 **12. References ..... 32**

44 **13. Authors..... 39**

45 **14. Acknowledgements ..... 40**

46

## 47 **List of Acronyms**

- 48 Agency for Healthcare Research and Quality (AHRQ)
- 49 Case Report Form (CRF)
- 50 Confidence Interval (CI)
- 51 Consolidated Standards for Reporting Trials (CONSORT)
- 52 Council for International Organizations of Medical Sciences (CIOMS)
- 53 Disease Risk Score (DRS)
- 54 Empirical Bayes Geometric Mean (EBGM)
- 55 Enhancing the Quality and Transparency of Health Research (EQUATOR)
- 56 EuroDrug Quality Indicator Meeting (DURQUIM)
- 57 European Commission (EC)
- 58 European Medicines Agency (EMA)
- 59 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)
- 60 European Surveillance of Antimicrobial Consumption (ESAC)
- 61 European Union (EU)
- 62 Exposure Propensity Score (EPS)
- 63 Food and Drug Administration (FDA)
- 64 General Practice Research Database (GPRD)
- 65 German Society for Epidemiology (DGEpi)
- 66 German Society for Social Medicine and Prevention (DGSPM)
- 67 High Dimension Propensity Score (HDPS)
- 68 Individual Case Safety Report (ICSR)
- 69 Information Component (IC)
- 70 International Committee of Medical Journal Editors (ICJME)
- 71 International Conference on Harmonisation of Technical Requirements for Registration of  
72 Pharmaceuticals for Human Use (ICH)
- 73 International Epidemiological Association (IEA)
- 74 IEA Good Epidemiological Practice Guidelines (GEP)
- 75 Instrumental Variables (IV)
- 76 International Society for Pharmacoconomics and Outcomes Research (ISPOR)
- 77 International Society for Pharmacoepidemiology (ISPE)
- 78 International Society of Pharmacovigilance (ISOP)
- 79 ISPE Good Pharmacovigilance Practice Guidelines (GPP)

- 80 Large Simple Trials (LST)
- 81 Meta-analysis of Observational Studies in Epidemiology (MOOSE)
- 82 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
- 83 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)
- 84 Propensity Score Calibration (PSC)
- 85 Proportional Reporting Ratio (PRR)
- 86 Quality Assurance (QA)
- 87 Quality control (QC)
- 88 Quality of Reporting of Meta-analyses (QUORUM)
- 89 Randomised Controlled Trial (RCT)
- 90 Reporting Odds Ratio (ROR)
- 91 Risk Evaluation and Mitigation Strategies (REMS)
- 92 Strengthening the Reporting of Observational studies in Epidemiology (STROBE)
- 93 United States (US)
- 94 Working Group for the Survey and Utilisation of Secondary Data (AGENS)
- 95
- 96 **All hyperlinks in the document were last accessed on-line on 12 May 2011.**

## 98 **1. Introduction**

99 This guide seeks to review existing methodological guidance for research in  
100 pharmacoepidemiology and pharmacovigilance. By providing a structured architecture for  
101 thinking and learning, the aim is to support high quality pharmacoepidemiological studies  
102 and to stimulate innovation that benefits patients and public health at large. The intention is  
103 not to duplicate the text from existing guidelines and textbooks, but rather to offer the  
104 researcher a single overview document and web resource. For each topic covered in this  
105 guide, readers are referred to specific existing guidance after a brief introduction or overview  
106 of the relevant text.

107 The identification and compilation of existing guidelines in the fields of  
108 pharmacoepidemiology and pharmacovigilance is a goal of the [European Network of Centres  
109 for Pharmacoepidemiology and Pharmacovigilance \(ENCEPP\)](#). In acknowledgement of the  
110 diverse nature and levels of expertise among present researchers in Europe, ENCEPP aims at  
111 encouraging participation across the spectrum of researchers. It considers the current  
112 overview document appropriate to serve both experienced and relatively new researchers in  
113 pharmacoepidemiology.

114 Readers are also referred to the ENCEPP [Checklist for Study Protocols](#), which objective is to  
115 increase the awareness about scientific and methodological developments in the field of  
116 pharmacoepidemiology, and the ENCePP [Code of Conduct](#) that seeks to provide a set of rules  
117 and principles for studies

118 In order to develop this inventory, the first step was to identify and review [a list of existing  
119 English language guidances](#). The review consisted of documenting the objective, scope,  
120 target audience, content and relevance of each guidance. Gaps in guidance in areas  
121 important to collaborative pharmacoepidemiology research were also identified. Where  
122 considered relevant, such gaps have been addressed with what ENCePP considers as good  
123 practice, in line with the intention from the outset to go further than compile an inventory of  
124 existing guidelines. This guide focuses on scientific rather than regulatory guidance.

125 The scope of the inventory is to be dynamic. It will be updated and expanded by structured  
126 review and also on an ad-hoc basis in response to comments received. New guidance may  
127 appear and new sections may be developed specifically targeted to the needs of  
128 collaborative research. Researchers are kindly requested to refer any additional guidance  
129 document (with an electronic link, where possible) they may be aware of, and that is  
130 considered relevant, to the [ENCEPP Secretariat](#) to assist in future updates. In the interim, to  
131 facilitate access to methodological aspects that are not specifically covered in textbooks or  
132 existing guidance, the researcher is referred to a list of references addressing a number of  
133 methodological challenges and lessons learned (see Section 5.2).

134 Researchers are also requested to self-refer to standard textbooks in epidemiology and  
135 pharmacoepidemiology research, in addition to those cited in the present document.

## 136 **2. Governance**

137 In Europe, European Union (EU) and national laws are the keys to what may and may not be  
138 done with regard to data access, data linkage and consent issues, including such domains as  
139 human rights and duty of confidentiality. While differing data custodians currently have

140 differing requirements related to what approvals are needed before data can be released,  
141 the requirements will fit within the overall need to meet all applicable EU and national laws  
142 and guidelines for the actual study. This includes situations where multi-country studies are  
143 being conducted and there may be transfer of data or information. In addition to meeting  
144 legislative requirements, studies also need to adhere to a set of principles that meet with the  
145 requirements of scientific and ethical reviews.

## 146 **2.1. General Principles for ENCePP studies**

147 The objective of the [ENCePP Code of Conduct](#) is to promote scientific independence. It aims  
148 to do so by providing a set of rules and principles for best practice of the investigator-study  
149 funder relationship as well as transparency in pharmacoepidemiology and pharmacovigilance  
150 studies.

151 By applying the principles of transparency and scientific independence, the Code aims to  
152 strengthen the confidence of the general public, researchers and regulators in the integrity  
153 and value of research. To this end, the Code addresses critical areas in the planning, conduct  
154 and reporting of studies and the interaction of investigators and study funders. At its core is  
155 the requirement to register studies before they start (see [ENCePP E-Register of Studies](#)) and  
156 the obligation to publish all study findings irrespective of positive or negative results.

157 The Code is an integral part of the '[ENCePP Study](#)' concept. 'ENCePP studies' need to comply  
158 with the provisions of the Code in their entirety and investigators seeking the ENCePP study  
159 seal need to confirm their intention to do so by submitting a completed and signed [Checklist](#)  
160 and [Declaration on compliance](#) as part of their application.

## 161 **2.2. Scientific standards, review and approval**

162 The standards for designing a pharmacoepidemiological and pharmacovigilance study are  
163 captured in the [ENCePP Checklist for Study Protocols](#).

164 Many research organisations (including those owning or hosting databases) have scientific  
165 review boards that ensure scientific standards are met. Some national competent authorities  
166 also have their own review board for registering/approving studies. In addition, it is good  
167 practice to invite experts to review the study results, as well as the protocol and any  
168 publications and/or communications thereof. The role of scientific committees in governance  
169 is also emphasised as being of particular importance.

## 170 **2.3. Ethical conduct, patient and data protection**

171 The [Declaration of Helsinki](#) and the provisions on processing of personal data and the  
172 protection of privacy as laid down in [Directive 95/46/EC](#) and [Regulation 45/2001](#) of the  
173 European Parliament and of the Council need to be followed in terms of the ethical conduct  
174 of studies. For interventional research, the [Clinical Trial Directive \(Directive 2001/20/EC\)](#)  
175 applies.

176 As post-authorisation studies are carried out with authorised medicinal products, relevant  
177 European and national legislation applies. Specifically, Marketing Authorisation Holders will  
178 need to comply with [Directive 2001/83/EC](#) and [Regulation \(EC\) No 726/2004](#) of the  
179 European Parliament and of the Council. The guidance in [Volume 9A](#) of the Rules Governing  
180 Medicinal Products in the EU and, for clinical trials, the [Guidelines for Good Clinical Practice](#)  
181 ([Commission Directive 2005/28/EC](#)) should also be followed.

182 Consideration of ethical issues, data ownership and privacy is an important part of the  
183 [International Society for Pharmacoepidemiology \(ISPE\)](#) guideline for [Good](#)  
184 [Pharmacoepidemiology Practices \(GPP\)](#), section IV. It includes a sub-section (IV.A) on  
185 protection of human subjects and a reference to the ISPE guidelines on [Data Privacy, Medical](#)  
186 [Record Confidentiality, and Research in the Interest of Public Health](#). The GPP also  
187 recommends a stand-alone section within the protocol containing a description of plans for  
188 protecting human subjects that includes consideration of the need for submitting the  
189 protocol to an Institutional Review Board/Independent Ethics Committee and the  
190 requirement of informed consent in accordance with local law.

191 The main scope of the [International Epidemiological Association \(IEA\) Good Epidemiological](#)  
192 [Practice \(GEP\)](#) guideline for proper conduct in epidemiological research is on the ethical  
193 principles of pharmacoepidemiological field studies, which could also apply to interventional  
194 studies, such as the role of ethics committees, patients' informed consent, use and storage  
195 of personal data and publication of results.

196 The [Council for International Organizations of Medical Sciences \(CIOMS\)](#) 2009 [International](#)  
197 [Ethical Guidelines for Epidemiological Studies](#) have as their objective the preparation of  
198 guidelines to indicate how the ethical principles that should govern the conduct of biomedical  
199 research involving human subjects could be effectively applied. The Guidelines set forth  
200 ethical guidance on how epidemiologists - as well as those who sponsor, review, or  
201 participate in the studies they conduct - should identify and respond to the ethical issues  
202 that are raised by the process of producing this information.

203 The [Agency for Healthcare Research and Quality \(AHRQ\)](#) of the United States has published  
204 [Registries to Evaluate Patient Outcomes: a User's guide, Second Edition](#), which is a reference  
205 for establishing, maintaining and evaluating the success of registries created to collect data  
206 about patient outcomes. In Section 1: 'Creating a registry' is a specific chapter dedicated to  
207 ethics, data ownership, and privacy. The concepts are useful although the authors indicate  
208 that this section focuses solely on United States (US) law.

209 The [Uniform Requirements for Manuscripts Submitted to Biomedical Journals](#) by the  
210 [International Committee of Medical Journal Editors \(ICJME\)](#) includes clear statements on  
211 ethical principles related to publication in biomedical journals addressing authorship and  
212 contributorship, editorship, peer review, conflicts of interest, privacy and confidentiality and  
213 protection of human subjects and animals in research.

214 From the examples provided above, it may be seen that there is a wide range of documents  
215 for protection of human subjects. The applicability of ethical requirements, however, varies  
216 based on the nature of the inquiry and the studies to be conducted. Certain human subject  
217 protections applicable to clinical studies (e.g. full informed consent) would not apply to other  
218 kinds of research (e.g. review of data from de-identified medical records). Furthermore,  
219 while protection of privacy is paramount, there may be situations in which the use of data  
220 for secondary analyses has public health benefits.

### 221 **3. General aspects of study protocol**

222 The study protocol is the core document of a study. A protocol should be drafted as one of  
223 the first steps in any research project, and should be amended and updated as needed  
224 throughout its course. Amendments should be justified. It must precisely describe  
225 everything that will be done in the study, so that the study can be reproduced. It is usually  
226 and profitably based on standard protocol outlines, which could be prepared for different

227 types of studies (e.g. cohort or case-control studies based on field data or database studies  
228 that include different information according to study type).

229 Chapter II of the [ISPE GPP](#) provides guidance on what is expected of a  
230 pharmacoepidemiology study protocol. The guideline states that the protocol should include  
231 a description of the data quality and integrity, including, for example, abstraction of original  
232 documents, extent of source data verification, and validation of endpoints. As appropriate,  
233 certification and/or qualifications of any supporting laboratory or research groups should be  
234 included, as well as validation steps taken or considered to standardise laboratory methods  
235 proposed. The guidelines recommend description of data management, statistical software  
236 programs and hardware to be used in the study, description of data preparation and  
237 analytical procedures, as well as the methods for data retrieval and collection. It should be  
238 borne in mind that, as stated in the GPP, adherence to guidelines will not guarantee valid  
239 research. The [ENCePP Checklist for Study Protocols](#) also seeks to stimulate researchers to  
240 consider important epidemiological principles when designing a pharmacoepidemiological  
241 study and writing a study protocol.

242 The protocol should cover at least the following aspects:

- 243 - The research question the study is designed to answer, which might be purely  
244 descriptive, exploratory or explanatory (hypothesis driven). The protocol should include a  
245 background description that expounds the origin (scientific, regulatory, etc.) and the  
246 state of present knowledge of the research question. It will also explain the context of  
247 the research question, including what data are currently available and how this data can  
248 or cannot contribute to answering the question. The context will also be defined in terms  
249 of what information sources can be used to generate appropriate data, and how the  
250 proposed study methodology will be shaped around these.
- 251 - The main study objective and possible secondary objectives, which are operational  
252 definitions of the research question. In defining secondary objectives, consideration could  
253 be given to time and cost, which may impose constraints and choices, for example in  
254 terms of sample size, duration of follow-up or data collection.
- 255 - The source and study populations to be used to answer the research question. The  
256 protocol should describe whether this population is already available (such as, in a  
257 database) or whether it needs to be recruited *de novo*. The limits of the desired  
258 population will be defined, including inclusion/exclusion criteria, timelines (such as index  
259 dates for inclusion in the study) and any exposure criteria and events defining cases and  
260 exposed study groups.
- 261 - Exposures of interest that need to be pre-specified, defined and described  
262 unambiguously, including duration of exposure or follow-up, visits or time-dependent  
263 appraisals and details of which data are collected when, using what methods.
- 264 - Outcomes of interest that need to be pre-specified, defined and described  
265 unambiguously, including data sources, operational definitions and methods of  
266 ascertainment such as data elements in field studies or appropriate codes in database  
267 studies.
- 268 - The covariates and potential confounders that need to be retrieved and measured.
- 269 - The statistical analysis of the resulting data, including statistical methods and software,  
270 adjustment strategies, and how the results are going to be presented.
- 271 - The identification of possible biases.

- 272 - Major assumptions, critical uncertainties and challenges in the design, conduct and  
273 interpretation of the results of the study given the research question and the data used.
- 274 - Ethical considerations, as described in the section on governance of the current  
275 document.
- 276 - The various data collection forms including the Case Report Form (CRF) or descriptions of  
277 the data elements may be appended to the protocol, allowing having an exact  
278 representation of the data collection. The study protocols could include a section  
279 specifying ways in which the CRF will be piloted, tested and finalised. Amendments of  
280 final CRFs should be justified. For field studies, physician or patient forms would be  
281 included depending on data collection methodology. Other forms may be included as  
282 needed, such as patient information, patient-oriented summaries, etc.

## 283 **4. Research question**

284 The research question and the associated objectives describe the knowledge or information  
285 to be gained from the study. It is important that current knowledge gaps are properly  
286 identified. Existing guidance on this aspect includes the [ISPE GPP](#) and the [ENCePP Checklist  
287 for Study Protocols](#).

288 These guidance documents emphasise that it should be clearly explained why the study is to  
289 be conducted (e.g. to answer an important public health concern, to confirm or further  
290 characterise a risk identified in a Risk Management Plan, to assess a new or emerging safety  
291 issue or to determine health outcomes or the benefit/risk profile). It should also be clear  
292 whether the results that will be reported represent *a priori* (pre-formed) hypotheses or  
293 exploratory analyses. If there is no *a priori* hypothesis, this should be clearly stated. The  
294 [ENCePP Checklist for Study Protocols](#) also suggests that the research objective should briefly  
295 state the target population, primary endpoints, questions of dose-dependency and the main  
296 outcome measures.

297 A critical and thorough review of the literature usually forms the basis for the background  
298 description and theoretical framework of the research question and should be included in a  
299 protocol. Such review aims at evaluating the pertinent information and at identifying gaps in  
300 knowledge. According to the [ISPE GPP](#), the review should include findings of relevant animal  
301 and human experiments, clinical studies, vital statistics and previous epidemiological studies.  
302 The findings of similar studies should be mentioned and gaps in knowledge that the study is  
303 intended to fill should be described.

304 In addition, previous findings are useful for the methodological planning of the current study.  
305 They may be used to discuss how the findings of the previous research may support the  
306 background, significance, research question, hypotheses, and/or design of the proposed  
307 study. They may also serve to determine the expected magnitude of the event(s) under  
308 study and, if available, in the target population, to characterise the various risk factors for  
309 the event and to identify the outcomes and measures that have been used in previous  
310 studies. The review assists in providing an assessment of the feasibility of the proposed  
311 study.

312 In addition to seeking information, the review should be a critical appraisal of the evidence  
313 in order to assess, analyse and synthesise previous research, and place it in its current  
314 context. Several methods for reviewing and synthesising findings from the literature exist,  
315 including narrative review, for which guidance is available in [Writing narrative literature  
316 reviews](#) (Baumeister RF, Leary MR. Rev of Gen Psychol 1997; 1 (3): 311-320).

## 317 **5. Study Design and Methods**

318 There exists a number of evolving methodological challenges that recur in  
319 pharmacoepidemiological research, that are still in development or that to date have not  
320 been adequately covered by recommendations, particularly in terms of how to deal with  
321 them. The following section presents such methodological challenges relating to study design,  
322 use of automated health data, bias and confounding and methods for controlling for  
323 confounding. It is reminded that these are not basic methodologies that are well covered in  
324 the textbooks cited. Furthermore, the granularity in the description of some of the methods  
325 is in line with the extent to which the issue is considered covered in existing guidance.

### 326 **5.1. General considerations**

327 The choice of study design and methods is a crucial part in every pharmacoepidemiological  
328 study and starts with the formulation of a relevant research question (whether non-steroidal  
329 anti-inflammatory drugs [NSAIDs] increase the risk of gastro-intestinal bleeding is cited  
330 throughout the present document as an illustrative working example). The study design and  
331 methods should follow the research question and are naturally interrelated.

332 The research question drives three key sequentially structured phases in the conduct of an  
333 epidemiological study: (1) the design of the 'occurrence relation' as defined in *Theoretical*  
334 *Epidemiology* (Miettinen O.S. John Wiley & Sons, 1985) as the relation of a parameter of  
335 occurrence to a determinant or a set of determinants, (e.g. the incidence rate ratio of  
336 gastro-intestinal bleeds among users and non-users of NSAIDs), (2) the design of the data  
337 collection to document empirically the occurrence relation (e.g. collection from a database of  
338 exposure [use of NSAIDs] and outcomes data [gastro-intestinal bleeding] in a cohort of  
339 patients that are/have been NSAIDs users), and (3) the design of the data analysis (from  
340 raw data to quantification of associations). These three phases are not independent. A  
341 hypothesised occurrence relation may lead to a certain array of designs for data collection  
342 given, in this example, the multi-source availability of data on use of NSAIDs (exposure) and  
343 on occurrence of gastro-intestinal bleeds in patients (outcomes). Finally, each design for  
344 data collection, given a well-defined occurrence relation, will be followed by only a few  
345 appropriate designs of data analysis. Note the selection of appropriate electronic health data  
346 sources is an important aspect of the design of data collection. Depending on the research  
347 question, other sources of data may be needed e.g. some claims databases may not have a  
348 'reason for stopping' a NSAID whereas another may have (see Section 6).

349 The choice of epidemiological methods to answer a research question is not always carved in  
350 stone, but is rather based on principles than on rules. These principles may provide  
351 opportunities for creativeness and new innovative methods, when appropriate and needed.  
352 However, there are certain 'dos and don'ts' and certain standards in order to assure validity  
353 and robustness of the study results.

354 General aspects of study designs, their relevance to types of research question and issues  
355 relating to internal and external validity, including biases and confounding, are covered by  
356 many textbooks on epidemiology and pharmacoepidemiology. The following list proposes a  
357 list of textbooks recommended for consultation. Researchers may find other textbooks more  
358 appropriate to their specific needs.

- 359 • *Epidemiology: Principles and Methods 2<sup>nd</sup> Edition* (B. MacMahon, D. Trichopoulos.  
360 Lippincott Williams & Wilkins, 1996) offers an introductory understanding of

- 361 epidemiological methods and processes, including on study designs and control for  
362 confounding.
- 363 • *Modern Epidemiology 3<sup>rd</sup> Edition* (K. Rothman, S. Greenland, T. Lash. Lippincott  
364 Williams & Wilkins, 2008) serves as a comprehensive textbook on methods in  
365 epidemiology. Chapter 8 deals with validity but rather than dichotomise validity into  
366 the two components, internal and external, details a view in which the essence of  
367 scientific generalisation is the formulation of abstract concepts relating the study  
368 factors.
  - 369 • *Pharmacoepidemiology 4<sup>th</sup> Edition* (B.L. Strom. Wiley, 2005) provides a complete  
370 review of epidemiological methods applied to the study of drugs. In Chapters 45 – 46,  
371 it emphasises that, whatever the source of the data, the veracity of a study's  
372 conclusion rests on the validity of the data.
  - 373 • *Pharmacoepidemiology and Therapeutic Risk Management 1<sup>st</sup> Edition* (A.G. Hartzema,  
374 H.H. Tilson and K.A. Chan, Editors. Harvey Whitney Books Company, 2008). In  
375 addition to a general review of drug-specific methodologies, this textbook illustrates  
376 practical issues with a large number of real life examples.
  - 377 • *Encyclopedia of Epidemiologic Methods* (M.H. Gail, J. Benichou, Editors. Wiley, 2000).  
378 This compilation of articles complements existing textbooks by providing a large  
379 coverage of specialised topics in epidemiological and statistical methods.
  - 380 • *Practical Statistics for Medical Research* (D. Altman. Chapman & Hall, 1990) presents  
381 a problem-based statistical text for medical researchers.

## 382 **5.2. Challenges and lessons learned**

### 383 **5.2.1. Drug exposure/outcome definition and validation**

384 Physicians rely on patient-supplied information on past drug use and illness to assist with  
385 the diagnosis of current disease. Chapter 45 of *Pharmacoepidemiology* (B. Strom, 4<sup>th</sup>  
386 Edition. Wiley, 2005) presents a literature review of the studies that have evaluated the  
387 validity of drug, diagnosis and hospitalisation data and the factors that influence the  
388 accuracy of these data. It presents information on the two primary information sources  
389 available for pharmacoepidemiology studies: questionnaires and administrative databases  
390 and concludes with a summary of the current knowledge in the field as well as directions for  
391 future research.

### 392 **5.2.2. Use of automated health databases**

393 The use of technology including administrative databases for pharmacoepidemiological  
394 research has limitations including the following:

- 395 - concordance of what is in the database with actual clinical reality. [Discordance of  
396 databases designed for claims payment versus clinical information systems:  
397 implications for outcomes research](#) (Jollis JG, Ancukiewicz M, DeLong ER, Pryor DB,  
398 Muhlbaier LH, Mark DB. *Ann Intern Med* 1993; 119: 844-850) was a comparative  
399 study of a clinical versus an insurance claims database for predictors of prognosis in  
400 patients with ischaemic heart disease. A finding was that claims data failed to identify  
401 more than half of the patients with prognostically important conditions when  
402 compared with the clinical information system.

- 403 - consistency and totality of data capture i.e. does the database reliably capture all of  
404 the patient's health care interactions or are there known gaps in coverage, capture,  
405 longitudinality or eligibility? Researchers using claims data rarely have the  
406 opportunity to carry out quality assurance of the whole data set. An example is  
407 provided in [Descriptive analyses of the integrity of a US Medicaid Claims Database](#)  
408 (Hennessy S, Bilker WB, Weber A, Strom B. *Pharmacoepidemiol Drug Saf* 2003; 12:  
409 103–111), This article concludes that performing such analyses can reveal important  
410 limitations of the data and whenever possible, researchers should examine the  
411 'parent' data set for apparent irregularities.
- 412 - bias in assessment of drug exposure from an administrative database. The relevance  
413 of these biases for quality control in more clinical databases are explored in [European  
414 Surveillance of Antimicrobial Consumption \(ESAC\): Data Collection Performance and  
415 Methodological Approach](#) (Vander Stichele RH, Elseviers MM, Ferech M, Blot S,  
416 Goossens H; ESAC Project Group. *Br J Clin Pharmacol* 2004; 58: 419-28). This article  
417 describes the performance and methodological approach in a retrospective data  
418 collection effort (1997–2001) through an international network of surveillance  
419 systems, aiming to collect publicly available, comparable and reliable data on  
420 antibiotic use in Europe. The data collected were screened for bias, using a checklist  
421 focusing on detection bias in sample and census data; errors in assigning medicinal  
422 product packages to the [Anatomical Therapeutic Chemical Classification System](#);  
423 errors in calculations of [Defined Daily Doses](#) per package; bias by over-the-counter  
424 sales and parallel trade; and bias in ambulatory/hospital care mix. The authors  
425 conclude that methodological rigour is needed to assure data validity and to ensure  
426 reliable cross-national comparison.
- 427 - validity of the data and the definitions used, which is not simply about source record  
428 validation of a particular endpoint. There are many possible ways to define endpoints  
429 and researchers that do validate may only seek to validate their choice. The following  
430 study investigated the range of methods used to validate diagnoses in a primary care  
431 database: [Validation and validity of diagnoses in the General Practice Research  
432 Database \(GPRD\): a systematic review](#) (Herrett E, Thomas SL, Schoonen WM,  
433 Smeeth L, Hall AJ. *Br J Clin Pharmacol* 2010; 69: 4-14). The findings concluded that  
434 a number of methods had been used to assess validity and that overall, estimates of  
435 validity were high. The quality of reporting of the validations was, however, often  
436 inadequate to permit a clear interpretation. Not all methods provided a quantitative  
437 estimate of validity and most methods considered only the positive predictive value of  
438 a set of diagnostic codes in a highly selected group of cases.

439 Another example of the hazards of using large linked databases is provided in [Vaccine safety  
440 surveillance using large linked databases: opportunities, hazards and proposed guidelines](#)  
441 (Verstraeten T, DeStefano F, Chen RT, Miller E. *Expert Rev Vaccines* 2003; 2(1): 21-9).

442 In general it is clear that the quality of pharmacoepidemiological studies that rely heavily on  
443 clinical databases from medical practice could be greatly enhanced by stimulating the quality  
444 of medical registration in electronic health records, through the provision of elaborate end-  
445 user terminologies and classification aides at the point-of-care. The U.S. Food and Drug  
446 Administration (FDA) Amendments Act of 2007 mandated that the FDA develop a system for  
447 using automated health care data to identify risks of marketed drugs and other medical  
448 products. The [Observational Medical Outcomes Partnership](#) is an initiative to research  
449 methods that are feasible and useful to analyse existing healthcare databases to identify and  
450 evaluate safety and benefit of drugs already on the market. The article [Advancing the](#)

451 [science of active surveillance: rationale and design for the Observational Medical Outcomes](#)  
452 [Partnership](#) (Stang PE, Ryan PB, Racossin JA, Overhage JM, Hartzema AG, Reich C, Welebob  
453 E, Scarnecchia T, Woodcock J. *Ann Intern Med* 2010; 153: 600-606) describes the  
454 governance structure, data-access model, methods-testing approach, and technology  
455 development of this effort, as well as the work that has been initiated.

456 Quality control and assurance are further addressed in section 8 of the present document.

### 457 **5.2.3. Bias and confounding**

#### 458 **5.2.3.1. Choice of time windows**

459 The paper [A study of the effects of exposure misclassification due to the time-window design](#)  
460 [in pharmacoepidemiologic studies](#) (van Staa TP, Abenhaim L, Leufkens H. *J Clin Epidemiol*  
461 1994; 47(2): 183 – 189) considers the effects of the time-window design on the validity of  
462 risk estimates in record linkage studies. With longer windows, a substantive attenuation of  
463 incidence rates of therapy was observed. The choice of prescription time windows can,  
464 therefore, influence the estimate of exposure risks. Time windows should cover the period  
465 with potential excess risk and be validated, accordingly.

#### 466 **5.2.3.2. Immortal time bias**

467 Immortal time in epidemiology refers to a period of cohort follow-up time during which death  
468 (or an outcome that determines end of follow-up) cannot occur. It is defined in the book  
469 *Modern Epidemiology* (K. Rothman, S. Greenland, T. Lash. 3rd Edition, Lippincott Williams &  
470 Wilkins, 2008 p. 106-107).

471 Bias from immortal time was first identified in the 1970s in epidemiology in the context of  
472 cohort studies of the survival benefit of heart transplantation. It recently resurfaced in  
473 pharmacoepidemiology, with several observational studies reporting that various  
474 medications can be extremely effective at reducing morbidity and mortality. These studies,  
475 while using different cohort designs, all involved some form of immortal time and the  
476 corresponding bias.

477 Immortal time bias can arise when the period between cohort entry and date of first  
478 exposure, e.g., to a drug, during which death has not occurred, is either misclassified or  
479 simply excluded and not accounted for in the analysis. [Immortal time bias in observational](#)  
480 [studies of drug effects](#) (Suissa S. *Pharmacoepidemiol Drug Saf* 2007; 16: 241-249)  
481 demonstrates how several observational studies used a flawed approach to design and data  
482 analysis, leading to immortal time bias, which can generate an illusion of treatment  
483 effectiveness. Observational studies with surprisingly beneficial drug effects should,  
484 therefore, be re-assessed to account for this bias.

485 [Immortal time bias in Pharmacoepidemiology](#) (Suissa S. *Am J Epidemiol* 2008; 167: 492-499)  
486 describes various cohort study designs leading to this bias, quantifies its magnitude under  
487 different survival distributions, and illustrates it by using data from a cohort of lung cancer  
488 patients. The author shows that for time-based, event-based, and exposure-based cohort  
489 definitions the bias in the rate ratio resulting from misclassified or excluded immortal time  
490 increases proportionately to the duration of immortal time. The findings support the  
491 conclusion that observational studies of drug benefit in which computerised databases are  
492 used must be designed and analysed properly to avoid immortal time bias.

493 [The Secret of Immortal Time Bias in Epidemiologic Studies](#) (Shariff SZ, Cuerden MS, Jain AK,  
494 Garg AX. J Am Soc Nephrol 2008; 19: 841-843) proposes two methods to account for  
495 immortal time with an example in nephrology i.e. comparing patients who had chronic  
496 kidney disease and attended multidisciplinary care clinics with those who received usual care.  
497 The first solution is *matching*. At the design stage, an extra criterion is added to the  
498 matching procedure; a non-multidisciplinary care clinic patient must be alive at the time  
499 when their matched patient attends the multidisciplinary care clinic. In this situation, cohort  
500 entry becomes the date of the multidisciplinary care clinic visit, and any time between a  
501 baseline serum creatinine test and the multidisciplinary care clinic visit is not counted in  
502 either of the groups. The other solution is to perform an analysis using *time-dependent*  
503 *covariates*. A time-dependent covariate is a predictor whose value may change over time.  
504 Immortal time bias can be avoided by acknowledging a change in exposure status using a  
505 time-dependent covariate. For example, a multidisciplinary care clinic patient would be  
506 considered unexposed from the date of study entry until he or she visits the multidisciplinary  
507 care clinic and exposed from that point forward.

#### 508 **5.2.3.3. Depletion of susceptibles**

509 Depletion of susceptibles is the effect whereby patients who remain on a drug are those who  
510 can tolerate the product while those who are susceptible to an adverse event select  
511 themselves out of the population at risk. The following article [Evidence of the depletion of](#)  
512 [susceptibles effect in non-experimental pharmacoepidemiologic research](#) (Moride Y,  
513 Abenheim L. J Clin Epidemiol 1994; 47 (7): 731-7) provides empirical evidence of this effect.  
514 It describes a hospital-based case-control study on NSAIDs and the risk of upper  
515 gastrointestinal bleeding. Recent use (within 30 days prior to admission) of non-aspirin  
516 NSAIDs increased the risk of upper gastrointestinal bleeding whereas use in the previous 3  
517 years was associated with a lower risk. The estimate of relative risk for first-time users was  
518 22.7 (CI 2.8-200.0) vs. 3.0 (CI 1.9-4.7) for those who had used the drugs at least once in  
519 the past 3 years. Thus, past use should be considered as a potential risk modifier in non-  
520 experimental risk assessment of events associated with drug use.

#### 521 **5.2.3.4. Confounding by indication**

522 Confounding by indication refers to an extraneous determinant of the outcome parameter  
523 that is present if a perceived high risk or poor prognosis is an indication for intervention.  
524 This means that differences in care, for example, between cases and controls may partly  
525 originate from differences in indication for medical intervention such as the presence of risk  
526 factors for particular health problems. The latter has frequently been reported in studies  
527 evaluating the efficacy of pharmaceutical interventions.

528 A good example can be found in [Confounding and indication for treatment in evaluation of](#)  
529 [drug treatment for hypertension](#) (Grobbee DE, Hoes AW. BMJ 1997; 315: 1151-1154). The  
530 article [Confounding by indication: the case of the calcium channel blockers](#) (Joffe MM.  
531 Pharmacoepidemiol Drug Saf 2000; 9: 37-41) reviews conceptual issues regarding  
532 confounding by indication. It demonstrates that studies with potential confounding by  
533 indication can benefit from appropriate analytic methods, including separating the effects of  
534 a drug taken at different times, sensitivity analysis for unmeasured confounders,  
535 instrumental variables and G-estimation.

536 With the more recent application of pharmacoepidemiological methods to assess  
537 effectiveness, confounding by indication is a greater challenge and the article [Approaches to](#)

538 [combat with confounding by indication in observational studies of intended drug effects](#)  
539 (McMahon AD. *Pharmacoepidemiol Drug Saf* 2003; 12: 551-8) focuses on its possible  
540 reduction in studies of intended effects.

#### 541 **5.2.3.5. Channelling**

542 Channelling is a form of allocation bias, where drugs with similar therapeutic indications are  
543 prescribed to groups of patients with prognostic differences. Claimed advantages of a new  
544 drug may channel it to patients with special pre-existing morbidity, with the consequence  
545 that disease states can be incorrectly attributed to use of the drug. How channelling towards  
546 high risk gastrointestinal patients occurred in the prescribing of newer NSAIDs is well  
547 demonstrated in [Channelling bias and the incidence of gastrointestinal haemorrhage in users  
548 of meloxicam, coxibs, and older, non-specific NSAIDs](#) (MacDonald TM, Morant SV, Goldstein  
549 JL, Burke TA, Pettitt D. *Gut* 2003; 52: 1265–70). In situations where indication or  
550 contraindication biases exist, and complex channelling effects can be expected, only  
551 randomised trials can be relied upon to provide unbiased treatment comparisons.

#### 552 **5.2.3.6. Unmeasured confounding**

553 Large health care utilisation databases are frequently used to analyse unintended effects of  
554 prescription drugs and biologics. Confounders that require detailed information on clinical  
555 parameters, lifestyle, or over-the-counter medications are often not measured in such  
556 datasets, causing residual confounding bias. [Sensitivity analysis and external adjustment for  
557 unmeasured confounders in epidemiologic database studies of therapeutics](#) (Schneeweiss S.  
558 *Pharmacoepidemiol Drug Saf* 2006; 15 (5) 291-303) provides a systematic approach to  
559 sensitivity analyses to investigate the impact of residual confounding in  
560 pharmacoepidemiological studies that use health care utilisation databases. In the article,  
561 four basic approaches to sensitivity analysis were identified: (1) sensitivity analyses based  
562 on an array of informed assumptions; (2) analyses to identify the strength of residual  
563 confounding that would be necessary to explain an observed drug-outcome association; (3)  
564 external adjustment of a drug-outcome association given additional information on single  
565 binary confounders from survey data using algebraic solutions; (4) external adjustment  
566 considering the joint distribution of multiple confounders of any distribution from external  
567 sources of information using propensity score calibration. The author concludes that  
568 sensitivity analyses and external adjustments can improve our understanding of the effects  
569 of drugs and biologics in epidemiological database studies. With the availability of easy-to-  
570 apply techniques, sensitivity analyses should be used more frequently, substituting  
571 qualitative discussions of residual confounding.

572 There has also been discussion about the amount of bias in exposure effect estimates that  
573 can plausibly occur due to residual or unmeasured confounding. In [The impact of residual  
574 and unmeasured confounding in epidemiologic studies: a simulation study](#) (Fewell Z, Davey  
575 Smith G, Sterne JAC. *Am J Epidemiol* 2007; 166: 646–55), the authors considered the  
576 extent and patterns of bias in estimates of exposure-outcome associations that can result  
577 from residual or unmeasured confounding, when there is no true association between the  
578 exposure and the outcome. The conclusion was that the validity of an epidemiological study  
579 may be threatened by both residual and unmeasured confounding. With plausible  
580 assumptions about residual and unmeasured confounding, effect sizes of the magnitude  
581 frequently reported in observational epidemiological studies can be generated. This study  
582 highlights the need to perform sensitivity analyses to assess whether unmeasured and  
583 residual confounding are likely problems.

584 **5.2.4. Methods to handle bias and confounding**

585 **5.2.4.1. New-user designs**

586 The practice of most observational studies to include many prevalent users, i.e. patients taking a  
587 therapy for some time before study follow-up began, can cause two types of bias. First, prevalent  
588 users are “survivors” of the early period of pharmacotherapy, which can introduce substantial bias if  
589 risk varies with time. Second, covariates for drug users at study entry often are plausibly affected by  
590 the drug itself. Failure to adjust for these factors on the causal pathway may introduce confounding.  
591 [Evaluating medication effects outside of clinical trials: new-user designs](#) (Ray WA. Am J Epidemiol  
592 2003; 158 (9): 915 – 920) reviews new-user designs, which avoid these biases by restricting the  
593 analysis to persons under observation at the start of the current course of treatment. In addition to  
594 defining new-user designs the article explains how they can be implemented as case-control studies  
595 and describes the logistical and sample size limitations involved.

596 **5.2.4.2. Disease risk scores**

597 An approach to controlling for confounding is to construct a multivariable confounder score  
598 which summarises potential confounding factors in a single score. [Stratification by a  
599 multivariate confounder score](#) (Miettinen OS. Am J Epidemiol 1976; 104: 609-20)  
600 demonstrates how the control of confounding may be based on stratification by the score,  
601 with stratum-specific contingency tables obtained and analysed in the usual manner. An  
602 example is a disease risk score (DRS) that estimates the probability or rate of disease  
603 occurrence conditional on being unexposed. The association between exposure and disease  
604 is then estimated, adjusting for the disease risk score in place of the individual covariates.  
605 [Use of disease risk scores in pharmacoepidemiologic studies](#) (Arbogast P. Stat Methods Med  
606 Res 2009; 18: 67-80) includes a brief discussion of the DRS history, a more detailed  
607 description of their construction and use, a summary of simulation studies comparing their  
608 performance to traditional models, a comparison of their utility with that of propensity  
609 scores, and some further topics for future research.

610 **5.2.4.3. Propensity scores**

611 Databases used in pharmacoepidemiologic studies often include records of prescribed  
612 medications and encounters with medical care providers, from which one can construct very  
613 detailed surrogate measures for both drug exposure and covariates that are potential  
614 confounders. It is often possible to track day-by-day changes in these variables. However,  
615 while this information can be critical for study success, its volume can pose challenges for  
616 statistical analysis. A propensity score is analogous to the disease risk score in that it  
617 combines a large number of possible confounders into a single variable (the score). The  
618 exposure propensity score (EPS) is the conditional probability of exposure to a treatment  
619 given observed covariates. In a cohort study, matching or stratifying treated and control  
620 subjects on EPS tends to balance all of the observed covariates. However, unlike random  
621 assignment of treatments, the propensity score may not also balance unobserved covariates.  
622 [Invited Commentary: Propensity Scores](#) (Joffe MM, Rosenbaum PR. Am J Epidemiol 1999;  
623 150: 327–33) reviews the uses and limitations of propensity scores and provide a brief  
624 outline of the associated statistical theory. The authors present results of adjustment by  
625 matching or stratification on the propensity score. The following article discusses the  
626 emerging high dimension propensity score (HDPS) model approach [High-dimensional  
627 Propensity Score Adjustment in Studies of Treatment Effects Using Health Care Claims Data](#)  
628 (Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. Epidemiol 2009;

629 20(4): 512-22). In doing so it addresses a frequent problem in propensity score adjustment  
630 and proposes a practical solution.

631 [Analytic Strategies to Adjust Confounding using Exposure Propensity Scores and Disease](#)  
632 [Risk Scores](#) (Stürmer T, Schneeweiss S, Brookhart MA, Rothman KJ, Avorn J, Glynn RJ. Am J  
633 Epidemiol 2005; 161(9): 891-898) illustrates the different ways that both EPS and DRS  
634 methods can be used to control for confounding in a large cohort study. The authors  
635 conclude that in the setting of claims data on an elderly population, various ways to apply  
636 EPSs and DRSs to control for confounding were not generally superior to “conventional”  
637 multivariable outcome modelling. Differences in effect estimates between analytic strategies  
638 became more pronounced with smaller study size. More recently in [Performance of](#)  
639 [propensity score calibration – a simulation study](#) (Stürmer T, Schneeweiss S, Rothman KJ,  
640 Avorn J, Glynn RJ. Am J Epidemiol 2007; 165(10): 1110-8) introduced ‘propensity score  
641 calibration’ (PSC). This technique combines propensity score matching methods with  
642 measurement error regression models to address confounding by variables unobserved in  
643 the main study by using variables observed in a validation study. Their analyses  
644 demonstrated that PSC greatly improves inference when the critical assumption of surrogacy  
645 holds, but when surrogacy does not hold, PSC estimation can exacerbate bias relative to  
646 uncorrected propensity score models.

#### 647 **5.2.4.4. Instrumental variables**

648 Instrumental variable (IV) methods were invented over 70 years ago, but remained  
649 uncommon in epidemiology for a long time. Over the past decade or so, non-parametric  
650 versions of IV methods have appeared that connect IV methods to causal and measurement-  
651 error models important in epidemiological applications. [An introduction to instrumental](#)  
652 [variables for epidemiologists](#) (Greenland S. Int J of Epidemiol 2000; 29:722-729) presents  
653 those developments, illustrated by an application of IV methods to non-parametric  
654 adjustment for non-compliance in randomised trials. The author mentions a number of  
655 caveats, but concludes that IV corrections can be valuable in many situations. Including  
656 when IV assumptions are questionable, the corrections can still serve as part of the  
657 sensitivity analysis or external adjustment. When, however, the assumptions are more  
658 defensible, as in field trials and in studies that obtain validation or reliability data, IV  
659 methods can form an integral part of the analysis.

660 The complexity of the issues associated with confounding by indication, channelling and  
661 selective prescribing is explored in [Evaluating short-term drug effects using a physician-](#)  
662 [specific prescribing preference as an instrumental variable](#) (Brookhart MA, Wang P, Solomon  
663 DH, Schneeweiss S. Epidemiology 2006; 17(3): 268-275). This article also proposes a  
664 potential approach to control confounding by indication in non-experimental studies of  
665 treatment effects. The use of this instrument is illustrated in a study comparing the effect of  
666 exposure to COX-2 inhibitors with non-selective NSAIDs on gastrointestinal complications.  
667 Contrary to randomised controlled trial (RCT) results showing that COX-2 inhibitors lead to a  
668 reduced risk of gastro-intestinal toxicity relative to non-selective NSAIDs, the author’s  
669 conventional multivariable analysis found no evidence of a gastro-protective effect  
670 attributable to COX-2 inhibitor use. In contrast to the conventional analysis, a physician-  
671 level instrumental variable approach (a time-varying estimate of a physician’s relative  
672 preference for a given drug, where at least two therapeutic alternatives exist) yielded  
673 evidence of a clinically significant protective effect due to COX-2 exposure, particularly for  
674 shorter term drug exposures. The authors also point out the possibility that a physician can  
675 influence the outcome in ways other than through the prescribing of an NSAID. For example,

676 physicians who frequently prescribe COX-2 inhibitors may also be more likely to co-prescribe  
677 proton pump inhibitors for additional gastro-protection. In such a situation, the protective  
678 effect due to COX-2 exposure is partly attributable to the use of a proton pump inhibitor.

#### 679 **5.2.4.5. G-estimation**

680 G-estimation is a method for estimating the joint effects of time-varying treatments using  
681 ideas from instrumental variables methods. The article [G-estimation of Causal Effects:  
682 Isolated Systolic Hypertension and Cardiovascular Death in the Framingham Heart Study](#)  
683 (Witteaman JCM, D'Agostino RB, Stijnen T, Kannel WB, Cobb JC, de Ridder MAJ, Hofman A,  
684 Robins JM. Am J Epidemiol 1998; 148(4) 390-401) demonstrates how the G-estimation  
685 procedure allows for appropriate adjustment of the effect of a time-varying exposure in the  
686 presence of time-dependent confounders that are themselves influenced by the exposure.

#### 687 **5.2.4.6. Marginal Structural Models**

688 In observational studies with exposures or treatments that vary over time, standard  
689 approaches for adjustment for confounding are biased when time-dependent confounders,  
690 which are also affected by previous treatment, exist. [Marginal Structural Models and Causal  
691 Inference in Epidemiology](#) (Robins JM, Hernán MA, Brumback B. Epidemiology 2000; 11(5):  
692 550-560) introduces marginal structural models, a class of causal models that allow for  
693 improved adjustment for confounding in these situations.

### 694 **5.3. Integrating and pooling studies**

695 Often more than one study is available for a research question so it is important to identify  
696 and integrate the evidence. In epidemiology, the focus of this activity is often not to obtain  
697 an estimate but to learn from the diversity of designs, results and associated gaps in  
698 knowledge.

699 A systematic review is a review of the literature aiming to answer a specific and clearly  
700 formulated research question. Systematic reviews use systematic and explicit methods to  
701 identify, select, critically appraise relevant research, and to collect and analyse data from  
702 the studies that are included in the review. The key characteristics are that the methods  
703 used to minimise bias are explicit and the findings are reproducible as stated in the  
704 [Cochrane Handbook for Systematic Review of Interventions](#).

705 For example, it has long been recognised that persons using NSAIDs are at a significantly  
706 increased risk of gastrointestinal complications, for instance, injury to the intestinal lining  
707 that can result in ulcers and/or gastrointestinal bleeding. To reduce the morbidity associated  
708 with NSAIDs, specific estimates for individual drugs and individual groups of patients with  
709 different risk profiles are needed. Therefore, a systematic review of a number of studies is  
710 appropriate to determine specific pharmacologic features of NSAID-associated gastro-  
711 intestinal toxicity and to explore multi-factorial determinants in the risk of gastro-intestinal  
712 bleeding among NSAID users, including clinical background, use of concomitant medications  
713 or a possible genetic susceptibility.

714 Frequently, a statistical technique known as meta-analysis is used to analyse and summarise  
715 the findings of a systematic review by quantitative pooling of the data from individual  
716 studies addressing the same question included in the systematic review. How meta-analysis  
717 can provide more precise estimates of the effects of health care than those derived from the  
718 individual studies included within a systematic review is demonstrated in [Quantitative](#)

719 [synthesis in systematic reviews](#) (Lau J, Ioannidis JP, Schmid CH. Ann Intern Med 1997; 127:  
720 820-826). In addition meta-analysis evaluates the consistency of results across studies and  
721 facilitates the exploration of the heterogeneity (clinical, methodological and/or statistical).  
722 Indeed, as shown in [Investigating causes of heterogeneity in systematic reviews](#) (Glasziou  
723 PP, Sanders SL. Stat Med 2002; 21: 1503-11), when very significant heterogeneity exists,  
724 the heterogeneity itself may deserve more emphasis than the pooled summary estimates.

725 Systematic review and meta-analysis can be conducted with different sources of information  
726 including clinical trials or epidemiological studies for the assessment of safety and tolerability  
727 profiles of therapeutic interventions. An example of a meta-analysis addressing confounding  
728 to determine a safety profile is provided in [Risk of venous thromboembolism from oral  
729 contraceptives containing gestodene and desogestrel versus levonorgestrel: a meta-analysis  
730 and formal sensitivity analysis](#) (Hennessy S, Berlin JA, Kinman JL, Margolis DJ, Marcus SM,  
731 Strom BL. Contraception 2001; 64: 125-133). Any systematic review and meta-analysis will,  
732 however, have the same limitations as the sources of information they use. There are also  
733 additional limitations pertaining to the actual statistical combination of data via a meta-  
734 analytic approach.

735 RCTs are considered the gold standard for establishing causal association for therapeutic  
736 interventions. They frequently have limitations relating to sample size, narrow population  
737 characteristics and indications, and short follow-up duration. Therefore RCTs alone and  
738 subsequent systematic review or meta-analysis of RCTs will not address issues relating to  
739 the incidence of diseases and will have little value in detecting rare events and in the  
740 evaluation of outcomes that are far in the future. Systematic review and meta-analysis of  
741 observational studies and other epidemiological sources are becoming as common as  
742 systematic review of published clinical trials and [Challenges in systematic reviews that  
743 assess treatment harms](#) (Chou R, Helfand M. Ann Intern Med 2005; 142:1090-9) shows why  
744 for different reasons both provide relevant information and knowledge for pharmacovigilance.  
745 It is emphasised that the limitations of data sources will not be compensated for by a  
746 systematic review and/or meta-analysis.

747 Section 6.4 further describes different approaches to integrating studies and pooling data.

## 748 **6. Data Sources**

749 There are two basic approaches for data collection. One is to use data already collected as  
750 part of administrative records or patient health care. The second option is *de novo* data  
751 collection, which is collection of primary data specifically for the study. Increasingly often, a  
752 combination of both approaches is used.

### 753 **6.1. Use of available data**

754 The use of already available electronic patient health care data in automated health  
755 databases for research has had a marked impact on pharmacoepidemiology research. The  
756 last two decades have witnessed the development of key data resources, expertise and  
757 methodology that have allowed the conduct of landmark studies in the field. Electronic  
758 medical records and record linkage of administrative health records are the main types of  
759 databases from a data structure and origin perspective. Examples of the first and second are  
760 the GPRD in the UK and the national or regional databases in the Nordic countries, Italy,  
761 Netherlands and other countries, respectively. The [ENCePP Inventory of Databases](#) contains  
762 key information on the databases that are registered in the ENCePP Network.

763 A comprehensive description of the main features and applications of frequently used  
764 databases for pharmacoepidemiology research in the United States and in Europe appears in  
765 the book *Pharmacoepidemiology* (B. Strom, 4th Edition, Wiley, August 2005, Chap. 13-22).  
766 As an increasing number of databases are now being made available for  
767 pharmacoepidemiological research, this list is inherently incomplete. It should be noted,  
768 however, that limitations exist in relation to pharmacoepidemiologic research using  
769 electronic health care utilisation databases, as detailed in [A review of uses of health care  
770 utilization databases for epidemiologic research on therapeutics](#) (Schneeweiss S, Avorn J. J  
771 Clin Epidemiol 2005; 58: 323-337).

772 General guidance for studies including those conducted in databases can be found in the  
773 [ISPE GPP](#), in particular sections IV-B (Study conduct, Data collection). This guidance  
774 emphasises the paramount importance of patient data protection.

775 The Working Group for the Survey and Utilisation of Secondary Data (AGENS) with  
776 representatives from the German Society for Social Medicine and Prevention (DGSPM) and  
777 the German Society for Epidemiology (DGEpi) developed a [Good Practice in Secondary Data  
778 Analysis Version 2](#) aiming to establish a standard for planning, conducting and analysing  
779 studies on the basis of secondary data, i.e. data collected for other purposes such as  
780 population-based disease registers. It is also aimed to be used as the basis for contracts  
781 between data owners (so-called primary users) and secondary users. It is divided in 11  
782 sections addressing, among other aspects, the study protocol, quality assurance and data  
783 protection.

784 The [International Society for Pharmacoconomics and Outcome Research \(ISPOR\)](#) working  
785 group on databases has published a [Checklist for Retrospective Database Studies](#) to assist  
786 decision makers in evaluating the quality of reporting in published studies that use health-  
787 related databases. It should be noted that the checklist focuses (in discussed problems and  
788 examples) on claims and encounter-based databases. It is meant to serve as a supplement  
789 to already available checklists for economic evaluations and will be most useful for health  
790 insurers (public or private). Of note, some important aspects for pharmacoepidemiological  
791 studies, such as outcome definition and validity, evaluation of biases, sensitivity analyses,  
792 ethical issues, data ownership and privacy, are not covered in the ISPOR guideline.

## 793 **6.2. De novo data collection**

794 Hospital or community based case-control studies using de novo data collection have allowed  
795 the evaluation of drug-disease associations for rare complex conditions that require very  
796 large base populations over several countries and in depth case assessment by clinical  
797 experts. Examples are [Appetite-Suppressant Drugs and the Risk of Primary Pulmonary  
798 Hypertension](#) (Abenheim LA, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T,  
799 Oakley C, Wouters E, Aubier M, Simonneau G, Bégaud B. for the International Primary  
800 Pulmonary Hypertension Study Group. N Engl J Med 1996; 335: 609-616); [The design of a  
801 study of the drug etiology of agranulocytosis and aplastic anemia](#) (Shapiro S. for the  
802 International Agranulocytosis and Aplastic Anemia Study. Eur J Clin Pharmacol 1983; 24:  
803 833-6); [Medication Use and the Risk of Stevens–Johnson Syndrome or Toxic Epidermal  
804 Necrolysis](#) (Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A,  
805 Bastuji-Garin S, Correia O, Locati F, Maja Mockenhaupt M, Paoletti C, Shapiro S, Shear N,  
806 Schöpf E, Kaufman DW. N Engl J Med 1995; 333: 1600-1608).

807 For some conditions, case-control surveillance networks have been developed that can be  
808 used for selected studies and for signal generation and clarification e.g. [Signal generation](#)

809 [and clarification: use of case-control data](#) (Kaufman DW, Rosenberg L, Mitchell AA.  
810 *Pharmacoepi Drug Safety* 2001; 10: 197-203).

811 General guidance on proper conduct of prospective patient-based studies can be found in the  
812 [ISPE GPP](#) and the [IEA GEP](#). The GPP is especially useful for its recommendations on aspects  
813 rarely covered by guidelines, such as data quality issues and archiving. Both guidelines  
814 address the importance of patient data protection and the ethical principles of research using  
815 patient health care and personal data.

816 Patient registers are sometimes requested by regulators at the time of authorisation of a  
817 medicinal product in order to determine clinical effectiveness and monitor safety. A registry  
818 should be considered a structure within which studies can be performed, i.e. a data source,  
819 where entry is defined either by diagnosis of a disease (disease registry) or prescription of a  
820 drug (exposure registry). AHRQ has published a comprehensive document on 'good registry  
821 practices' entitled [Registries for Evaluating Patient Outcomes: A User's Guide. Second  
822 Edition](#), the purpose of which is to guide the planning, design, implementation, analysis,  
823 interpretation, and evaluation of the quality of a registry. A section also covers linking of  
824 registries to other data sources. This section is, however, focused on the US. References to  
825 research review, funding and regulatory bodies are, therefore, US centric and specific  
826 recommendations, in particular on ethical, privacy ownership and regulatory aspects, cannot  
827 be transferred to the European situation.

828 Surveys in pharmacoepidemiology, in the areas of disease epidemiology and risk  
829 minimisation evaluation efforts, are increasing. Such surveys require a sampling strategy  
830 that allows for external validity and maximised response rates. Useful textbooks on these  
831 aspects are *Survey Sampling* (L. Kish, Wiley, 1995) and *Survey Methodology* (R.M. Groves,  
832 F.J. Fowler, M.P. Couper, J.M. Lepkowski, E. Singer, R. Tourangeau, 2<sup>nd</sup> Edition, Wiley 2009).  
833 Depending of the purpose of the survey, questionnaires are often used. They should be  
834 validated based on accepted measures including, if appropriate, construct, criterion and  
835 content validity, inter-rater and test-retest reliability, sensitivity and responsiveness.  
836 Although primarily focused on quality of life research, the book *Quality of Life: the  
837 assessment, analysis and interpretation of patient-related outcomes* (P.M. Fayers, D.  
838 Machin, 2<sup>nd</sup> Edition, Wiley, 2007) offers a comprehensive review of the theory and practice  
839 of developing, testing and analysing questionnaires in different settings. *Health  
840 Measurement Scales: a practical guide to their development and use* (D. L. Streiner, G. R.  
841 Norman, 4<sup>th</sup> Edition, Oxford University Press, 2008) is a very helpful guide to those involved  
842 in measuring subjective states such as attitudes, feelings, quality of life, educational  
843 achievement and aptitude, and learning style in patients and healthcare providers. Many  
844 other examples of the development and testing of questionnaires have also been published  
845 in the scientific literature.

846 RCTs are a form of *de novo* data collection. There are numerous textbooks and publications  
847 on methodological and operational aspects of clinical trials, although they are not covered  
848 here. An essential guideline on clinical trials is the European Medicines Agency [Note for  
849 Guidance on Good Clinical Practice](#), which specifies obligations for the conduct of clinical  
850 trials to ensure that the data generated in the trial is valid.

### 851 **6.3. Signal detection methodology and application**

852 Quantitative analysis of spontaneous adverse drug reaction reports is increasingly used in  
853 drug safety research. [Quantitative signal detection using spontaneous ADR reporting](#) (Bate  
854 A, Evans SJW. *Pharmacoepidemiol Drug Saf* 2009; 18: 427-436) describes the core concepts

855 behind the most common methods, the proportional reporting ratio (PRR), reporting odds  
856 ratio (ROR), information component (IC) and empirical Bayes geometric mean (EBGM). The  
857 authors also discuss the role of Bayesian shrinkage in screening spontaneous reports and the  
858 importance of changes over time in screening the properties of the measures. Additionally  
859 they discuss three major areas of controversy and ongoing research: stratification, method  
860 evaluation and implementation in addition to giving some suggestions as to where emerging  
861 research is likely to lead.

862 The 2010 report of [Council for International Organizations of Medical Sciences \(CIOMS\)](#)  
863 Working Group VIII [Practical Aspects of Signal Detection in Pharmacovigilance](#) provides a  
864 comprehensive resource for those considering how to strengthen their pharmacovigilance  
865 systems and practices in terms of signal management.

866 The [Guideline on the use of statistical signal detection methods in the Eudravigilance data](#)  
867 [analysis system](#) describes quantitative methods implemented in signal detection by the EMA  
868 together with the elements for their interpretation and their potential limitations in the frame  
869 of pharmacovigilance. It encompasses the use of quantitative methods in [EudraVigilance](#)  
870 applied to the evaluation of Individual Case Safety Reports (ICSRs) originating from health  
871 care professionals and involving authorised medicinal products.

872 Other large observational databases such as claims databases are potentially useful as part  
873 of a larger signal detection strategy. In addition, there are a number of ongoing initiatives to  
874 develop observational data as electronic systems that will complement existing methods of  
875 safety surveillance e.g. the [IMI PROTECT](#), [EU-ADR](#) and [Mini-Sentinel](#) projects (see Section  
876 6.4).

877 Useful commentary and points of caution to consider before incorporating data mining as a  
878 routine component of any pharmacovigilance program is provided in [Data mining for signals](#)  
879 [in spontaneous reporting databases: proceed with caution](#) (Stephenson WP, Hauben M.  
880 *Pharmacoepidemiol Drug Saf* 2007; 16: 359–365), which also includes a review of data  
881 mining methodologies employed and their limitations.

## 882 **6.4. Hybrid studies**

883 The use of the term 'hybrid studies' in the current document relates to efforts at bridging the  
884 pharmacoepidemiological principles and practices of interventional and non-interventional  
885 study design, conduct and analysis. One of the primary aims for doing this is to better reflect  
886 'real life' populations and circumstances.

### 887 **6.4.1. Large simple trials**

888 RCT are considered the gold standard for demonstrating the efficacy of medicinal products.  
889 This design can also be used to obtain unbiased estimates of the risk for adverse outcomes.  
890 However, large sample sizes are required when the risk is small or delayed (with a large  
891 expected attrition rate), when the population exposed to the risk is heterogeneous (e.g.  
892 different indications and age groups), when several risks need to be assessed in the same  
893 trial (e.g. risks of stroke and of myocardial infarction) or when many confounding factors  
894 need to be balanced between treatment groups. In such circumstances, the cost and  
895 complexity of a RCT may outweigh its advantages over observational studies. A study design  
896 which, ethical considerations permitting, allowed drug allocation to be randomised in an  
897 otherwise normal clinical setting, and which relied upon the routine collection of primary and  
898 secondary health care records, could overcome the size limitations and atypical settings of

899 conventional clinical trials. It would also avoid the channelling bias that may, in some cases,  
900 make it impossible to interpret the results of purely observational studies. A Large Simple  
901 Trial (LST) is such a study design that keeps the volume and complexity of data collection to  
902 a minimum. Outcomes that are simple and objective can be measured from the routine  
903 process of care using epidemiological follow-up methods, for example by using  
904 questionnaires or hospital discharge records. LST methodology is discussed in Chapter 39 of  
905 the book *Pharmacoepidemiology* (B. Strom, 4th Edition, Wiley, August 2005), which includes  
906 a list of conditions appropriate for the conduct of a LST and a list of conditions which make a  
907 LST feasible. Examples of LSTs are [Assessment of the safety of paediatric ibuprofen: a  
908 practitioner based randomised clinical trial](#) (Lesko SM, Mitchel AA. JAMA 1995; 279: 929-  
909 933) and [Comparative mortality associated with ziprasidone and olanzapine in real-world  
910 use among 18,154 patients with schizophrenia: The Zodiac Observational Study of Cardiac  
911 Outcomes \(ZODIAC\)](#) (Strom BL, Eng SM, Faich G, Reynolds RF, D'Agostino RB, Ruskin J,  
912 Kane JM. Am J Psychiatry 2011; 168(2): 117-9).

913 Note that the use of the term 'simple' in the expression 'LST' refers to data structure and not  
914 data collection. It is used in relation to situations in which a small number of outcomes are  
915 measured. The term may not adequately reflect the complexity of the studies undertaken.

#### 916 **6.4.2. Randomised database studies**

917 Randomised database studies can be considered a special form of an LST where patients  
918 included in the trial are enrolled in a health care system with electronic records. Randomised  
919 database studies attempt to combine the advantages of randomisation and observational  
920 database studies. In a randomised database study, eligible patients may be identified and  
921 flagged automatically by the software, with the advantage of allowing comparison of  
922 included and non-included patients. Database screening or record linkage can be used to  
923 detect and measure outcomes of interest otherwise assessed through the normal process of  
924 care. Patient recruitment, informed consent and proper documentation of patient information  
925 are hurdles that still need to be addressed in accordance with the applicable legislation for  
926 RCTs. These and other aspects of randomised database studies are discussed in Chapter 17  
927 of the book *Pharmacoepidemiology and Therapeutic Risk Management* (A.G. Hartzema, H.H.  
928 Tilson and K.A. Chan, Editors, 1<sup>st</sup> Edition, Harvey Whitney Books Company, 2008), which  
929 illustrates with examples the practical implementation of randomised studies in general  
930 practice databases. Another use of databases in RCT is the long-term follow-up of patients in  
931 observational studies after RCT termination, for example to assess long-term safety and  
932 effectiveness at regular intervals using objective outcomes. There are few published  
933 examples of randomised database studies, but this design could become more common in  
934 the near future with the increasing computerisation of medical records.

#### 935 **6.5. Research networks**

936 Networks of centres active in pharmacoepidemiology and pharmacovigilance are rapidly  
937 changing the landscape of drug safety research in Europe. Although collaborations for  
938 multinational studies are not new, they have been strongly encouraged over the last years  
939 by the drug safety research funded by the European Commission (EC). The funding resulted  
940 in the conduct of groundwork necessary to overcome the hurdles of data sharing across  
941 countries.

942 Networking implies collaboration between investigators, which is based on trust and  
943 willingness to share and to maximise the advantage of bundling expertise. The [ENCePP](#)

944 [Database of Research Resources](#) may facilitate such collaborations by providing an inventory  
945 of research centres and data sources available for specific pharmacoepidemiology and  
946 pharmacovigilance studies in Europe. It allows the identification of centres and data sets by  
947 country, type of research and other relevant fields. In addition, an important component of  
948 ENCePP is the potential for meta-analyses to maximise the information gathered for an issue  
949 that is addressed in different databases. ENCePP also provides opportunities to perform  
950 pooling of person level analytical datasets of individual studies (person level meta-analysis).  
951 In the US, [the HMO Research Network](#) is a consortium of health maintenance organisations  
952 that have formal, recognised research capabilities.

953 From a methodological point of view, research networks have many advantages:

- 954 - By increasing the size of study populations, networks may shorten the time needed  
955 for obtaining the desired sample size. Hence, networks can facilitate research on rare  
956 events and accelerate investigation of drug safety issues;
- 957 - Heterogeneity of drug exposure across countries allows studying the effect of more  
958 individual drugs;
- 959 - Multinational studies may provide additional knowledge on whether a drug safety  
960 issue exists in several countries and on reasons for any differences between countries,  
961 which can lead to important information for regulators and marketing authorization  
962 holders;
- 963 - Involvement of experts from various countries addressing case definitions,  
964 terminologies, coding in databases and research practices provides opportunities to  
965 increase consistency of observational studies;
- 966 - Requirement to share data forces harmonisation of data elaboration and transparency  
967 in analyses, and benchmarking of data management.

968 Different models have been applied for combining data from various countries ranging from  
969 a very disparate to a more integrated approach:

- 970 - Meta-analysis of results of individual studies with potentially different design e.g.  
971 [Variability in risk of gastrointestinal complications with individual NSAIDs: results of a  
972 collaborative meta-analysis](#) (Henry D, Lim Lynette L-Y, Garcia Rodriguez LA, Perez  
973 Gutthann S, Carson JL, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, Hill S,  
974 Fries JT. *BMJ* 1996; 312 :1563-1566), which compared the relative risks of serious  
975 gastrointestinal complications reported with individual NSAIDs by conducting a  
976 systematic review of twelve hospital and community based case-control and cohort  
977 studies, found a relation between use of the drugs and admission to hospital for  
978 haemorrhage or perforation.
- 979 - Pooling of results from common protocol studies conducted in different databases,  
980 allowing assessment of database/population characteristics and of choices of study  
981 design and analysis as determinants of variability (e.g. [IMI PROTECT](#) project).
- 982 - Distributed data approach in which data partners maintain physical and operational  
983 control over electronic data in their existing environments (e.g. [Mini-Sentinel](#) project).  
984 A common data model standardises administrative and clinical information across  
985 data partners, whom execute standardised programs provided by an operations  
986 centre or project workgroups and typically share the output of these programs in  
987 summary form. The Mini-Sentinel pilot focuses on drugs, vaccines, other biologics,

988 and medical devices (the vaccine safety activities together constitute the [Post-  
989 Licensure Rapid Immunization Safety Measurement \(PRISM\) Program](#)).

990 - Pooling of aggregated data (person-time based) extracted locally from databases or  
991 electronic health records using a common data model and common software, and  
992 transmitted electronically to a central data warehouse for further analysis (e.g. [EU-  
993 ADR](#) project).

994 - Pooling of properly non-identifiable individual level data gathered locally (either from  
995 databases or field studies) to a central data warehouse for statistical analysis (e.g.  
996 [VAESCO](#) project).

997 - Pooling of elaborated individual-level data extracted locally from databases or  
998 electronic health records using common software and transmitted electronically to a  
999 central location for further analysis by multiple collaborators (e.g. [SOS-NSAIDS  
1000](#) project).

1001 These different models have different strengths and weaknesses and present different  
1002 challenges. These may include:

1003 - Differences in culture and experience between academia, public institutions and  
1004 private partners;

1005 - Different ethical and governance requirements in each country regarding processing  
1006 of anonymised or pseudo-anonymised health care data;

1007 - Mapping of differing disease coding systems (ICD-9, ICD10, READ, ICPC) and  
1008 languages of narrative medical information.

1009 - Choice of data sharing model and access rights of partners;

1010 - Validation of diagnoses and access to source documents for validation;

1011 - Issues linked to intellectual property and authorship;

1012 - Sustainability and funding mechanisms, especially when private funding (e.g. from  
1013 pharmaceutical companies) is involved and when the study receives funding from  
1014 several sponsors.

1015 Experience has shown that many of these difficulties can be overcome by full involvement  
1016 and good communication between partners, and a project agreement between network  
1017 members defining roles and responsibilities and addressing issues of intellectual property  
1018 and authorship.

1019 Technical solutions also exist for data sharing and mapping of terminologies. A distributed  
1020 data model and a JAVA (freely available) based data elaboration software was developed by  
1021 the [EU-ADR](#) project to allow for pooling of data from drug safety studies across borders. This  
1022 distributed data model and way of data sharing has been shown to be feasible, fast and to  
1023 deal effectively with ethical and governance issues. It has been used in several other EC  
1024 funded projects and in the United-States.

1025 Many of the current research networks have operated mainly with EC funds and under EC  
1026 grant agreements. The coming years should demonstrate whether and how the expertise  
1027 and infrastructures can be maintained and used in the conduct of regulatory post-  
1028 authorisation studies.

## 1029 **7. Statistical Analysis Plan**

1030 There is a considerable body of literature explaining statistical methods for observational  
1031 studies but very little addressing the statistical analysis plan. Planning analyses for  
1032 randomised clinical trials is covered in a number of publications and much of this applies  
1033 equally to non-randomised design. A good reference in this respect is the [International  
1034 Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals  
1035 for Human Use \(ICH\) ICH E9 'Statistical Principles for Clinical Trials'](#). While specific guidance  
1036 on the statistical analysis plan for epidemiological studies is sparse, the following principles  
1037 will apply to most of the studies.

1038 A study is generally designed with the objective of addressing a set of research questions.  
1039 However, the initial product of a study is a set of numerical and categorical observations that  
1040 do not usually provide a direct answer to the questions that the study is designed to address.  
1041 The statistical analysis plan details the mathematical transformations that will be performed  
1042 on the observed data in the study and the patterns of results that will be interpreted as  
1043 supporting alternative answers to the questions. It will also explain the rationale behind this  
1044 decision making process and the way that this rationale has influenced the study design. An  
1045 important part of the statistical analysis plan will explain how problems in the data will be  
1046 handled in such calculations, for example missing or partial data.

1047 The statistical analysis plan should be sufficiently detailed so that it can be followed in the  
1048 same way by any competent analyst. Thus it should provide clear and complete templates  
1049 for each analysis.

1050 Pre-specified statistical analyses can be challenging for data that are not collected  
1051 specifically to answer the study questions. This is usually the case in retrospective  
1052 observational studies. However, thoughtful specification of the way missing values will be  
1053 handled or the use of a small part of the data as a pilot set to guide analysis can be useful  
1054 techniques to overcome such problems. A feature common to most studies is that some not  
1055 pre-specified analyses will be performed in response to chance observations in the data. It is  
1056 important to distinguish between such data-driven analyses and the pre-specified findings.  
1057 Post-hoc modifications to the analysis strategy should be noted and explained. The statistical  
1058 analysis plan provides a confirmation of this process.

1059 A particular concern in retrospective studies is that decisions about the analysis should be  
1060 made blinded to any knowledge of the results. This should be a consideration in the study  
1061 design, particularly when feasibility studies are to be performed to inform the design phase.  
1062 Feasibility studies should be independent of the main study results.

1063 The statistical analysis plan is usually structured to reflect the protocol and will address,  
1064 where relevant, the following points:

- 1065 1. The statistical model used to address each primary and secondary objective.
- 1066 2. Formal definitions of any outcomes e.g. 'fatal myocardial infarction' might be defined  
1067 as 'death within 30 days of a myocardial infarction'.
- 1068 3. Formal definitions for other variable – e.g. thresholds for abnormal levels of blood  
1069 parameters.
- 1070 4. Sample size considerations making explicit the data source from which the expected  
1071 variation of relevant quantities and the clinically relevant differences are derived  
1072 should be presented. It should be noted that in retrospective observational studies

- 1073 where no additional data can be collected sample size is not a relevant consideration  
1074 and the ethical injunction against 'underpowered' studies has no obvious force  
1075 provided the results, in particular the 'absence of effect' and 'insufficient evidence',  
1076 are properly presented and interpreted.
- 1077 5. Blinding to exposure variables of evaluators making subjective judgements about the  
1078 study.
- 1079 6. Methods of adjusting for confounding, including
- 1080 6.1 Which confounders will be considered;
- 1081 6.2 Criteria for any selection of a subset of confounders.
- 1082 7. Handling of missing data, including
- 1083 7.1 How missing data will be reported;
- 1084 7.2 Methods of imputation;
- 1085 7.3 Sensitivity analyses for handling missing data;
- 1086 7.4 How censored data will be treated, with rationale.
- 1087 8. Fit of the model, including
- 1088 8.1 Criteria for assessing fit;
- 1089 8.2 Alternative models in the event of clear lack of fit.
- 1090 9. Interim analyses – if considered:
- 1091 9.1 Criteria, circumstances and possible drawbacks for performing an interim  
1092 analysis and possible actions (including stopping rules) that can be taken  
1093 on the basis of such an analysis.
- 1094 10. Description of achieved patient population:
- 1095 10.1 Description of target population;
- 1096 10.2 Departures from targeted population.
- 1097 11. Treatment of multiplicity issues not elsewhere covered.

## 1098 **8. Quality Control and Quality Assurance**

1099 Although quality assurance is the rule for RCTs, the practice is less well established for  
1100 observational studies, which may also be used to assess the safety and effectiveness of  
1101 specific pharmacologic interventions. In an RCT the vast majority of data is quality assured  
1102 but it may not be feasible to do the same for large pharmacoepidemiological studies making  
1103 secondary use of data collected for another purpose. However, use of the results of such  
1104 studies in outcomes research requires knowledge of the quality and validity of the data and  
1105 of the studies themselves. In particular, there ideally needs to be some level of validation of  
1106 the recording and coding for electronic data sets. It is considered the responsibility of  
1107 database owners to provide researchers with the minimal level of validity and sensitivity of  
1108 the coded data. It is also acknowledged that there is a need to move towards better quality  
1109 control/assurance in terms of data quality assurance and study methodology. Quality should  
1110 be mentioned in the study protocol in terms of quality assurance but this may, for example,  
1111 lead to sensitivity analyses.

1112 Quality control (QC) is the observation techniques and activities that are used to fulfill  
1113 requirements for quality. Quality Assurance (QA) is defined as the planned and systematic  
1114 activities implemented in a quality system so that quality requirements for a product or  
1115 service will be fulfilled. In general, QA defines the standards to be followed in order to meet  
1116 the requirements, whereas QC ensures that these defined standards are followed at every  
1117 step.

1118 Aspects of research quality control that require close attention include data collection, data  
1119 recording, numbers and qualifications of people making measurements and recording data,  
1120 numbers. It also includes QC measures that are necessary to verify accuracy and  
1121 consistency of the collected data, data entry into computer files, storage of originals and  
1122 copies of data sheets and computer files, assignment of tasks and responsibilities, and data  
1123 analyses. Quality criteria specific to a study should be defined to ensure scientific validity of  
1124 the results. These criteria may involve the following items: independent scientific committee,  
1125 sampling investigator recruitment, study organisation and quality control of the collected  
1126 data and may include on-site control visits to participating researchers.

1127 In general, the following are the steps to implement QA in the research plan: identifying the  
1128 expectations; determining the standards; measuring and comparing performances;  
1129 analysing; planning and controlling.

1130 The two following articles are examples of quality control implementations in  
1131 pharmacovigilance/pharmacoepidemiological studies. The [Norwegian Prescription Database \(NorPD\)](#)  
1132 (Karu F. Norsk epidemiologi 2008; 18(2): 129-136) details the quality checks  
1133 applied to the database. The article [Feasibility study and methodology to create a quality-  
1134 evaluated database of primary care data](#) (Bourke A, Dattani H, Robinson M. Inform Prim  
1135 Care 2004; 12(3): 171-7) details the study conducted to build and test a model for  
1136 collection of computerised retrospective primary care data in the UK, to assess its quality for  
1137 use in medical and pharmaceutical research. The main quality outcome measures were  
1138 indicators of the completeness of data recording. It was concluded that in the group of  
1139 practices studied, levels of recording were generally assessed to be of sufficient quality to  
1140 enable a database of quality-evaluated, anonymised primary care records to be created.

1141 Section II 'Operating Registries' of the AHRQ [Registries to Evaluate Patient Outcomes: a  
1142 User's guide, Second Edition](#) provides a practical guide to the day-to-day operational issues  
1143 and decisions for producing and interpreting high-quality registries. It is a very good  
1144 reference, albeit US focused. Chapter 10 'Data Collection and Quality Assurance' reviews key  
1145 areas of data collection, cleaning, storing, and quality assurance for registries. It contains a  
1146 practical example of a performance-linked access system that ensures that only appropriate  
1147 patients receive a treatment. It also details how these systems can help sponsors to monitor  
1148 the patient population, and to learn more about adverse events and the frequency of these  
1149 events

1150 Section VII 'Archiving' in the [ISPE GPP](#) points out that copies of all quality assurance reports  
1151 and audits should be included within the archived documents.

1152 The [EuroDrug Quality Indicator Meeting \(DURQUIM\) Indicators of prescribing quality in drug  
1153 utilisation research](#) is a report of a meeting at which a first draft of a database of prescribing  
1154 quality indicators, already subjected to validation procedures, was made.

1155 The following study [A systematic literature review: Prescribing quality indicators for type 2  
1156 diabetes mellitus and cardiovascular risk management](#) (Martirosyan L, Voorham J, Haaijer-  
1157 Ruskamp FM, Wolffenbuttel BHR, Denig P. Pharmacoepidemiol Drug Saf 2010; 19(4): 319-

1158 34) describes the validity of existing prescribing indicators for type 2 diabetes mellitus and  
1159 cardiovascular risk management.

1160 The authors of [Validation and validity of diagnoses in the General Practice Research](#)  
1161 [Database \(GPRD\): a systematic review](#) (Herrett E, Thomas SL, Schoonen WM, Smeeth L,  
1162 Hall AJ. Br J Clin Pharmacol 2010; 69: 4-14) assessed the quality of the methods used to  
1163 validate diagnoses in the GPRD, a primary care database containing anonymised patient  
1164 records for about 6% of the UK population that has been widely used for observational  
1165 studies. The article contains methodological and reporting recommendations to further  
1166 strengthen the use of the GPRD in research that are potentially applicable to other  
1167 databases.

1168 The following references are also useful guidance in terms of ensuring quality in  
1169 pharmacoepidemiological research: the CIOMS [International Ethical Guidelines for](#)  
1170 [Epidemiological Studies](#), the AGENS, DGSM and DGEpi [Good Practice in Secondary Data](#)  
1171 [Analysis Version 2](#) and the [ENCePP Checklist for Study Protocols](#).

## 1172 **9. Safety reporting (Adverse Events)**

1173 Observational studies or registers can provide the initial evidence leading to the  
1174 identification of a new safety concern that may impact on patients and require a regulatory  
1175 action to minimise the risk. Follow-ups of large numbers of persons using a structured data  
1176 collection system may identify and characterise adverse reactions within the limits of study  
1177 design, objectives, sample size and duration. Therefore, consideration should be given to the  
1178 expedited reporting of adverse reactions to competent authorities when designing a study  
1179 and writing a protocol.

1180 Chapter VI of the [ISPE GPP](#) provides general recommendations for adverse event reporting  
1181 from pharmacoepidemiology studies. This text should be consulted by investigators when  
1182 designing a non-interventional study. It specifies six conditions which, if obtained, generally  
1183 require expedited individual case reporting: 1) the study prospectively gathers data on  
1184 individual patients, 2) the study involves direct contact with patients, 3) study personnel are  
1185 trained on gathering and reporting adverse events and determining whether events might be  
1186 considered "expected" for a specific product, 4) a serious event is identified by someone who  
1187 has direct contact with the patient, 5) the event is considered unexpected, and 6) the  
1188 reporter believes there is a causal association with the product or that causality cannot be  
1189 ruled out. The GPP further specify that analyses of database studies can identify an  
1190 unexpected increase in risk associated with a particular exposure but such studies typically  
1191 do not require reporting of individual cases. While these ISPE recommendations are helpful,  
1192 the EU obligations to companies sponsoring a post-authorisation study are specified in  
1193 [Volume 9A](#).

1194 The following general recommendations should be followed for studies carried out in the EU:

- 1195 – For a company-sponsored non-interventional post-authorisation study, the provisions  
1196 included in Part I (Guidelines for Marketing Authorisation Holders), Chapter 7.4.2.  
1197 (Reporting of Adverse Reactions) of [Volume 9A](#) (page 93 for the version dated  
1198 September 2008) should be followed. These provisions specify that the usual  
1199 regulatory requirements for reporting of adverse reactions should be fulfilled. This  
1200 means that marketing authorisation holders should ensure that they are notified by  
1201 the investigator of serious adverse reactions and, if specified in the protocol, of  
1202 events. However, it is acknowledged that for certain study designs, such as case-

1203 control or retrospective cohort studies, it is not feasible or appropriate to make a  
1204 causality assessment at the individual case level, and therefore expedited reporting is  
1205 not required. In case of doubt, the reporting requirements for a specific study should  
1206 be clarified with the competent authority. Marketing authorisation holders should  
1207 check whether additional national requirements apply in countries where the study  
1208 will be carried-out.

1209 – For a non-interventional post-authorisation study which is not sponsored by a  
1210 company, there are no legal reporting obligations at the European level. Investigators  
1211 should however enquire whether national obligations exist. Obligations or  
1212 recommendations may also be specified by an ethical committee or a data safety  
1213 monitoring board.

1214 – If the study qualifies as an interventional trial, the reporting criteria laid down in  
1215 Directive 2001/20/EC and related guidance ([Volume 10 of the Rules Governing](#)  
1216 [Medicinal Products in the European Union](#)) should be followed.

1217 Any update of the Rules Governing Medicinal Products in the EU can be found on the  
1218 [Eudralex website](#).

1219 Chapter 12 of the AHRQ [Registries to Evaluate Patient Outcomes: a User's guide, Second](#)  
1220 [Edition](#) addresses the identification, processing, and reporting of adverse events detected in  
1221 situations in which a registry has individual patient contact. This chapter should be read in  
1222 the context of the regulatory requirements applicable in the US. It also presents the  
1223 enforceable framework established by the FDA for risk management of products with known  
1224 safety concerns, called Risk Evaluation and Mitigation Strategies (REMS).

## 1225 **10. Communication**

1226 Aspects of research communication include, but are not limited to, reports to health  
1227 authorities, sponsors, presentations in scientific fora, scientific publications, patient focused  
1228 communications and websites. For marketing authorisation holders, study results should also  
1229 be reflected in regulatory documents such as the risk management plan and the periodic  
1230 safety update report.

1231 The [ISPE GPP](#) contain a section on communication (section V) which includes a statement  
1232 that there is an ethical obligation to disseminate findings of potential scientific or public  
1233 health importance and that research sponsors (government agencies, private sector, etc.)  
1234 shall be informed of study results in a manner that complies with local regulatory  
1235 requirements.

1236 The [Guidelines for Submitting Adverse Event Reports for Publication](#) endorsed by ISOP and  
1237 ISPE aim to introduce readers to the key elements that have to be included when someone  
1238 wishes to report and publish results about adverse drug events. The information is clearly  
1239 and coherently presented in the cited guideline. The required data are divided based on  
1240 three levels of requests: 'required', 'highly desirable' and 'if relevant'.

1241 The [Enhancing the Quality and Transparency of Health Research \(EQUATOR\)](#) network is an  
1242 international initiative that aims to enhance the reliability and value of the published health  
1243 research literature. The article [A catalogue of reporting guidelines for health research](#)  
1244 (Simera I, Moher D, Hoey J, Schulz KF, Altman DG. Eur J Clin Invest 2010; 40(1): 35-53)  
1245 presents a collection of tools and guidelines available on the [EQUATOR website](#) relating to  
1246 resources, education and training to facilitate good research reporting and the development,

1247 dissemination and implementation of robust reporting guidelines to increase the accuracy  
1248 and transparency of health research reporting.

1249 The [Strengthening the Reporting of Observational studies in Epidemiology \(STROBE\)](#)  
1250 [Statement Guidelines for reporting observational studies](#) has established recommendations  
1251 for improving the quality of reporting of observational studies and seeks to ensure a clear  
1252 presentation of what was planned, done, and found. Of note, the aim of these guidelines was  
1253 not to prescribe the reporting of observational research in a rigid format, but to address  
1254 what should be the critical information that a publication on an observational study should  
1255 contain. In this regard, the guidance provided is complete, with practical examples that  
1256 facilitate interpretation and understanding of the recommendations, though it is of limited  
1257 usefulness for the design and conduct of epidemiological research projects. The  
1258 recommendations are limited to cohort, case-control, and cross-sectional studies, though  
1259 other types of epidemiological studies might benefit from most of the recommendations at  
1260 the time of drafting the manuscript. No recommendation on ethical considerations,  
1261 ownership of data and criteria for establishing the authorship are given. This is a major  
1262 limitation of these recommendations, since these aspects are highly relevant for the  
1263 reporting and publishing of studies.

1264 The [Meta-analysis of Observational Studies in Epidemiology \(MOOSE\)](#) group has developed  
1265 [a consensus statement](#) and recommendations for reporting meta-analyses of observational  
1266 studies in epidemiology. It is equivalent to the [STROBE Statement Guidelines for reporting](#)  
1267 [observational studies](#) and the Consolidated Standards of Reporting Trials [Consolidated](#)  
1268 [Standards for Reporting Trials \(CONSORT\) 2010 Statement](#) for RCTs, in that they have  
1269 communication as their primary objective and take the form of a list of minimum  
1270 requirements for adequate reporting. The MOOSE article is quite similar to the others in its  
1271 structure, scope, length and depth of detail and is useful for the declared audience of  
1272 researchers, readers, reviewers and editors. The structure of the article is slightly confusing  
1273 though, as the formal 'Results' includes subheadings such as 'background', 'search strategy',  
1274 'results' and 'discussion'. The authors recommend a broad inclusion of studies and to  
1275 conduct post-hoc sensitivity on the dependence of the results on factors, such as quality of  
1276 underlying papers, design, accounting for confounders etc. The authors comment on the  
1277 particular problems in merging observational studies with highly variable sets of confounders  
1278 that were or were not controlled for, but they do not suggest any solution or give any  
1279 references to possible ways to address it.

1280 The [Preferred Reporting Items for Systematic Reviews and Meta-analyses \(PRISMA\)](#)  
1281 [Statement](#) is an evidence-based minimum set of items for reporting in systematic reviews  
1282 and meta-analyses consisting of a 27-item checklist and a flow diagram. While focused on  
1283 randomised trials, PRISMA can also be used as a basis for reporting systematic reviews of  
1284 other types of research, particularly evaluations of interventions. PRISMA may also be useful  
1285 for critical appraisal of published systematic reviews, although it is not a quality assessment  
1286 instrument to gauge the quality of a systematic review. PRISMA is a successor to the [Quality](#)  
1287 [of Reporting of Meta-analyses \(QUORUM\) Statement](#) and the associated QUORUM flow chart.

1288 Additional guidance is provided in the ENCePP [Checklist for Study Protocols](#) and [Code of](#)  
1289 [Conduct](#) and the [IEA GEP](#) guideline that have been reviewed elsewhere in the present  
1290 document.

1291 Some of the points that are emphasised by the cited guidelines are:

- 1292 – Sources of research funding should always be disclosed whether in oral or written  
1293 presentation.

- 1294 – A dissemination and communication strategy should be predefined as part of the  
1295 funding contract.
- 1296 – All results with a scientific or public health impact must be made publicly available  
1297 without undue delay.
- 1298 – Quantitative measures of association should be reported rather than just results of  
1299 testing.
- 1300 – Authorship should conform to the guidelines established by the [International  
1301 Committee of Medical Journal Editors \(ICJME\)](#) 'Uniform Requirements for Manuscripts  
1302 Submitted to Biomedical Journals'.
- 1303 – For a case report (or series) on suspected adverse drug reactions, minimum  
1304 requirements include an account of the patients medical history and disposition, a  
1305 detailed account of the dispensed product (substances, brand, route of administration)  
1306 and a detailed account of the adverse event (nature, timing, severity, outcome).

## 1307 **11. Update of the Guide**

1308 In line with the scope of the present inventory to be dynamic, researchers are kindly  
1309 requested to refer any additional guidance document (with an electronic link, where  
1310 possible) that they may be aware of, and that is considered relevant, to the [ENCePP  
1311 Secretariat](#) for possible inclusion in future updates.

1312 Systematic updates of this electronic document will be performed every year. More frequent  
1313 amendments may be performed for important modifications. An open access, interactive  
1314 platform for comments is under consideration.

## 1315 **12. References**

1316 **All hyperlinks in the document were last accessed on-line on 12 May 2011.**

1317 Abenheim LA, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, Higenbottam T, Oakley C,  
1318 Wouters E, Aubier M, Simonneau G, Bégaud B. for the International Primary Pulmonary  
1319 Hypertension Study Group. [Appetite-Suppressant Drugs and the Risk of Primary Pulmonary  
1320 Hypertension](#) N Engl J Med 1996; 335: 609-616.

1321 AGENS, DGSM and DGEpi [Good Practice in Secondary Data Analysis Version 2](#)  
1322 <http://www.dgepi.de/pdf/infoboard/stellungnahme/gps-version2-final%20ENG.pdf>

1323  
1324  
1325 Altman D. *Practical Statistics for Medical Research*. Chapman & Hall, 1990.

1326  
1327 WHO Collaborating Centre for Drug Statistics Methodology [Anatomical Therapeutic Chemical  
1328 Classification System](#) [http://www.whocc.no/atc/structure\\_and\\_principles/](http://www.whocc.no/atc/structure_and_principles/)

1329  
1330 [Agency for Healthcare Research and Quality \(AHRQ\)](#) <http://www.ahrq.gov/>

1331  
1332 AHRQ [Registries for Evaluating Patient Outcomes: A User's Guide. Second Edition](#)  
1333 [http://www.effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%202nd%20ed%20  
1334 0final%20to%20Eisenberg%209-15-10.pdf](http://www.effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%202nd%20ed%20final%20to%20Eisenberg%209-15-10.pdf)  
1335

1336 Arbogast P. [Use of disease risk scores in pharmacoepidemiologic studies](#) Stat Methods Med  
1337 Res 2009; 18: 67-80.  
1338  
1339 Bate A, Evans SJW. [Quantitative signal detection using spontaneous ADR reporting](#)  
1340 Pharmacoepidemiol Drug Saf 2009; 18: 427 – 436.  
1341  
1342 Baumeister RF, Leary MR. [Writing narrative literature reviews](#) Rev of Gen Psychol 1997; 1  
1343 (3): 311-320.  
1344  
1345 Bourke A, Dattani H, Robinson M. [Feasibility study and methodology to create a quality-  
1346 evaluated database of primary care data](#) Inform Prim Care 2004; 12(3): 171-7.  
1347  
1348 Brookhart MA, Wang P, Solomon DH, Schneeweiss S. [Evaluating short-term drug effects  
1349 using a physician-specific prescribing preference as an instrumental variable](#) Epidemiology  
1350 2006; 17(3): 268-275.  
1351  
1352 [ENCePP Checklist for Study Protocols](#)  
1353 [http://www.encepp.eu/standards\\_and\\_guidances/index.html](http://www.encepp.eu/standards_and_guidances/index.html)  
1354  
1355 Chou R, Helfand M. [Challenges in systematic reviews that assess treatment harms](#) Ann  
1356 Intern Med 2005; 142:1090-9.  
1357  
1358 [Council for International Organizations of Medical Sciences \(CIOMS\)](#) <http://www.cioms.ch/>  
1359  
1360 CIOMS [International Ethical Guidelines for Epidemiological Studies](#)  
1361 [http://www.cioms.ch/frame\\_ethical\\_guidelines\\_2009.htm](http://www.cioms.ch/frame_ethical_guidelines_2009.htm)  
1362  
1363 CIOMS Working Group VIII [Practical Aspects of Signal Detection in Pharmacovigilance](#)  
1364 [http://www.cioms.ch/frame\\_WGVIIIblurbDRAFT.htm](http://www.cioms.ch/frame_WGVIIIblurbDRAFT.htm)  
1365  
1366 [Clinical Trial Directive \(Directive 2001/20/EC\)](#)  
1367 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:32001L0020:EN:HTML>  
1368  
1369 [ClinicalTrials.gov](#) <http://www.clinicaltrials.gov/>  
1370  
1371 [Cochrane Collaboration](#) <http://ukcc.cochrane.org/>  
1372  
1373 [Cochrane Handbook for Systematic Reviews of Interventions](#) [http://www.cochrane-  
handbook.org/](http://www.cochrane-<br/>1374 handbook.org/)  
1375  
1376 [CONSORT statement](#) <http://www.consort-statement.org/>  
1377  
1378 [Declaration of Helsinki](#) <http://www.wma.net/en/30publications/10policies/b3/index.html>  
1379  
1380 [Directive 2001/83/EC](#)  
1381 [http://eur-  
lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20070126:en:PDF](http://eur-<br/>1382 lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0083:20070126:en:PDF)  
1383  
1384 [Directive 95/46/EC](#) [http://ec.europa.eu/justice/policies/privacy/docs/95-46-ce/dir1995-  
46\\_part1\\_en.pdf](http://ec.europa.eu/justice/policies/privacy/docs/95-46-ce/dir1995-<br/>1385 46_part1_en.pdf)

1386 DURQUIM [Indicators of prescribing quality in drug utilisation research](#)  
1387 <http://www.springerlink.com/content/a3ccdbuey2ed7cc>  
1388  
1389 [European Network of Centres for Pharmacoepidemiology and Pharmacovigilance \(ENCePP\)](#)  
1390 <http://www.encepp.eu/structure/index.html>  
1391  
1392 [ENCePP Code of Conduct](#) [http://www.encepp.eu/code\\_of\\_conduct/index.html](http://www.encepp.eu/code_of_conduct/index.html)  
1393  
1394 [ENCePP Declaration on compliance](#)  
1395 [http://www.encepp.eu/documents/code\\_of\\_conduct/ENCePP Code of Conduct\\_Declaration](http://www.encepp.eu/documents/code_of_conduct/ENCePP Code of Conduct_Declaration)  
1396 [on compliance.doc](#)  
1397  
1398 [ENCePP E-Register of Studies](#) [http://www.encepp.eu/encepp\\_studies/e\\_register.html](http://www.encepp.eu/encepp_studies/e_register.html)  
1399  
1400 [ENCePP Inventory of Databases](#) <http://www.encepp.eu/encepp/resourcesDatabase.jsp>  
1401  
1402 [EQUATOR Network](#) <http://www.equator-network.org/>  
1403  
1404 [EU-ADR](#) <http://www.euadr-project.org/>  
1405  
1406 [Eudralex website](#)  
1407 [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/index\\_en.htm](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/index_en.htm)  
1408  
1409 [EudraVigilance](#) <http://eudravigilance.ema.europa.eu/highres.htm>  
1410  
1411 [EuroDrug Quality Indicator Meeting \(DURQUIM\)](#)  
1412 <http://www.pharmacoepi.org/eurodrug/durquim.cfm>  
1413 Fayers PM, Machin D. *Quality of Life: the assessment, analysis and interpretation of patient-*  
1414 *related outcomes*. 2<sup>nd</sup> Edition, Wiley, 2007.  
1415  
1416 Fewell Z, Davey Smith G, Sterne JAC. [The impact of residual and unmeasured confounding](#)  
1417 [in epidemiologic studies: a simulation study](#) *Am J Epidemiol* 2007; 166: 646–55.  
1418  
1419 Gail MH, Benichou J, Editors. *Encyclopedia of Epidemiologic Methods*. Wiley, 2000.  
1420  
1421 Glasziou PP, Sanders SL. [Investigating causes of heterogeneity in systematic reviews](#) *Stat*  
1422 *Med* 2002; 21: 1503-11.  
1423  
1424 Greenland S. [An introduction to instrumental variables for epidemiologists](#) *Int J of Epidemiol*  
1425 2000; 29: 722-729.  
1426  
1427 Grobbee DE, Hoes AW. [Confounding and indication for treatment in evaluation of drug](#)  
1428 [treatment for hypertension](#) *BMJ* 1997; 315: 1151-1154.  
1429  
1430 Groves RM, Fowler FJ, Couper MP, Lepkowski JM, Singer E, Tourangeau R. *Survey*  
1431 *Methodology*. 2<sup>nd</sup> Edition, Wiley, 2009.  
1432  
1433 [Guideline on the use of statistical signal detection methods in the Eudravigilance data](#)  
1434 [analysis system](#)

1435 [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guideline/2009/11/WC500011434.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/11/WC500011434.pdf)  
1436  
1437  
1438 Hartzema AG, Tilson HH and Chan KA, Editors. *Pharmacoepidemiology and Therapeutic Risk Management*. 1<sup>st</sup> Edition, Harvey Whitney Books Company, 2008.  
1439  
1440  
1441 Hennessy S, Bilker WB, Weber A, Strom B. [Descriptive analyses of the integrity of a US Medicaid Claims Database](#) *Pharmacoepidemiol Drug Saf* 2003; 12: 103–111.  
1442  
1443  
1444 Henry D, Lim Lynette L-Y, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, Hill S, Fries JT. [Variability in risk of gastrointestinal complications with individual NSAIDs: results of a collaborative meta-analysis](#) *BMJ* 1996; 312: 1563-1566.  
1445  
1446  
1447  
1448  
1449 Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. [Validation and validity of diagnoses in the General Practice Research Database \(GPRD\): a systematic review](#) *Br J Clin Pharmacol* 2010; 69: 4-14.  
1450  
1451  
1452  
1453 [International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use \(ICH\)](#) <http://www.ich.org/home.html>  
1454  
1455  
1456 [ICH E9 'Statistical Principles for Clinical Trials'](#)  
1457 [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2009/09/WC500002928.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002928.pdf)  
1458  
1459  
1460 [International Committee of Medical Journal Editors \(ICJME\)](#) <http://www.icmje.org/>  
1461  
1462 ICMJE [Uniform Requirements for Manuscripts Submitted to Biomedical Journals](#)  
1463 [http://www.icmje.org/urm\\_main.html](http://www.icmje.org/urm_main.html)  
1464  
1465 [International Epidemiological Association \(IEA\)](#) <http://www.ieaweb.org/>  
1466  
1467 [IEA Good Epidemiological Practice Guideline](#)  
1468 [http://www.ieaweb.org/index.php?view=article&catid=20:good-epidemiological-practice-gep&id=15:good-epidemiological-practice-gep&format=pdf&option=com\\_content&Itemid=43](http://www.ieaweb.org/index.php?view=article&catid=20:good-epidemiological-practice-gep&id=15:good-epidemiological-practice-gep&format=pdf&option=com_content&Itemid=43)  
1469  
1470  
1471  
1472 [IMI PROTECT](#) <http://www.imi-protect.eu/wp2.html>  
1473  
1474 [International Society for Pharmacoepidemiology \(ISPE\)](#) <http://www.pharmacoepi.org/>  
1475  
1476 [ISPE Guidelines on Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health](#) <http://www.pharmacoepi.org/resources/privacy.cfm>  
1477  
1478  
1479 [ISPE Guidelines for Good Pharmacoepidemiology Practices](#)  
1480 [http://www.pharmacoepi.org/resources/guidelines\\_08027.cfm](http://www.pharmacoepi.org/resources/guidelines_08027.cfm)  
1481  
1482 [International Society of Pharmacovigilance \(ISOP\)](#) <http://www.isoonline.org/>  
1483

1484 ISPE/ISOP [Guidelines for Submitting Adverse Event Reports for Publication](http://www.ncbi.nlm.nih.gov/pubmed/19804709)  
1485 <http://www.ncbi.nlm.nih.gov/pubmed/19804709>  
1486  
1487 [International Society for Pharmacoeconomics and Outcomes Research \(ISPOR\)](http://www.ispor.org/)  
1488 <http://www.ispor.org/>  
1489  
1490 ISPOR [Checklist for Retrospective Database Studies](http://onlinelibrary.wiley.com/doi/10.1046/j.1524-4733.2003.00242.x/pdf)  
1491 <http://onlinelibrary.wiley.com/doi/10.1046/j.1524-4733.2003.00242.x/pdf>  
1492  
1493 Joffe MM. [Confounding by indication: the case of the calcium channel blockers](#)  
1494 *Pharmacoepidemiol Drug Saf* 2000; 9: 37-41.  
1495  
1496 Joffe MM, Rosenbaum PR. [Invited Commentary: Propensity Scores](#) *Am J Epidemiol* 1999;  
1497 150: 327–33.  
1498  
1499 Jollis JG, Ancukiewicz M, DeLong ER, Pryor DB, Muhlbaier LH, Mark DB. [Discordance of](#)  
1500 [databases designed for claims payment versus clinical information systems: implications for](#)  
1501 [outcomes research](#) *Ann Intern Med* 1993; 119: 844-850.  
1502  
1503 Karu F. [Norwegian Prescription Database \(NorPD\)](#) *Norsk epidemiologi* 2008; 18 (2): 129-  
1504 136.  
1505  
1506 Kaufman DW, Rosenberg L, Mitchell AA. [Signal generation and clarification: use of case-](#)  
1507 [control data](#) *Pharmacoepi Drug Safety* 2001; 10: 197-203.  
1508  
1509 Kish L. *Survey Sampling*. Wiley, 1995.  
1510  
1511 Lesko SM, Mitchel AA. [Assessment of the safety of paediatric ibuprofen: a practitioner based](#)  
1512 [randomised clinical trial](#) *JAMA* 1995; 279: 929-933.  
1513  
1514 Lau J, Ioannidis JP, Schmid CH. [Quantitative synthesis in systematic reviews](#) *Ann Intern Med*  
1515 1997; 127: 820-826.  
1516  
1517 MacDonald TM, Morant SV, Goldstein JL, Burke TA, Pettitt D. [Channelling bias and the](#)  
1518 [incidence of gastrointestinal haemorrhage in users of meloxicam, coxibs, and older, non-](#)  
1519 [specific NSAIDs](#) *Gut* 2003; 52: 1265–70.  
1520  
1521 MacMahon B, Trichopoulos D. *Epidemiology: Principles and Methods*. 2<sup>nd</sup> Edition, Lippincott  
1522 Williams & Wilkins, 1996  
1523  
1524 Martirosyan L, Voorham J, Haaijer-Ruskamp FM, Wolffenbuttel BHR, Denig P. [A systematic](#)  
1525 [literature review: Prescribing quality indicators for type 2 diabetes mellitus and](#)  
1526 [cardiovascular risk management](#) *Pharmacoepidemiol Drug Saf* 2010; 19(4): 319-34.  
1527  
1528 McMahon AD. [Approaches to combat with confounding by indication in observational studies](#)  
1529 [of intended drug effects](#) *Pharmacoepidemiol Drug Saf* 2003; 12: 551-8.  
1530  
1531 Miettinen OS. [Stratification by a multivariate confounder score](#) *Am J Epidemiol* 1976; 104:  
1532 609-20.  
1533

1534 Miettinen OS. *Theoretical Epidemiology*. John Wiley & Sons, 1985.  
1535  
1536 Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF, for the QUORUM Group.  
1537 [Improving the quality of reports of meta-analyses of randomised controlled trials: the](#)  
1538 [Quorum statement](#) Lancet 1999; 354(9193): 1896-1900.  
1539  
1540 Moher D, Liberati A, Tetzlaff J, Altman DG. [Preferred reporting items for systematic reviews](#)  
1541 [and meta-analyses: the PRISMA statement](#) BMJ 2009; 339: b2535.  
1542  
1543 Moride Y, Abenhaim L. [Evidence of the depletion of susceptibles effect in non-experimental](#)  
1544 [pharmacoepidemiologic research](#) J Clin Epidemiol 1994; 47 (7): 731-7.  
1545  
1546 [Note for Guidance on Good Clinical Practice](#)  
1547 <http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf>  
1548  
1549 [Observational Medical Outcomes Partnership](#) <http://omop.fnih.org/node/22>  
1550  
1551 [PRISMA](#) <http://www.prisma-statement.org/>  
1552  
1553 Ray WA. [Evaluating medication effects outside of clinical trials: new-user designs](#) Am J Epidemiol  
1554 2003; 158 (9): 915 – 920.  
1555  
1556 [Regulation \(EC\) No 726/2004](#)  
1557 <http://ec.europa.eu/health/files/eudralex/vol->  
1558 [1/reg\\_2004\\_726\\_cons/reg\\_2004\\_726\\_cons\\_en.pdf](http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726_cons/reg_2004_726_cons_en.pdf)  
1559  
1560 [Regulation \(EC\) 45/2001](#) <http://eur->  
1561 [lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:008:0001:0022:EN:PDF](http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:008:0001:0022:EN:PDF)  
1562  
1563 Robins JM, Hernán MA, Brumback B. [Marginal Structural Models and Causal Inference in](#)  
1564 [Epidemiology](#) Epidemiology 2000; 11(5): 550-560.  
1565  
1566 Rothman K, Greenland S, Lash T. *Modern Epidemiology*. 3<sup>rd</sup> Edition, Lippincott Williams &  
1567 Wilkins, 2008.  
1568  
1569 Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S,  
1570 Correia O, Locati F, Maja Mockenhaupt M, Paoletti C, Shapiro S, Shear N, Schöpf E, Kaufman  
1571 DW. [Medication Use and the Risk of Stevens–Johnson Syndrome or Toxic Epidermal](#)  
1572 [Necrolysis](#) N Engl J Med 1995; 333: 1600-1608.  
1573  
1574 Schneeweiss S. [Sensitivity analysis and external adjustment for unmeasured confounders in](#)  
1575 [epidemiologic database studies of therapeutics](#) Pharmacoepidemiol Drug Saf 2006; 15: 291-  
1576 303.  
1577  
1578 Schneeweiss S, Avorn J. [A review of uses of health care utilization databases for](#)  
1579 [epidemiologic research on therapeutics](#) J Clin Epidemiol 2005; 58: 323-337.  
1580

1581 Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. [High-dimensional](#)  
1582 [Propensity Score Adjustment in Studies of Treatment Effects Using Health Care Claims Data](#)  
1583 *Epidemiol* 2009; 20(4): 512-22.

1584  
1585 Schulz KF, Altman DG, Moher D, for the CONSORT Group. [Consort 2010 Statement: Updated](#)  
1586 [Guidelines for Reporting Parallel Group Randomized Trials](#) *BMJ* 2010; 340: c332.

1587  
1588 Shariff SZ, Cuerden MS, Jain AK, Garg AX. [The Secret of Immortal Time Bias in](#)  
1589 [Epidemiologic Studies](#) *J Am Soc Nephrol* 2008; 19: 841-843.

1590  
1591 Shapiro S. for the International Agranulocytosis and Aplastic Anemia Study. [The design of a](#)  
1592 [study of the drug etiology of agranulocytosis and aplastic anemia](#) *Eur J Clin Pharmacol* 1983;  
1593 24: 833-6.

1594  
1595 Simera I, Moher D, Hoey J, Schulz KF, Altman DG. [A catalogue of reporting guidelines for](#)  
1596 [health research](#) *Eur J Clin Invest* 2010; 40(1): 35-53.

1597  
1598 [SOS-NSAIDS](#) <http://www.sos-nsaids-project.org/>

1599  
1600 Stang PE, Ryan PB, Racossin JA, Overhage JM, Hartzema AG, Reich C, Welebob E,  
1601 Scarnecchia T, Woodcock J. [Advancing the science of active surveillance: rationale and](#)  
1602 [design for the Observational Medical Outcomes Partnership](#) *Ann Intern Med* 2010; 153: 600-  
1603 606.

1604  
1605 Stephenson WP, Hauben M. [Data mining for signals in spontaneous reporting databases:](#)  
1606 [proceed with caution](#) *Pharmacoepidemiol Drug Saf* 2007; 16: 359–365.

1607  
1608 Streiner DL, Norman GR. *Health Measurement Scales: A practical guide to their development*  
1609 *and use*. 4<sup>th</sup> Edition, Oxford University Press, 2008.

1610  
1611 [STROBE Statement](#) <http://www.strobe-statement.org/index.php?id=available-checklists>

1612  
1613 Strom BL. *Pharmacoepidemiology*. 4<sup>th</sup> Edition, Wiley, 2005.

1614  
1615 Strom BL, Eng SM, Faich G, Reynolds RF, D'Agostino RB, Ruskin J, Kane JM. [Comparative](#)  
1616 [mortality associated with ziprasidone and olanzapine in real-world use among 18,154](#)  
1617 [patients with schizophrenia: The Zodiac Observational Study of Cardiac Outcomes \(ZODIAC\)](#)  
1618 *Am J Psychiatry* 2011; 168(2): 117-9.

1619  
1620 Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson D, Rennie D, Moher D, Becker BJ, Sipe  
1621 TA, Thacker SB, for the MOOSE Group. [Meta-analysis of Observational Studies in](#)  
1622 [Epidemiology](#) *JAMA* 2000; 283(15): 2008-2012.

1623  
1624 Stürmer T, Schneeweiss S, Brookhart MA, Rothman KJ, Avorn J, Glynn RJ. [Analytic](#)  
1625 [Strategies to Adjust Confounding using Exposure Propensity Scores and Disease Risk Scores](#)  
1626 *Am J Epidemiol* 2005; 161(9):891-898.

1627  
1628 Stürmer T, Schneeweiss S, Rothman KJ, Avorn J, Glynn RJ [Performance of propensity score](#)  
1629 [calibration – a simulation study](#). *Am J Epidemiol* 2007; 165(10): 1110-8.

1630

1631 Suissa S. [Immortal time bias in observational studies of drug effects](#) *Pharmacoepidemiol*  
1632 *Drug Saf* 2007; 16: 241-249.  
1633  
1634 Suissa S. [Immortal time bias in Pharmacoepidemiology](#) *Am J Epidemiol* 2008; 167: 492-499.  
1635  
1636 van Staa TP, Abenham L, Leufkens H. [A study of the effects of exposure misclassification](#)  
1637 [due to the time-window design in pharmacoepidemiologic studies](#) *J Clin Epidemiol* 1994;  
1638 47(2): 183 – 189.  
1639  
1640 Vander Stichele RH, Elseviers MM, Ferech M, Blot S, Goossens H; ESAC Project Group.  
1641 [European Surveillance of Antimicrobial Consumption \(ESAC\): Data Collection Performance](#)  
1642 [and Methodological Approach](#) *Br J Clin Pharmacol* 2004; 58: 419-28.  
1643  
1644 [VAESCO](#) <https://brightoncollaboration.org/vaesco.html>  
1645  
1646 [Volume 9A of the Rules Governing Medicinal Products in the European Union](#)  
1647 [http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-9/pdf/vol9a\\_09-](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-9/pdf/vol9a_09-)  
1648 [2008\\_en.pdf](http://ec.europa.eu/enterprise/sectors/pharmaceuticals/files/eudralex/vol-9/pdf/vol9a_09-)  
1649  
1650 [Volume 10 Clinical trials guidelines](#)  
1651 <http://ec.europa.eu/health/documents/eudralex/vol-10/>  
1652  
1653 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE  
1654 Initiative. [The Strengthening the Reporting of Observational Studies in Epidemiology](#)  
1655 [\(STROBE\) statement: guidelines for reporting observational studies](#) *J Clin Epidemiol* 2008;  
1656 61(4): 344-9.  
1657  
1658 [World Health Organisation \(WHO\)](#) <http://www.who.int/en/>  
1659  
1660 WHO Collaborating Centre for Drug Statistics Methodology [Anatomical Therapeutic Chemical](#)  
1661 [Classification System](#) [http://www.whocc.no/atc/structure\\_and\\_principles/](http://www.whocc.no/atc/structure_and_principles/)  
1662  
1663 WHO Collaborating Centre for Drug Statistics Methodology [Defined Daily Dose](#)  
1664 [http://www.whocc.no/ddd/definition\\_and\\_general\\_considera/](http://www.whocc.no/ddd/definition_and_general_considera/)  
1665  
1666 Witteman JCM, D'Agostino RB, Stijnen T, Kannel WB, Cobb JC, de Ridder MAJ, Hofman A,  
1667 Robins JM. [G-estimation of Causal Effects: Isolated Systolic Hypertension and Cardiovascular](#)  
1668 [Death in the Framingham Heart Study](#) *Am J Epidemiol* 1998; 148(4) 390-401.  
1669

## 1670 **13. Authors**

1671 Ana Marta Anes  
1672 Alejandro Arana  
1673 Kevin Blake  
1674 Stephen Evans  
1675 Annie Fourrier-Réglat

1676 Jesper Hallas  
1677 Xavier Kurz  
1678 Hubert Leufkens  
1679 Nicholas Moore  
1680 Yola Moride  
1681 John Parkinson  
1682 Susana Perez-Gutthann  
1683 Jim Slattery  
1684 Miriam Sturkenboom  
1685 Milena Jadrijevic-Mladar Takac  
1686 Michael Theodorakis  
1687 Robert Vander Stichele  
1688

## 1689 **14. Acknowledgements**

1690 Peter Arlett  
1691 Ulf Bergman  
1692 Gonzalo Calvo  
1693 Olaf Klungel  
1694 Herve Le Louet  
1695 Consuelo Pedros  
1696 Stefanie Prilla  
1697 Annalisa Rubino  
1698 Ivana Silva  
1699 Camilla Stephens