



London, 25 July 2011  
Doc.Ref. EMEA/540136/2009

European Network of Centres for  
Pharmacoepidemiology and  
Pharmacovigilance

## ENCePP Checklist for Study Protocols (Revision 1)

Adopted by the ENCePP Steering Group on 19/08/2011

The purpose of the Checklist developed by ENCePP is to stimulate consideration of important epidemiological principles when designing a pharmacoepidemiological or pharmacovigilance study and writing a study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. ENCePP welcomes innovative designs and new methods of research. The user is also referred to the [ENCePP Guide on Methodological Standards in Pharmacoepidemiology](#) which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each of the questions of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

<b>Section 1: Research question</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
1.1 Does the formulation of the research question clearly explain:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—5
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—5
1.1.2 The objectives of the study?				
1.2 Does the formulation of the research question specify:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—11
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.2.3 if applicable, that there is no <i>a priori</i> hypothesis?				

Comments:

<b>Section 2: Source and study populations</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
2.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—6
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—6
2.2.2 Age and sex?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—6
2.2.3 Country of origin?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—6
2.2.4 Disease/indication?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.2.5 Co-morbidity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.2.6 Seasonality?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—6

Comments:

--

<b>Section 3: Study design</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—6
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—10
3.4 Is sample size considered?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.5 Is statistical power calculated?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

—Statistical power and sample size are relevant in RCT; in observational studie precision is important - 95% confidence limits will be reported as measure of precision
---

<b>Section 4: Data sources</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—14
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—14
4.1.3 Covariates?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—14
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—14
4.2.2 Endpoints? (e.g. date of occurrence, multiple event,	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—14

<b>Section 4: Data sources</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
severity measures related to event) 4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	——14
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	——14
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	——14
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	——14
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	——14

Comments:

<b>Section 5: Exposure definition and measurement</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	——6
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	——12
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.4 Is exposure classified based on biological mechanism of action?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

<b>Section 6: Endpoint definition and measurement</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
6.1 Does the protocol describe how the endpoints are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	——8
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	——12

Comments:

<b>Section 7: Biases and Effect modifiers</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
7.1 Does the protocol address: 7.1.1 Selection biases?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	——11

<b>Section 7: Biases and Effect modifiers</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—11
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.4 Does the protocol address other limitations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—11

Comments:

<b>Section 8: Analysis plan</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
8.1 Does the plan include measurement of absolute effects?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—9
8.2 Is the choice of statistical techniques described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—10
8.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—10
8.4 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—10
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.5.2 Effect modifiers?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.6.2 Effect modification?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

<b>Section 9: Quality assurance, feasibility and reporting</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—11
9.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—11
9.3 Does the protocol describe quality issues related to the data source(s)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—11
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—12
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—12
9.5.2 Study progress? (e.g. end of data collection, other milestones)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—12
9.5.3 Study completion?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—12
9.5.4 Reporting? (i.e. interim reports, final study report)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—12
9.6 Does the protocol include a section to document future amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—13

<b>Section 9: Quality assurance, feasibility and reporting</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
9.7 Are communication methods to disseminate results described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—12
9.8 Is there a system in place for independent review of study results?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—13

Comments:

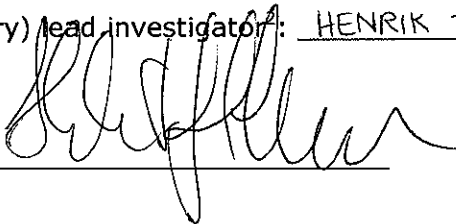
<b>Section 10: Ethical issues</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Page Number(s)</b>
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	—13
10.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.3 Have data protection requirements been described?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

Name of the coordinating study entity<sup>1</sup>: Department of Clinical Epidemiology, Aarhus University Hospital

Name of (primary) lead investigator<sup>2</sup>: HENRIK TOFT SØRENSEN

Date: 31/07/12

Signature: 

<sup>1</sup> A legal person, institution or organisation which takes responsibility for the design and/or the management of a study. The (primary) lead investigator is the person authorised to represent the coordinating study entity.

<sup>2</sup> A person with the scientific background and experience required for the conduct of a particular pharmacoepidemiological or pharmacovigilance study. The lead investigator is responsible for the conduct of a study at a study site. If a study is conducted at several study sites by a team of investigators, the (primary) lead investigator is the investigator who has overall responsibility for the study across all sites.