European Medicines Agency

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Checklist of Methodological Research Standards for ENCePP Studies

Draft for public consultation

The purpose of the checklist is to improve the quality of studies by stimulating consideration of important epidemiological principles for designing a pharmacoepidemiological (PE) or pharmacovigilance (PV) study and writing a study protocol. The checklist is intended to promote quality of such studies, not their uniformity. ENCePP welcomes innovative designs and new methods of research. However, it is possible that some of the questions below do not apply to such innovations, in which case, the answer 'N/A' (Not Applicable) can be checked. **Please fill the 'Comments' field included at each section in situations where a listed question does not apply or where your answer is "No", in order to help ENCePP keep the checklist of methodological research standards in line with the developments in science and methodology.**

The (Primary) Lead Investigator of the study for which the status of "ENCePP Study" is applied for must:

- *Make the following declaration by answering "yes" or "no" to each question related to the information contained in the study protocol. If the answer is 'yes', the page(s) of the study protocol where the issue is addressed should be recorded. The space available at the end of each section should be used to provide comments, in particular to provide an explanation on why the answer 'No' or 'Not Applicable' (N/A) has been chosen.*
- *Provide an electronic copy of the supporting study protocol.*
- *Sign the checklist.*

The undersigned declares upon honour the following answers in relation to the company or organisation that he/she represents. Signature should be by the (Primary) Lead Investigator.

Section 1: Research question

	Yes	No	N/A	Page Number(s)
1.1 Does the formulation of the research question clearly explain why the study is conducted? (e.g. to answer an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☐	☐	☐	
1.2 Does the formulation of the research question specify:				
1.2.1 Target population (or relevant subgroup)	☐	☐	☐	
1.2.2 Hypotheses to be tested (if appropriate, otherwise statement that there is no a priori hypothesis)	☐	☐	☐	
1.2.3 Primary endpoints	☐	☐	☐	
1.2.4 Dose-dependent or duration-dependent response	☐	☐	☐	
1.2.5 Main statistical parameter(s) (e.g. incidence rate, relative risk).	☐	☐	☐	
1.3 Are the implications of the study for benefit-risk assessment of the medicine(s) or pharmaceutical policy making discussed?	☐	☐	☐	

ENCePP Secretariat, European Medicines Agency
7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
E-mail: encepp_secretariat@emea.europa.eu http://www.encepp.eu

Comments:

Section 2: Study population

	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	☐	☐	☐	
2.2 Is the study population described in terms of:				
2.2.1 Age and sex	☐	☐	☐	
2.2.2 Country of origin	☐	☐	☐	
2.2.3 Method of identification (any inclusion/exclusion criteria or event used to sample the study population from the source population)	☐	☐	☐	
2.2.4 Disease/indication	☐	☐	☐	
2.2.5 Co-morbidity	☐	☐	☐	

Comments:

Section 3: Study design

	Yes	No	N/A	Page Number(s)
3.1 Is the choice and rationale of study design explained? (e.g. cohort, case-control, RCT, new or alternative design)	☐	☐	☐	

Comments:

Section 4: Data sources

	Yes	No	N/A	Page Number(s)
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, GP prescribing, claims data, self-report, face-to-face interview, etc)	☐	☐	☐	
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)	☐	☐	☐	
4.1.3 Covariates (e.g. age, sex, clinical history, co-morbidity, co-medications, etc.)	☐	☐	☐	
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)	☐	☐	☐	
4.2.2 Events (e.g. date of occurrence, multiple event, 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.)	☐	☐	☐	
4.3 Is the coding system described for diseases/events (e.g. ICD-10, MedDRA) and exposure? (e.g. ATC for medicines)	☐	☐	☐	

Comments:

Section 5: Exposure measurement

	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe methods to be used for the measurement of exposure?	☐	☐	☐	
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)	☐	☐	☐	
5.3 Is exposure classified according to time windows (e.g. current user, former user, non-use) or biological mechanism of action?	☐	☐	☐	

Comments:

Section 6: Endpoint definition and measurement

	Yes	No	N/A	Page Number(s)
6.1 Is the choice of endpoint(s) under investigation described in terms of rationale in relation to the study hypotheses?	☐	☐	☐	
6.2 Does the protocol describe methods to be used for the identification and measurement of endpoints(s)?	☐	☐	☐	
6.3 Does the protocol discuss the validity of event measurement (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)?	☐	☐	☐	

Comments:

Section 7: Biases

	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address:				
7.1.1 Selection biases	☐	☐	☐	
7.1.2 Information biases	☐	☐	☐	
7.1.3 Immortal time bias	☐	☐	☐	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				

Comments:

Section 8: Analysis plan

	Yes	No	N/A	Page Number(s)
8.1 Is a calculation of the sample size provided?	☐	☐	☐	
8.2 Is statistical power calculated according to different assumptions for patient recruitment and results?	☐	☐	☐	
8.3 Does the plan explain the choice of the measure(s) of effect? (e.g. RR/OR, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☐	
8.4 Does the plan include measurement of absolute effects?	☐	☐	☐	
8.5 Is the choice of statistical techniques explained in the plan?	☐	☐	☐	
8.6 Are descriptive and stratified analyses included in the plan?	☐	☐	☐	
8.7 Does the plan explain the method for identifying:				
8.7.1. Confounders	☐	☐	☐	
8.7.2. Effect modifiers	☐	☐	☐	
8.8 Does the plan explain how the analysis will address:				
8.8.1. Confounding	☐	☐	☐	
8.8.2. Effect modification	☐	☐	☐	

Comments:

Section 9: Quality assurance and feasibility

	Yes	No	N/A	Page Number(s)
9.1 Does the protocol provide information on the software and IT environment (incl. database maintenance and anti-fraud protection)?	☐	☐	☐	
9.2 Are methods of quality assurance described?	☐	☐	☐	
9.3. Does the protocol adequately describe and or reference quality issues related to the actual data source?	☐	☐	☐	
9.4. Does the protocol discuss study feasibility (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☐	

Comments:

Section 10: Ethical issues

	Yes	No	N/A	Page Number(s)
11.1 Have ethics approval requirements been described?	☐	☐	☐	
11.2 Is any outcome of an ethical review procedure been addressed and if applicable commented?	☐	☐	☐	
11.3 Have data protection requirements been described?	☐	☐	☐	

Comments:

Name of the Coordinating Study Entity: _____

Name of (Primary) Lead Investigator: _____

Date: xx/yy/zzzz

Signature: _____

Stamp (if applicable)