EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

# Checklist of Methodological Standards for ENCePP Study Protocols

As adopted by the ENCePP Steering Group on 19/03/2010

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". This will help ENCePP keep the *Checklist of Methodological Standards for ENCePP Study Protocols* 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.*
- *Amend and re-submit the checklist as necessary in case of changes to the protocol.*

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: | ☒ | ☐ | ☐ | 3-5 |
| 1.1.1. 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) | ☒ | ☐ | ☐ | 3 |
| 1.1.2 The objectives of the study | | | | |
| 1.2 Does the formulation of the research question specify: | | | | |
| 1.2.1 Target population (or relevant subgroup) (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 3-4 |
| 1.2.2 Hypotheses to be tested (if appropriate, otherwise statement that there is no *a priori* hypothesis) | ☒ | ☐ | ☐ | 6 |

| | Yes | No | N/A | Page Number(s) |
|---|---|---|---|---|
| 1.3 Are the potential implications of the study results for benefit-risk assessment of the medicine(s) or pharmaceutical policy making discussed? | ☒ | ☐ | ☐ | 3-5 |

Comments:

## Section 2: Source and study populations

| | Yes | No | N/A | Page Number(s) |
|---|---|---|---|---|
| 2.1 Is the source population described? | ☒ | ☐ | ☐ | 3-4 |
| 2.2 Is the study population planned to be recruited defined in terms of: | | | | |
| 2.2.1 Age and sex | ☒ | ☐ | ☐ | 8 |
| 2.2.2 Country of origin | ☒ | ☐ | ☐ | 23-25 |
| 2.2.3 Disease/indication | ☒ | ☐ | ☐ | 7 |
| 2.2.4 Co-morbidity | ☒ | ☐ | ☐ | |
| 2.3 Does the protocol define how the study population will be sampled from the source population ? (e.g. any inclusion/exclusion criteria or event) | ☒ | ☐ | ☐ | 8 |

Comments:

For point 2.2.4 co-morbid condition are collected on page 4 of the case report forms

## 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) | ☒ | ☐ | ☐ | 7 |
| 3.2 Is the study design explained? | ☒ | ☐ | ☐ | 7 |
| 3.3 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated? | ☒ | ☐ | ☐ | 7 |
| 3.4 Does the protocol specify whether a dose-dependent or duration-dependent response is measured? | ☒ | ☐ | ☐ | 14-15 |
| 3.5 Does the protocol 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) | ☒ | ☐ | ☐ | 14-15 |
| 3.6 Is a calculation of the sample size provided, or is statistical power calculated according to different assumptions for patient recruitment and results? | ☒ | ☐ | ☐ | 15 |

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) | ☒ | ☐ | ☐ | 7 |
| 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) | ☒ | ☐ | ☐ | 7 |
| 4.1.3 Covariates | ☒ | ☐ | ☐ | 12 |
| 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) | ☒ | ☐ | ☐ | 7 |
| 4.2.2 Endpoints (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 7 |
| 4.2.3 Covariates (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.) | ☒ | ☐ | ☐ | 12 |
| 4.3 Is the coding system described for diseases, endpoints and exposure? (e.g. ICD-10, MedDRA, WHO DD ATC) | ☒ | ☐ | ☐ | 14 |

Comments:

## Section 5: Exposure definition and measurement

| | Yes | No | N/A | Page Number(s) |
|---|---|---|---|---|
| 5.1 Does the protocol describe how exposure is defined and measured (e.g. operational details for defining and categorising exposure)? | ☒ | ☐ | ☐ | 8 |
| 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) | ☒ | ☐ | ☐ | 6 |
| 5.3 Is exposure classified according to time windows (e.g. current user, former user, non-use) or biological mechanism of action? | ☒ | ☐ | ☐ | 8 |

Comments:

5.2 drug exposure specific case report form page

## Section 6: Endpoint definition and measurement

| | Yes | No | N/A | Page Number(s) |
|---|---|---|---|---|
| 6.1 Is the choice of endpoint(s) under investigation explained in terms of rationale in relation to the study hypothesis(-es)? | ☒ | ☐ | ☐ | 7,14 |

| | Yes | No | N/A | Page Number(s) |
|---|---|---|---|---|
| 6.2 Does the protocol describe how the endpoints are defined and measured? | ☒ | ☐ | ☐ | 7,14 |
| 6.3 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) | ☒ | ☐ | ☐ | 7,14 |

Comments:

## Section 7: Biases and Effect modifiers

| | Yes | No | N/A | Page Number(s) |
|---|---|---|---|---|
| 7.1 Does the protocol address: | | | | |
| 7.1.1 Selection biases | ☒ | ☐ | ☐ | 8,14 |
| 7.1.2 Information biases | ☒ | ☐ | ☐ | 14 |
| 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) | | | | |
| 7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect) | ☒ | ☐ | ☐ | 8-9 |

Comments:

For effect modifiers see section on page 8 choice of the comparator group

## Section 8: Analysis plan

| | Yes | No | N/A | Page Number(s) |
|---|---|---|---|---|
| 8.1 Does the plan include measurement of absolute effects? | ☒ | ☐ | ☐ | 14 |
| 8.2 Is the choice of statistical techniques explained in the plan? | ☒ | ☐ | ☐ | 14 |
| 8.3 Are descriptive and stratified analyses included in the plan? | ☒ | ☐ | ☐ | 14 |
| 8.4 Does the plan explain the method for identifying: | | | | |
| 8.4.1. Confounders | ☒ | ☐ | ☐ | 14 |
| 8.4.2. Effect modifiers | ☒ | ☐ | ☐ | 14 |
| 8.5 Does the plan explain how the analysis will address: | | | | |
| 8.5.1. Confounding | ☒ | ☐ | ☐ | 14 |
| 8.5.2. Effect modification | ☒ | ☐ | ☐ | 14 |

Comments:

## Section 9: Quality assurance, feasibility and reporting

| | 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)? | ☒ | ☐ | ☐ | 10 |
| 9.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 13 |
| 9.3 Does the protocol adequately describe and or reference quality issues related to the actual data source? | ☒ | ☐ | ☐ | 10 |
| 9.4 Does the protocol discuss study feasibility (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 11, Table2 |
| 9.5 Does the protocol specify timelines/milestones for | | | | |
| 9.5.1 Monitoring the study progress and completion of the study | ☒ | ☐ | ☐ | Table 3 |
| 9.5.2 Reporting (i.e. interim reports, final study report) | ☒ | ☐ | ☐ | Table 3 |

Comments:

## Section 10: Ethical issues

| | Yes | No | N/A | Page Number(s) |
|---|---|---|---|---|
| 10.1 Have ethics approval requirements been described? | ☒ | ☐ | ☐ | 13 |
| 10.2 Is any outcome of an ethical review procedure been addressed and if applicable commented? | ☒ | ☐ | ☐ | 13 |
| 10.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 13 |

Comments:

Name of the coordinating study entity[1]: FOR PRINTO NICOLINO RUPERTO, MD, MPH

Name of (primary) lead investigator[2]: Nico Wulffraat, MD, MPH NICOLINO RUPERTO, MD, MPH

Date: 10/5/2011

Signature:

Stamp (if applicable)

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

[2] 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.

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