EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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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.

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:	☒	☐	☐	6-8
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)	☒	☐	☐	5,8
1.1.2 The objectives of the study?				
1.2 Does the formulation of the research question specify:	☒	☐	☐	5,8
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	5,8
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 if applicable, that there is no *a priori* hypothesis?				

Comments:

A signal of disproportionate reporting concerning risk of cardiac valve calcification leading to cardiac valve insufficiency associated with use of biphosphonates was found in Eudravigilance.

Section 2: Source and study populations	Yes	No	N/A	Page Number(s)
2.1 Is the source population described?	☒	☐	☐	9-10,12
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	9
2.2.2 Age and sex?	☒	☐	☐	12
2.2.3 Country of origin?	☒	☐	☐	9,10,12
2.2.4 Disease/indication?	☒	☐	☐	12-19
2.2.5 Co-morbidity?	☒	☐	☐	12-19
2.2.6 Seasonality?	☐	☐	☒	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	12

Comments:

Seasonality is not an issue in this case.

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	8-9
3.2 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☐	☐	☐	9-12
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)	☐	☐	☐	17-19
3.4 Is sample size considered?	☒	☐	☐	8
3.5 Is statistical power calculated?	☐	☒	☐	

Comments:

Estimation of the statistical power of the EU-ADR Alliance database network for the investigation of the relationship between cardiac valve disorders and use of biphosphonates will be done in the subsequent traditional hypothesis-testing study.

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, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	9-17
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)	☒	☐	☐	9-16
4.1.3 Covariates?	☒	☐	☐	9-19
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,	☒	☐	☐	9-17

Section 4: Data sources	Yes	No	N/A	Page Number(s)
number of days of supply prescription, daily dosage, prescriber)				
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9-19
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9-17
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☐	☐	13-16
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	☒	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☐	17
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	11

Comments:

Endpoints are described in terms of disease coding terminologies used in the databases.

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)	☒	☐	☐	17
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)	☒	☐	☐	17
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	17
5.4 Is exposure classified based on biological mechanism of action?	☒	☐	☐	6,17
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	19

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	12-18
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)	☒	☐	☐	

Comments:

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number(s)

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address: 7.1.1 Selection biases? 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)	☐ ☐	☐ ☐	☒ ☒	
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	18-19
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	7,18-19
7.4 Does the protocol address other limitations?	☒	☐	☐	17-19

Comments:

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☒	☐	
8.2 Is the choice of statistical techniques described?	☒	☐	☐	17-19
8.3 Are descriptive analyses included?	☒	☐	☐	17-19
8.4 Are stratified analyses included?	☒	☐	☐	17-19
8.5 Does the plan describe the methods for identifying: 8.5.1 Confounders? 8.5.2 Effect modifiers?	☒ ☐	☐ ☒	☐ ☐	17-19
8.6 Does the plan describe how the analysis will address: 8.6.1 Confounding? 8.6.2 Effect modification?	☒ ☐	☐ ☒	☐ ☐	17-19

Comments:

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9-11
9.2 Are methods of quality assurance described?	☒	☐	☐	9-11
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	9-11
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
9.5 Does the protocol specify timelines for				

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number(s)
9.5.1 Study start?	☐	☒	☐	
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☐	☒	☐	
9.5.3 Study completion?	☐	☒	☐	
9.5.4 Reporting? (i.e. interim reports, final study report)	☐	☒	☐	
9.6 Does the protocol include a section to document future amendments and deviations?	☐	☒	☐	
9.7 Are communication methods to disseminate results described?	☐	☒	☐	
9.8 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Study timelines, progress reports, as well as communication and dissemination strategies are specified in another document - the tender agreement/contract.

Section 10: Ethical issues	Yes	No	N/A	Page Number(s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	9
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
10.3 Have data protection requirements been described?	☒	☐	☐	9,11

Comments:

All database holders in the EU-ADR Alliance obtained ethical approval from their respective ethics committees and ensured that use of patient data for this study complies with European directives and national regulations, as well as local database governance rules regarding ethical and legal conduct.

Name of the coordinating study entity[1]: Erasmus University Medical Center

Name of (primary) lead investigator[2]: Miriam Sturkenboom

Date: 29/5/2013

Signature:

Prof. dr. M.C.J.M. Sturkenboom

[1] 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.

[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.