EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

# ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. 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 question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number 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.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

**Study title:** Association of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) on coronavirus disease (COVID-19) incidence and complications

**EU PAS Register® number: 35296**
**Study reference number (if applicable):**

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | X | ☐ | ☐ | 4. Amendments and Updates |
| 1.1.2 End of data collection[2] | X | ☐ | ☐ | 4. Amendments and Updates |

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1.3 Progress report(s) | ☐ | ☐ | X | |
| 1.1.4 Interim report(s) | ☐ | ☐ | X | |
| 1.1.5 Registration in the EU PAS Register® | X | ☐ | ☐ | 4. Amendments and Updates |
| 1.1.6 Final report of study results. | X | ☐ | ☐ | 4. Amendments and Updates<br>12. Plans for Disseminating and Communicating Study Results |

Comments:

These are analyses of pre-existing data so there is no start or end to data collection. Rather, in the protocol document we describe the start and end of analysis.

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | X | ☐ | ☐ | |
| 2.1.1 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) | X | ☐ | ☐ | 5. Rationale and Background |
| 2.1.2 The objective(s) of the study? | X | ☐ | ☐ | 6. Study Objectives |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | X | ☐ | ☐ | 6. Study Objectives<br>7. Research Methods, Hypothesis 1, Patient Cohort<br>7. Research Methods, Hypothesis 2, Patient Cohort |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | X | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | X | ☐ | ☐ | 5. Rationale and Background |

Comments:

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design) | X | ☐ | ☐ | 3. Abstract<br>7. Research Methods, Data Sources |

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | X | ☐ | ☐ | 7. Research Methods, Data Sources |
| 3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Analyses<br>7. Research Methods, Hypothesis 2, Analyses |
| 3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)) | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Analysis<br>7. Research Methods, Hypothesis 2, Analysis |
| 3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | X | ☐ | ☐ | 11. Management and Reporting of Adverse Events and Adverse Reactions |

Comments:

| |
|---|
| |

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 4.1 Is the source population described? | X | ☐ | ☐ | 7. Research Methods, Data Sources<br>7. Research Methods, Hypothesis 1, Patient Cohort<br>7. Research Methods, Hypothesis 2, Patient Cohort |
| 4.2 Is the planned study population defined in terms of: | | | | |

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 4.2.1 Study time period | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Patient Cohort<br>7. Research Methods, Hypothesis 1, Exposures<br>7. Research Methods, Hypothesis 2, Patient Cohort |
| 4.2.2 Age and sex | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Patient Cohort<br>7. Research Methods, Hypothesis 2, Patient Cohort |
| 4.2.3 Country of origin | X | ☐ | ☐ | 7. Research Methods, Data Sources |
| 4.2.4 Disease/indication | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Patient Cohort<br>7. Research Methods, Hypothesis 2, Patient Cohort |
| 4.2.5 Duration of follow-up | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Patient Cohort<br>7. Research Methods, Hypothesis 2, Patient Cohort |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Patient Cohort<br>7. Research Methods, Hypothesis 2, Patient Cohort |

Comments:

| | | | | |
|---|---|---|---|---|
| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
| 5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Patient Cohort<br>7. Research Methods, Hypothesis 1, Exposures<br>7. Research Methods, Hypothesis 2, Patient Cohort<br>7. Research Methods, Hypothesis 2, Exposures<br>16.1 Exposure Cohort Definitions |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | X | ☐ | ☐ | 9. Strengths and Limitations |
| 5.3 Is exposure categorised according to time windows? | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Exposures<br>7. Research Methods, Hypothesis 2, Exposures |
| 5.4 Is intensity of exposure addressed? (e.g. dose, duration) | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Analyses<br>7. Research Methods, Hypothesis 2, Analyses<br>9. Strengths and Limitations |
| 5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | X | ☐ | ☐ | 5. Rationale and Background<br>7. Research Methods, Hypothesis 1, Exposures<br>7. Research Methods, Hypothesis 2, Exposures |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.6 Is (are) (an) appropriate comparator(s) identified? | **X** | ☐ | ☐ | 5. Rationale and Background<br>7. Research Methods, Hypothesis 1, Controls or Comparators<br>7. Research Methods, Hypothesis 1, Analyses<br>7. Research Methods, Hypothesis 2, Analyses |

Comments:

Our study design does not specifically assess the validity of exposure measurement; however it is addressed in the "9 Strengths and Limitations", which includes a discussion of potential bias. We propose to assess the duration / recency of prior exposure in a sub-analysis, if/as sufficient sample size becomes available.

| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | **X** | ☐ | ☐ | 6. Study Objectives<br>7. Research Methods, Hypothesis 1, Outcomes<br>7. Research Methods, Hypothesis 2, Outcomes |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | **X** | ☐ | ☐ | 6. Study Objectives<br>7. Research Methods, Hypothesis 1, Outcomes<br>7. Research Methods, Hypothesis 2, Outcomes<br>16.2 Outcome Cohort Definitions |
| 6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study) | **X** | ☐ | ☐ | 9. Strengths and Limitations |

| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management) | **X** | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Outcomes<br>7. Research Methods, Hypothesis 2, Outcomes |

Comments:

Our study design does not specifically assess the validity of outcome measurement; however it is addressed in the "9 Strengths and Limitations", which includes a discussion of potential bias.

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication) | **X** | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Analyses<br>7. Research Methods, Hypothesis 2, Analyses<br>9. Strengths and Limitations |
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias) | **X** | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Controls or Comparators<br>7. Research Methods, Hypothesis 1, Analyses<br>7. Research Methods, Hypothesis 2, Analyses<br>9. Strengths and Limitations<br>15.5 Overview of ACE / ARB Medications and their Use |

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Analyses<br>7. Research Methods, Hypothesis 2, Analyses<br>9. Strengths and Limitations |

Comments:

| |
|---|
| |

| **Section 8: Effect measure modification** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | X | ☐ | ☐ | 9. Strengths and Limitations |

Comments:

| |
|---|
| |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | X | ☐ | ☐ | 7. Research Methods, Data Sources<br>7. Research Methods, Hypothesis 1, Patient Cohort<br>7. Research Methods, Hypothesis 1, Exposures<br>7. Research Methods, Hypothesis 2, Patient Cohort<br>7. Research Methods, Hypothesis 2, Exposures |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | X | ☐ | ☐ | 7. Research Methods, Data Sources<br>7. Research Methods, Hypothesis 1, Outcomes<br>7. Research Methods, Hypothesis 2, Outcomes |
| 9.1.3 Covariates and other characteristics? | X | ☐ | ☐ | 7. Research Methods, Data Sources<br>7. Research Methods, Hypothesis 1, Covariates<br>7. Research Methods, Hypothesis 2, Covariates |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | X | ☐ | ☐ | 7. Research Methods, Data Sources<br>7. Research Methods, Hypothesis 1, Patient Cohort<br>7. Research Methods, Hypothesis 1, Exposures<br>7. Research Methods, Hypothesis 2, Patient Cohort<br>7. Research Methods, Hypothesis 2, Exposures |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | X | ☐ | ☐ | 7. Research Methods, Data Sources<br>7. Research Methods, Hypothesis 1, Outcomes<br>7. Research Methods, Hypothesis 2, Outcomes |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | X | ☐ | ☐ | 7. Research Methods, Data Sources<br>7. Research Methods, Hypothesis 1, Covariates<br>7. Research Methods, Hypothesis 2, Covariates |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Exposures<br>7. Research Methods, Hypothesis 2, Exposures |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Outcomes<br>7. Research Methods, Hypothesis 2, Outcomes<br>16.2 Outcome Cohort Definitions |
| 9.3.3 Covariates and other characteristics? | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Covariates<br>7. Research Methods, Hypothesis 2, Covariates |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☐ | ☐ | X | 7. Research Methods, Hypothesis 1, Covariates<br>7. Research Methods, Hypothesis 2, Covariates |

Comments:

| |
|---|
| |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Are the statistical methods and the reason for their choice described? | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Covariates<br>7. Research Methods, Hypothesis 2, Covariates |
| 10.2 Is study size and/or statistical precision estimated? | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Analyses<br>7. Research Methods, Hypothesis 2, Analyses |
| 10.3 Are descriptive analyses included? | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Analyses<br>7. Research Methods, Hypothesis 2, Analyses |
| 10.4 Are stratified analyses included? | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Analyses<br>7. Research Methods, Hypothesis 2, Analyses |
| 10.5 Does the plan describe methods for analytic control of confounding? | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Analyses<br>7. Research Methods, Hypothesis 2, Analyses<br>9. Strengths and Limitations |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | X | ☐ | ☐ | 7. Research Methods, Hypothesis 2, Outcomes<br>9. Strengths and Limitations |
| 10.7 Does the plan describe methods for handling missing data? | ☐ | ☐ | X | |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.8 Are relevant sensitivity analyses described? | X | ☐ | ☐ | 7. Research Methods, Hypothesis 1, Analyses<br>7. Research Methods, Hypothesis 2, Analyses |

Comments:

| |
|---|
| |

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☐ | X | ☐ | 10. Protection of Human Subjects |
| 11.2 Are methods of quality assurance described? | X | ☐ | ☐ | 7. Research Methods, Data Sources |
| 11.3 Is there a system in place for independent review of study results? | X | ☐ | ☐ | 2.2 Sponsor<br>5. Rationale and Background<br>12. Plans for Disseminating and Communicating Study Results |

Comments:

| |
|---|
| Patient-level data are not stored by the study team. They are held at independent research sites who run program packages on data instances formatted to the OMOP common data model (CDM) and return unidentifiable, aggregated results. |

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | |
| 12.1.1 Selection bias? | X | ☐ | ☐ | 9. Strengths and Limitations |
| 12.1.2 Information bias? | X | ☐ | ☐ | 9. Strengths and Limitations |
| 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods). | X | ☐ | ☐ | 9. Strengths and Limitations |

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates) | X | ☐ | ☐ | 7. Research Methods, Data Sources<br>9. Strengths and Limitations |

Comments:

| |
|---|
| |

| **Section 13: Ethical/data protection issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☐ | ☐ | X | |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | X | |
| 13.3 Have data protection requirements been described? | ☐ | ☐ | ☐ | 10. Protection of Human Subjects |

Comments:

| |
|---|
| We plan to obtain IRB approval at each study site before executing analyses. |

| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | X | ☐ | ☐ | 4. Amendments and Updates |

Comments:

| |
|---|
| |

| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | X | ☐ | ☐ | 12. Plans for Disseminating and Communicating Study Results |
| 15.2 Are plans described for disseminating study results externally, including publication? | X | ☐ | ☐ | 12. Plans for Disseminating and Communicating Study Results |

Comments:

| |
|---|
| |

Name of the main author of the protocol: Marc A. Suchard (Principal Investigator)

Date: 2/4/2020

Signature: