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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:**
**Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate: utilisation and prescribing trends**

**EU PAS Register® number: 31001**
**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] | ☒ | ☐ | ☐ | 6 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 6 |
| 1.1.3 Progress report(s) | ☐ | ☐ | ☒ | |
| 1.1.4 Interim report(s) | ☒ | ☐ | ☐ | 6 |

[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.

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| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1.5 Registration in the EU PAS Register® | ☒ | ☐ | ☐ | 6 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 6 |

Comments:

1.1.3. Progress reports were not a requirement of the project. However, the planned interim analysis will provide information on progress.

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | ☒ | ☐ | ☐ | 4, 8 |
| 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) | ☒ | ☐ | ☐ | 7, 8 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 4, 8 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 4, 9.2 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☒ | ☐ | ☐ | 8, 9.7.3* |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☒ | ☐ | ☐ | 8, 9.7.3* |

Comments:

*2.1.4-2.1.5: Tests are described in section 8, Objectives and section 9.7.3, Data analysis, but the hypotheses are not formally defined

| **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) | ☒ | ☐ | ☐ | 9.1 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 9.2, 11 |
| 3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☒ | ☐ | ☐ | 9.7.2, 9.7.3 |
| 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)) | ☐ | ☒ | ☐ | 9.7.2, 9.7.3 |
| 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) | ☒ | ☐ | ☐ | 11 |

Comments:

We do state that we will estimate the regression coefficient in section 9.7.3, and that we estimate a change associated with implementation of the intervention. However, it is not explicitly stated that this coefficient represents a risk ratio. We will make this addition to the final protocol (risk ratios).

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 9.2, 9.4 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period | ☒ | ☐ | ☐ | 9.2 |
| 4.2.2 Age and sex | ☒ | ☐ | ☐ | 9.2 |
| 4.2.3 Country of origin | ☒ | ☐ | ☐ | 9.2 |
| 4.2.4 Disease/indication | ☒ | ☐ | ☐ | 9.3.3,9.7.3 |
| 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | 9.2 |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 9.2 |

Comments:

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| **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) | ☒ | ☐ | ☐ | 9.3.1 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☒ | ☐ | ☐ | 9.4, 9.8.2 |
| 5.3 Is exposure categorised according to time windows? | ☒ | ☐ | ☐ | 9.3.1 |
| 5.4 Is intensity of exposure addressed? (e.g. dose, duration) | ☒ | ☐ | ☐ | 9.3.1 |
| 5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☒ | ☐ | ☐ | 9.3.1 |
| 5.6 Is (are) (an) appropriate comparator(s) identified? | ☒ | ☐ | ☐ | 9.7.4 |

Comments:

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| We do not explicitly refer to pharmacokinetics and dynamics, but take this into account when defining how exposure windows will be modeled. |

| **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? | ☒ | ☐ | ☐ | 8, 9.3.2 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3.2 |
| 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) | ☒ | ☐ | ☐ | 9.3.2, 9.8 |

| **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) | ☐ | ☐ | ☒ | |

Comments:

Not applicable to this study

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication) | ☒ | ☐ | ☐ | 9.7.2, 9.7.3 |
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias) | ☒ | ☐ | ☐ | 9.2, 9.7.3 |
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☒ | ☐ | ☐ | 9.9 |

Comments:

The descriptive part of our study (drug utilization) is not subject to confounding. The ITS design is quasi-experimental and does not require additional adjustment for confounding.

All women of childbearing age (using valproate – objectives 2-4) are included, so no selection bias.

| **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) | ☒ | ☐ | ☐ | 9.3.3,9.7.3 |

Comments:

Stratified ITS analyses will be conducted

| **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) | ☒ | ☐ | ☐ | 9.2,9.4 |
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 9.2,9.4 |
| 9.1.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 9.2,9.4 |
| 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) | ☒ | ☐ | ☐ | 9.2,9.4 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 9.2,9.4 |

| **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) | ☒ | ☐ | ☐ | 9.2,9.4 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☒ | ☐ | ☐ | 9.2,9.3.1 |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | ☒ | ☐ | ☐ | 9.2,9.3.2 |
| 9.3.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 9.2,9.3.3 |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☒ | ☐ | ☐ | 9.4 |

Comments:

There is not much use of linkage in our study. However, where it will be used (i.e. to confirm pregnancies) the linkage is described in the site-specific database descriptions.

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Are the statistical methods and the reason for their choice described? | ☒ | ☐ | ☐ | 9.7 |
| 10.2 Is study size and/or statistical precision estimated? | ☒ | ☐ | ☐ | 9.5 |
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.7.1,9.7.3 |
| 10.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 9.7.3 |
| 10.5 Does the plan describe methods for analytic control of confounding? | ☒ | ☐ | ☐ | 9.7.2, 9.7.3 |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☒ | ☐ | ☐ | 9.7.5 |
| 10.7 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 9.7.4 |
| 10.8 Are relevant sensitivity analyses described? | ☒ | ☐ | ☐ | 9.7.5 |

Comments:

The descriptive part of our study (drug utilization) is not subject to confounding. The ITS design is quasi-experimental and does not require additional adjustment for confounding.

Outcome misclassification will be accounted for at a design level (through quality assessment and checking, and use of a common data model), and explored in sensitivity analyses.

| **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) | ☒ | ☐ | ☐ | 9.6 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9.8 |
| 11.3 Is there a system in place for independent review of study results? | ☐ | ☒ | ☐ | |

Comments:

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| **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? | ☐ | ☐ | ☒ | |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 9.9 |
| 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). | ☐ | ☒ | ☐ | |
| 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) | ☒ | ☐ | ☐ | 9.5, 9.9 |

Comments:

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| All women of childbearing age (using valproate – objectives 2-4) are included, so no selection bias.<br>The descriptive part of our study (drug utilization) is not subject to confounding. The ITS design is quasi-experimental and does not require additional adjustment for confounding. |

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

Comments:

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| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | ☒ | ☐ | ☐ | 5 |

Comments:

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| **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)? | ☒ | ☐ | ☐ | 6, 12 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 6, 12 |

Comments:

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Name of the main author of the protocol: Prof dr Olaf Klungel

Date: 22/August/2019

Signature: