



ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Intravenous Iron Postauthorisation Safety Study (PASS): Evaluation of the Risk of Severe Hypersensitivity Reactions

Study reference number:

| <u>Section 1: Milestones</u> | Yes | No | N/A | Section Number |
|--|-------------------------------------|--------------------------|--------------------------|----------------|
| 1.1 Does the protocol specify timelines for 1.1.1 Start of data collection ¹ | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4, 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.

| Section 1: Milestones | Yes | No | N/A | Section Number |
|---|-------------------------------------|-------------------------------------|--------------------------|-----------------------|
| 1.1.2 End of data collection ¹ | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4, 6 |
| 1.1.3 Study progress report(s) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| 1.1.4 Interim progress report(s) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| 1.1.5 Registration in the EU PAS Register | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4, 6 |
| 1.1.6 Final report of study results | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4, 6 |

Comments:

| Section 2: Research question | Yes | No | N/A | Section Number |
|---|-------------------------------------|--------------------------|-------------------------------------|-----------------------|
| 2.1 Does the formulation of the research question and objectives clearly explain: | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | |
| 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) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4, 7.1 |
| 2.1.2 The objective(s) of the study? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4, 8 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4, 9.1 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| 2.1.5 If applicable, that there is no <i>a priori</i> hypothesis? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |

Comments:

Rather than testing a statistical difference between treatments with a priori hypothesis the study aims at measuring and comparing risk estimates among groups.

| Section 3: Study design | Yes | No | N/A | Section Number |
|---|-------------------------------------|--------------------------|-------------------------------------|-----------------------|
| 3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4, 9.1 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.4 |
| 3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.7.3 |
| 3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 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) | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | 11 |

¹ Date from which the analytical dataset is completely available.

Comments:

3.5: Current guidelines from ISPE (2015) and the EMA *Guideline on Good Pharmacovigilance Practices: Module VI – Management and Reporting of Adverse Reactions to Medicinal Products* (EMA, 2014) indicate that non-interventional studies such as the one described in this protocol, conducted using medical chart reviews or electronic claims and health care records, do not require reporting of adverse events/reactions

| <u>Section 4: Source and study populations</u> | Yes | No | N/A | Section Number |
|--|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 4.1 Is the source population described? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.2.1, 9.4 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.2.2 |
| 4.2.2 Age and sex? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.2.1 |
| 4.2.3 Country of origin? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.4 |
| 4.2.4 Disease/indication? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.2.3 |
| 4.2.5 Duration of follow-up? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.2.3.5 |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.2.3.3, 9.2.3.4 |

Comments:

| <u>Section 5: Exposure definition and measurement</u> | 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) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4, 9.3.1 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| 5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use) | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| 5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |

Comments:

| <u>Section 6: Outcome definition and measurement</u> | Yes | No | N/A | Section Number |
|--|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4, 9.3.2 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4, 9.3.2 |

| <u>Section 6: Outcome definition and measurement</u> | Yes | No | N/A | Section Number |
|---|-------------------------------------|--------------------------|-------------------------------------|-----------------------|
| 6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.3.2.1 |
| 6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management) | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |

Comments:

| <u>Section 7: Bias</u> | Yes | No | N/A | Section Number |
|---|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 7.1 Does the protocol describe how confounding will be addressed in the study? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.1, 9.3.3, 9.7.2 |
| 7.1.1. Does the protocol address confounding by indication if applicable? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.1, 9.3.3, 9.7.2 |
| 7.2 Does the protocol address: | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.7.4 |
| 7.2.1. Selection biases (e.g. healthy user bias) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.7.4 |
| 7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.7.4 |
| 7.3 Does the protocol address the validity of the study covariates? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.1, 9.3.2.1, |

Comments:

| <u>Section 8: Effect modification</u> | Yes | No | N/A | Section Number |
|---|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.7.2, 9.7.4 |

Comments:

| <u>Section 9: Data sources</u> | 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) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 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) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.4 |
| 9.1.3 Covariates? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.4 |

| <u>Section 9: Data sources</u> | Yes | No | N/A | Section Number |
|---|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 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) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.4, 9.3.1 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.4, 9.3.2 |
| 9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.4, 9.3.3 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.3.1 |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA)) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.3.2 |
| 9.3.3 Covariates? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.3.3 |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.4.1, 9.4.2 |

Comments:

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| <u>Section 10: Analysis plan</u> | Yes | No | N/A | Section Number |
|--|-------------------------------------|-------------------------------------|--------------------------|-----------------------|
| 10.1 Is the choice of statistical techniques described? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.7 |
| 10.2 Are descriptive analyses included? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.7.1 |
| 10.3 Are stratified analyses included? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.7.3 |
| 10.4 Does the plan describe methods for adjusting for confounding? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.7.2, 9.7.3, 9.7.4 |
| 10.5 Does the plan describe methods for handling missing data? | <input type="checkbox"/> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | |
| 10.6 Is sample size and/or statistical power estimated? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.5 |

Comments:

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| <u>Section 11: Data management and quality control</u> | 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) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.8 |
| 11.2 Are methods of quality assurance described? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.8 |
| 11.3 Is there a system in place for independent review of study results? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 3 |

Comments:

11.3 Plan to set up scientific advisory board review of study results

| <u>Section 12: Limitations</u> | Yes | No | N/A | Section Number |
|---|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | |
| 12.1.1 Selection bias? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.9 |
| 12.1.2 Information bias? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 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) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.9 |
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 9.1, 9.2.3.5 |

Comments:

| <u>Section 13: Ethical issues</u> | Yes | No | N/A | Section Number |
|--|-------------------------------------|--------------------------|-------------------------------------|-----------------------|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 10 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> | |
| 13.3 Have data protection requirements been described? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 10 |

Comments:

| <u>Section 14: Amendments and deviations</u> | Yes | No | N/A | Section Number |
|---|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 14.1 Does the protocol include a section to document amendments and deviations? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 5 |

Comments:

| <u>Section 15: Plans for communication of study results</u> | Yes | No | N/A | Section Number |
|---|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 12 |
| 15.2 Are plans described for disseminating study results externally, including publication? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 12 |

Comments:

Comments:

Name of the main author of the
protocol: Joan Fortuny, MD, PhD _____

Date: 04 May 2017

Signature:

