



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 oral retinoid containing medicinal products: utilization and prescribing trends

EU PAS Register® number:

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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.2 End of data collection ²	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.3 Progress report(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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
1.1.4 Interim report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
1.1.5 Registration in the EU PAS Register®	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Comments:

There is no progress report required for this study. Rather, an interim analysis will be conducted. This will be discussed in the final study report.

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"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4,8
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
2.1.4 Which hypothesis(-es) is (are) to be tested?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.2
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.2

Comments:

One of the objectives of the study is synthetic and therefore poses no *a priori* hypothesis.

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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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"/>	9.2, 11
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.4
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))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.4
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 checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11

Comments:

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5

Section 4: Source and study populations		Yes	No	N/A	Section Number
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
4.2.2	Age and sex	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
4.2.3	Country of origin	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
4.2.4	Disease/indication	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.4
4.2.5	Duration of follow-up	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2

Comments:

All women of child-bearing age registered in one of the participating data sources will be included regardless of her country of origin.

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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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 checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.8.2
5.3	Is exposure categorised according to time windows?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.3
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1, 9.3.3
5.6	Is (are) (an) appropriate comparator(s) identified?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.4

Comments:

--

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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.8.2

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)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Comments:

The outcomes assessed in this study are not relevant for health technology assessment.

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8, 9.3.3
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8, 9.7
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9

Comments:

By design we deal with confounding by indication, we select cohorts by type of retinoid which makes them indication specific, subsequently time periods are compared within the same cohort and the same database.

A strong confounding factor will be age which will be stratified for, gender is controlled for by restriction to women. -All women of childbearing age are included for the first objective, all women receiving a prescription for a study drug are included in the other objectives, this mitigates potential selection bias.

This will be discussed in the final study report.

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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.3, 9.7.4

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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.1, 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"/>	9.2.1, 9.4
9.1.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.1, 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	Yes	No	N/A	Section Number
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"/>	9.2.1, 9.4
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"/>	9.2.1, 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.1, 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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.1
9.3.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.1
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"/>	9.2.1

Comments:

Linkage is only necessary in those data sources which make use of birth or pregnancy registries to link mothers and infants.

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.3
10.2 Is study size and/or statistical precision estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5.1
10.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.1
10.4 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.4
10.5 Does the plan describe methods for analytic control of confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9.1
10.7 Does the plan describe methods for handling missing data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.5
10.8 Are relevant sensitivity analyses described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.7

Comments:

Because we are using interrupted time series to compare two periods, concerns of bias and confounding are mitigated.

By design we deal with confounding by indication, we select cohorts by type of retinoid which makes them indication specific, subsequently time periods are compared within the same cohort and the same database.

A strong confounding factor will be age which will be stratified for, gender is controlled for by restriction to women. -All women of childbearing age are included for the first objective, all women receiving a prescription for a study drug are included in the other objectives, this mitigates potential selection bias.

This will be discussed in the final study report.

<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"/>	9.6.4
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 type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Comments:

<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? 12.1.2 Information bias? 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 checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	9.9
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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5, 9.9

Comments:

<u>Section 13: Ethical/data protection 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 checked="" type="checkbox"/>	<input type="checkbox"/>	
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10

Comments:

The protocol has not yet been submitted for ethics review.

<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:

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)?	<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:

Name of the main author of the protocol: Caitlin Dodd, PhD

Date: 31/July/2019

Signature: *Caitlin Dodd*

