

## 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: Ranitidine and other histamine-H<sub>2</sub>-receptor antagonists – A drug utilisation study**

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

<b>Section 1: Milestones</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection <sup>1</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Page 12
1.1.2 End of data collection <sup>2</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
1.1.3 Progress report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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"/>	

<sup>1</sup> 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.

<sup>2</sup> Date from which the analytical dataset is completely available.

Comments:

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<b><u>Section 2: Research question</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
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"/>	
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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"/>	
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:

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<b><u>Section 3: Study design</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
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"/>	Study design – page 15
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"/>	Datasources – page 21
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Variables 15-17 & Data analysis page 24-25
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 type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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"/>	

Comments:

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<b><u>Section 4: Source and study populations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Datasources Page 21

<b><u>Section 4: Source and study populations</u></b>		<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
4.2	Is the planned study population defined in terms of:				Method section – Setting page 15
	4.2.1 Study time period	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	4.2.2 Age and sex	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	4.2.3 Country of origin	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	4.2.4 Disease/indication	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
	4.2.5 Duration of follow-up	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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"/>	Method section – Setting page 15

Comments:

<b><u>Section 5: Exposure definition and measurement</u></b>		<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
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"/>	Drug Exposure page 15
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"/>	Quality control page page 26-29
5.3	Is exposure categorised according to time windows?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Drug Exposure page 15
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Creation drug eras – page 5
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Drug exposure – Duration of use of H2RA – Dose of H2RA Page 15-17
5.6	Is (are) (an) appropriate comparator(s) identified?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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

Comments:

For these questions, N/A was answered as DUS was not considered as an outcome

<b><u>Section 7: Bias</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Limitations page 29
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"/>	Limitations page 29

Comments:

<b><u>Section 8: Effect measure modification</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
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"/>	Data analysis page 24-25

Comments:

<b><u>Section 9: Data sources</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
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"/>	Drug Exposure page 15
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 type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b><u>Section 9: Data sources</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
9.1.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Covariates page 20
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"/>	Drug Exposure page 15
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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"/>	Covariates page 20
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"/>	Drug Exposure page 15
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.3.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Covariates page 20
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

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<b><u>Section 10: Analysis plan</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
10.1 Are the statistical methods and the reason for their choice described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Data analysis page 24-25
10.2 Is study size and/or statistical precision estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Study Size page 23
10.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Data analysis page 24-25
10.4 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Data analysis page 24-25
10.5 Does the plan describe methods for analytic control of confounding?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.7 Does the plan describe methods for handling missing data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Quality control page 26-29

<b><u>Section 10: Analysis plan</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
10.8 Are relevant sensitivity analyses described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Data analysis page 24-25

Comments:

<b><u>Section 11: Data management and quality control</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
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"/>	Quality control page 26-29
11.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Quality control page 26-29
11.3 Is there a system in place for independent review of study results?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

<b><u>Section 12: Limitations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
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 type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	Limitations page 29
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 type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Comments:

<b><u>Section 13: Ethical/data protection issues</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Protection of human subjects Page 30
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b><u>Section 13: Ethical/data protection issues</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Protection of human subjects Page 30

Comments:

<b><u>Section 14: Amendments and deviations</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
14.1 Does the protocol include a section to document amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Page 11 amendments and updates

Comments:

<b><u>Section 15: Plans for communication of study results</u></b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Section Number</b>
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Milestones & Disseminating and communication Page 32
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Milestones & Disseminating and communication Page 32

Comments:

Name of the main author of the protocol: Katia Verhamme

Date: 03/Feb/2020

Signature: \_\_\_\_\_