

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 alpha-1 blocker (α -1B)
on coronavirus disease (COVID-19) susceptibility and severity

EU PAS Register® number: EUPAS36231

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	<input type="checkbox"/>	<input type="checkbox"/>	4. Milestones and Amendments
1.1.2 End of data collection ²	X	<input type="checkbox"/>	<input type="checkbox"/>	4. Milestones and Amendments
1.1.3 Progress report(s)	<input type="checkbox"/>	<input type="checkbox"/>	X	
1.1.4 Interim report(s)	<input type="checkbox"/>	<input type="checkbox"/>	X	
1.1.5 Registration in the EU PAS Register®	X	<input type="checkbox"/>	<input type="checkbox"/>	4. Milestones and

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.

1.1.6 Final report of study results.	X	<input type="checkbox"/>	<input type="checkbox"/>	Amendments 4. Milestones and Amendments 12. Plans for Disseminating and Communicating Study Results
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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	<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)	X	<input type="checkbox"/>	<input type="checkbox"/>	5. Rationale and Background
2.1.2 The objective(s) of the study?	X	<input type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Patient Cohort
2.1.4 Which hypothesis(-es) is (are) to be tested?	X	<input type="checkbox"/>	<input type="checkbox"/>	6. Study Objectives
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input type="checkbox"/>	X	

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	<input type="checkbox"/>	<input type="checkbox"/>	3. Abstract 7. Research Methods, Data Sources
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Data Sources
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Analysis
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	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, 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	<input type="checkbox"/>	<input type="checkbox"/>	11. Management and Reporting of Adverse Events and Adverse Reactions

Comments:

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Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Data Sources & Patient Cohort
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Patient Cohort & Exposures
4.2.2 Age and sex	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Patient Cohort
4.2.3 Country of origin	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Data Sources
4.2.4 Disease/indication	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Patient Cohort
4.2.5 Duration of follow-up	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, 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	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Patient Cohort

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)	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Patient Cohort & Exposures 14.1 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	<input type="checkbox"/>	<input type="checkbox"/>	9. Strengths and Limitations
5.3 Is exposure categorised according to time windows?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Exposures
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Exposures 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	X	<input type="checkbox"/>	<input type="checkbox"/>	5. Rationale and Background

drug?				7. Research Methods, Exposures
5.6 Is (are) (an) appropriate comparator(s) identified?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Patient Cohort & Controls or Comparators & Analysis

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.

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	<input type="checkbox"/>	<input type="checkbox"/>	6. Study Objectives 7. Research Methods, Outcomes
6.2 Does the protocol describe how the outcomes are defined and measured?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Outcomes 14.2 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	<input type="checkbox"/>	<input type="checkbox"/>	9. Strengths and Limitations
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"/>	X	

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	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Analysis 9. Strengths and Limitations
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Controls or Comparators & Analysis 9. Strengths and Limitations
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Analysis,

				9. Strengths and Limitations
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Comments:

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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	<input type="checkbox"/>	<input type="checkbox"/>	9. Strengths and Limitations

Comments:

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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	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Data Sources
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	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Data Sources
9.1.3 Covariates and other characteristics?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Data Sources
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	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Data Sources & Patient Cohort & Exposures
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Data Sources & Patient Cohort & Outcomes
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Data Sources & 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	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Exposures 14.1 Exposure Cohort Definitions
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Outcomes 14.2 Outcome Cohort Definitions

9.3.3 Covariates and other characteristics?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Covariates
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"/>	X	7. Research Methods, Data Sources

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	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Analysis
10.2 Is study size and/or statistical precision estimated?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Analysis
10.3 Are descriptive analyses included?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Analysis
10.4 Are stratified analyses included?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Analysis
10.5 Does the plan describe methods for analytic control of confounding?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Analysis
10.6 Does the plan describe methods for analytic control of outcome misclassification?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Analysis 9. Strengths and Limitations
10.7 Does the plan describe methods for handling missing data?	<input type="checkbox"/>	<input type="checkbox"/>	X	
10.8 Are relevant sensitivity analyses described?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Analysis

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)	<input type="checkbox"/>	X	<input type="checkbox"/>	10. Protection of Human Subjects
11.2 Are methods of quality assurance described?	X	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Data Sources
11.3 Is there a system in place for independent review of study results?	X	<input type="checkbox"/>	<input type="checkbox"/>	2.2 Sponsor 12. Plans for Disseminating and Communicating Study Results

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
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12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias?	X	<input type="checkbox"/>	<input type="checkbox"/>	9. Strengths and Limitations
12.1.2 Information bias?	X	<input type="checkbox"/>	<input type="checkbox"/>	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	<input type="checkbox"/>	<input type="checkbox"/>	9. Strengths and Limitations
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	<input type="checkbox"/>	<input type="checkbox"/>	7. Research Methods, Data Sources 9. Strengths and Limitations

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 type="checkbox"/>	<input type="checkbox"/>	X	
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input type="checkbox"/>	X	
13.3 Have data protection requirements been described?	<input type="checkbox"/>	<input type="checkbox"/>	X	10. Protection of Human Subjects

Comments:

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

<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 type="checkbox"/>	<input type="checkbox"/>	X	4. Milestones and Amendments

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)?	X	<input type="checkbox"/>	<input type="checkbox"/>	12. Plans for Disseminating and Communicating Study Results
15.2 Are plans described for disseminating study results externally, including publication?	X	<input type="checkbox"/>	<input type="checkbox"/>	12. Plans for Disseminating and Communicating Study Results

Comments:

Name of the main author of the protocol: Akihiko Nishimura

Date: 07/07/2020

Signature: 