Study title: Real-world effectiveness of different COVID-19 vaccines in Spain: a cohort study based on public electronic health records (BIFAP)

EU PAS Register® number: Not-applicable
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)	☒	☐	☐	6
1.1.4 Interim report(s)	☐	☒	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	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:	☒	☐	☐	7,8
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?	☒	☐	☐	7,8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7,8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	7,8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.5 NA: There is a priori hypothesis of the efficacy reported in trials and expected replicated in real world.

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

[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 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7, 9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.2
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))	☒	☐	☐	9.7.3
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)	☐	☐	☒	

Comments:

To 3.5: NA since this a an observational effectiveness study using secondary data

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2; 9.3.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2; 9.3.1
4.2.2 Age and sex	☒	☐	☐	9.2; 9.3.1
4.2.3 Country of origin	☒	☐	☐	9.2; 9.3.1
4.2.4 Disease/indication	☒	☐	☐	9.3.1*
4.2.5 Duration of follow-up	☒	☐	☐	9.2;9.3.1$^{\Psi}$
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.3.1

Comments:

The last date available in the data source at data collection will be the end of the Study time period.

*The study population is defined in terms of Exposure (instead of Disease/Indication)

$^{\Psi}$Duration of follow-up: Inclusion date and stop date to follow-up define the Duration of follow-up.

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)	☒	☐	☐	9.1.1.3

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.1.1.4
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.1.1.4
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.1.1.4
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1;9.1.1.4*

Comments:

*We have discarded to select other control groups due to the reason explained in 9.1.

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; 9.3.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8; 9.3.3
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)	☒	☐	☐	8; 9.1.1.2
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:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3.4
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.1*;9.1.1.4$^{\Psi}$
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.1.1.2; 9.1.1.4;9.7.3.1;9.9

Comments:

*The choice of an exchangeable comparator is described as well as the reasons to discard other potential reference groups, informing about the efforts to avoid Selection Bias.

$^{\Psi}$ Also, in order to avoids selection bias, the date to start the contributed and compared time in each compared group is provided and justified. That date (Time zero) allows to align the evaluation of eligibility criteria, covariate assessment and exposure assignment.

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)	☒	☐	☐	9.7.4.1

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)	☒	☐	☐	9.3.1; 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)	☒	☐	☐	9.3.3; 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.4; 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)	☒	☐	☐	9.3.1; 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.3; 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.4; 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)	☒	☐	☐	9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.3
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

The coding of COVID and covid-19 vaccines will be assessed in feasibility analysis. Since COVID confirmation will came from lab result it easy that it will not adjust systematic classifications but original ones. Regarding vaccines, we expect that the either ATC07 (J07????) or National Code (CNF) specific for pharmaceuticals in Spain is available for all vaccinations. For a particular patient, data are linked in the regions that provide the complete data to the Data Source (BIFAP) based on a unique identifier.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.3.1
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7.4
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.3.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	9.7.4.3*
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.5
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.4.2

Comments:

* Quantitative bias analyses will not be performed to evaluate the potential impact of differential misclassification of the outcome on the observed study estimate. This is because no validation studies are planned for the outcome (identified through lab results considered gold-standard in the clinical practice).

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)	☐	☒	☐	9.8*
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:

*Data storage and quality assurance will be performed according to the BIFAP governance that can be consulted in the website of BIFAP.

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?	☒	☐	☐	9.9¶
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).	☒	☐	☐	9.9Ψ
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

Comments:

¶Selective recruitment into the study of vaccinated/unvaccinated subjects from those recorded in the database with quality criteria (up-to-standard information) that are not representative of the general vaccinated/unvaccinated subjects respectively in the source population could produce selection bias. Some examples are described in the protocol '9.9 Limitations of the Research Methods' section.

* If vaccinated individuals had less likelihood of screening or test than unvaccinated (due to a feeling of induced immunoprotection among vaccinated), we would artificially observe more cases among unvaccinated, directing toward a biased higher vaccine effectiveness estimation. The opposite could also be true, i.e. if vaccinated individuals had more likelihood of screening because they have a health/test-seeking behaviour, we would artificially observe more cases among vaccinated, directing toward a biased lower vaccine effectiveness estimation.

ΨNo information about the job and type of residence will be available. Consequently, confusion may still be present due to the higher probability of infection among them versus other social groups. That aspect would direct towards a reduction in the effectiveness estimations.

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

Comments:

ΨNot yet sent to ethics committee review.

*Reference to the BIFAP governance document (www.bifap.aemps.es) have been provided regarding data protection.

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:

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?	☒	☐	☐	12

Comments:

*The study progress reports as included in the section 6-Milestones and Timeline will be circulated among the participants of the collaborating public institutions for communication and review.

Name of the main author of the protocol: Elisa Martín Merino

Date: 20/April/2021

Signature : 

[The most current revision of the ENCePP Checklist for Study Protocols at the time of protocol finalisation, available here: http://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml]