Annex 2. ENCePP Checklist for Study Protocols

Adopted by the ENCePP Steering Group on 19/08/2011

The purpose of the Checklist developed by ENCePP is to stimulate consideration of important epidemiological principles when designing a pharmacoepidemiological or pharmacovigilance study and writing a study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. ENCePP welcomes innovative designs and new methods of research. 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 of the questions of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) 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.

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 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)	☒	☐	☐	14-18
1.1.2 The objectives of the study?	☒	☐	☐	18-20
1.2 Does the formulation of the research question specify:				
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be categorized in)	☒	☐	☐	25
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
1.2.3 if applicable, that there is no *a priori* hypothesis?	☒	☐	☐	19

Comments:

Study is an active surveillance project describing primarily describing adverse events after vaccination, hence not stating a formal hypothesis.

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	☒	☐	☐	25
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	☒	☐	☐	27
2.2.2 Age and sex?	☒	☐	☐	25
2.2.3 Country of origin?	☒	☐	☐	25
2.2.4 Disease/indication?	☒	☐	☐	25
2.2.5 Co-morbidity?	☒	☐	☐	25
2.2.6 Seasonality?	☒	☐	☐	27
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	25-28

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	24-25
3.2 Is the study design described? (e.g. cohort, case-control, categorized controlled trial, new or alternative design)	☒	☐	☐	24-25
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	34-35
3.4 Is sample size considered?	☒	☐	☐	32-33
3.5 Is statistical power calculated?	☐	☒	☐	32-33

Comments:

Sample size is guided by requirements specified in EMA guidance, and no power calculations are made. The potential precision of the sample size in terms of being able to evaluate the frequency of adverse event rates is considered.

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	☒	☐	☐	25
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc)	☒	☐	☐	24-25
4.1.3 Covariates?	☒	☐	☐	31
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	25
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	40-44
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	31
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	34
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	24

Comments:

Only limited information on diseases are collected, primarily to determine if the participants fit an at-risk indication for influenza vaccination. Diseases are not endpoints, rather the endpoints are adverse events which are coded.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorizing exposure)	☒	☐	☐	24
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	29
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	29
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	34-35

Comments:

Exposure relates to influenza vaccination timing and batch information, and the information is validated since it will come from medical records at the investigator site (as distinct from participant self-reporting). One or two dose vaccination information will be collected.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	24-25, 28
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	28

Comments:

Prospective measurement of endpoints. Many of the solicited endpoints are collected in the same way that they are collected in influenza clinical trials.

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?	☒	☐	☐	28-29
7.1.2 Information biases?	☐	☒	☐	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)				
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	31
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☒	☐	
7.4 Does the protocol address other limitations?	☒	☐	☐	37

Comments:

The use of internet only for participant data entry may introduce some selection biases and impact on generalisability, but the speed and simplicity of data collection is important for enhanced active surveillance. Previous influenza vaccination history and history of previous adverse reactions may be potential confounders, but for simple surveillance reporting, no adjustments for these variables are planned.

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☒	☐	☐	34-35
8.2 Is the choice of statistical techniques described?	☒	☐	☐	34-35
8.3 Are descriptive analyses included?	☒	☐	☐	34-35
8.4 Are stratified analyses included?	☒	☐	☐	34-35
8.5 Does the plan describe the methods for identifying:				
8.5.1 Confounders?	☒	☐	☐	34-35
8.5.2 Effect modifiers?	☐	☒	☐	

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.6 Does the plan describe how the analysis will address:				
8.6.1 Confounding?	☐	☒	☐	
8.6.2 Effect modification?	☐	☒	☐	

Comments:

Limited information on potential confounders is collected, but there are no a priori plans for assessing their impact.

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	35-37
9.2 Are methods of quality assurance described?	☒	☐	☐	35-37
9.3 Does the protocol describe quality issues related to the data source(s)?	☒	☐	☐	20-23
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	20-23
9.5 Does the protocol specify timelines for				
9.5.1 Study start?	☒	☐	☐	14
9.5.2 Study progress? (e.g. end of data collection, other milestones)	☒	☐	☐	27-28
9.5.3 Study completion?	☒	☐	☐	14, 27-28
9.5.4 Reporting? (i.e. interim reports, final study report)	☒	☐	☐	27-28, 45-46
9.6 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	14
9.7 Are communication methods to disseminate results described?	☒	☐	☐	45-46
9.8 Is there a system in place for independent review of study results?	☒	☐	☐	34

Comments:

Study results will be analysed by a 3rd party provider separate to the Sponsor, and results will be submitted to the regulatory agency for review. Data entry, access controls, security and archiving will be managed in accordance with national and international standards, legislation, and Sponsor standard operating procedures.

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	38-39
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
10.3 Have data protection requirements been described?	☒	☐	☐	39

Comments: The protocol is to be submitted to, and approved by appropriately constituted Ethics Committee/Institutional Review Board(s) prior to any participants being enrolled.

Name of the coordinating study entity[1]: bioCSL Pty Ltd

Name of (primary) lead investigator[2]: Dr James Larcombe (*G.P.; Sedgefield, Co. Durham, U.K.*)

Date: 13/08/2014

Protocol Author Signature:

Dr Neil Formica, Public Health Physician

[1] A legal person, institution or organisation which takes responsibility for the design and/or the management of a study. The (primary) lead investigator is the person authorised to represent the coordinating study entity.

[2] A person with the scientific background and experience required for the conduct of a particular pharmacoepidemiological or pharmacovigilance study. The lead investigator is responsible for the conduct of a study at a study site. If a study is conducted at several study sites by a team of investigators, the (primary) lead investigator is the investigator who has overall responsibility for the study across all sites.