# Protocol Abstract

## Post-Authorisation Safety Study (PASS) Information

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| **Title** | Observational influenza vaccine active surveillance study: A Phase IV Prospective Multi-Centre Cohort Study to Evaluate the Reactogenicity of bioCSL's influenza virus vaccine (2015/2016 formulation). |
| **Protocol version identifier** | **CSLCT-SAF-15-07** (Final Version 1.1 10 June 2015) |
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# Abstract

## Title

Observational influenza vaccine active surveillance study: A Phase IV Prospective Multi-Centre Cohort Study to Evaluate the Reactogenicity of bioCSL's influenza virus vaccine (2015/2016 formulation).

## Rationale and background

It is a requirement by the European Medicine's Agency (EMA) for manufacturer's of influenza vaccines licensed in Europe to develop an enhanced safety surveillance system focusing on signal detection for Influenza Virus Vaccines (IVV), as outlined in the EMA Interim guidance on enhanced safety surveillance for seasonal influenza vaccines (EMA/PRAC/222346/2014) [Pharmacovigilance Risk Assessment Committee, EMA. April 2014]. This interim guidance focuses on requirements and principles for annual enhanced safety surveillance, to rapidly detect any increased local and systemic reactogenicity that may arise during the influenza vaccine product life-cycle, such as may occur due to significant changes in the manufacturing process or that may potentially arise with updated IVV strains.

It is envisaged that this Post-Authorisation Safety Study (PASS) will be implemented in years when there is at least one IVV strain change, or if there are significant changes in the manufacturing process. In the instance when there is neither of these changes, it is possible that the study may not be implemented in a given year, following consultation between bioCSL and regulatory agencies. The vaccine formulation used for the PASS will be in accordance with the EMA recommendations for influenza vaccine composition for the given season.

## Research question and objectives

This protocol defines an enhanced active surveillance system that will collect and descriptively summarise participant self-reported reactogenicity data, which will be supplemented by primary care or other health provider data on the details of vaccination, and any Medically attended Adverse Events (MAE) in the seven day period after each bioCSL influenza vaccination in a given year.

Descriptive summaries of the reactogenicity and other safety data as defined in the primary and secondary study objectives will allow indirect comparison of data from the study with previous safety data, and data arising from the enhanced safety surveillance system over time, to facilitate safety signal detection for bioCSL's influenza virus vaccine.

***Primary objective***

To characterise the reactogenicity (local, systemic and allergic reactions) within seven days after each influenza vaccination with bioCSL's influenza virus vaccine in participants routinely indicated for influenza vaccination in specified age groups.

***Secondary objective***

To assess the frequency and severity of medically attended adverse events occurring within seven days after each influenza vaccination with bioCSL's influenza virus vaccine, in participants routinely indicated for influenza vaccination in specified age groups.

## Study design

This observational research study will be implemented through the primary care research network of the National Institute for Health Research (NIHR) in the United Kingdom, through either general practice or pharmacy investigator sites.

People who have, or are just about to be, routinely vaccinated with bioCSL's influenza virus vaccine will be invited to enrol in the study. Study participants will be asked to report solicited adverse events occurring within seven days after each vaccination and medically attended adverse events occurring within seven days after each vaccination, via an internet based survey. The rates of adverse events after vaccination in the overall cohort, and in pre-specified age sub-groups of the cohort will be described.

***Primary Outcome Measures***

The reactogenicity of bioCSL's influenza virus vaccine will be assessed in the vaccinated cohort (according to age-indicated dosing regimen) by summarising reports of solicited adverse events occurring within seven days after each vaccination. Solicited events include injection site, systemic and allergic reactions as listed below in all age groups:

- Local: pain, erythema, induration.
- Systemic: fever, headache, malaise, myalgia, arthralgia, nausea, vomiting.
- Allergic: rash, hives, generalised skin itch, red and inflamed eyes, facial and/or tongue swelling

Participants will also be asked to indicate if they did not experience any adverse events, to distinguish between no reported Adverse Events (AEs) and missing data.

Information on the use of medicines available without prescription to treat pain and fever will also be collected.

***Secondary Outcome Measures***

Medically attended Adverse Events (MAE) are defined as any event that requires hospitalisation or a face-to-face consultation with a doctor. It is expected that this definition of medically attended events will cover most important severe adverse events following vaccination not captured as solicited events.

Information on MAEs will be recorded for medical attendances that relate to events occurring within seven days after each influenza vaccination.

If two doses are indicated in children from 5 years to less than 9 years, the second dose is given at least 4 weeks after the first dose.

## Population

This observational post-marketing study is designed to capture the population receiving bioCSL's influenza virus vaccine regardless of age or health status in order to provide a picture of the safety profile in routine practice. Pregnant and immune-compromised participants, and children aged less than 5 are not excluded from this study if they have been administered bioCSL's influenza virus vaccine as part of routine care, or inadvertently prior to enrolment in the study.

The source of the population will be people who present to general practice or pharmacies for influenza vaccination, either through mass vaccination clinics or opportunistic vaccination during routine consultations or pharmacy visit for the influenza vaccination season, and have received bioCSL's influenza virus vaccine.

*Inclusion Criteria*

Participants must meet all of the following inclusion criteria to be eligible to participate in this study:

- Receipt of at least one vaccination of bioCSL's influenza virus vaccine after 1 July 2015

AND:

- Capable of understanding the purposes and risks of the study, and
- Are able to provide informed consent, and
- Willing and able to adhere to all protocol requirements, and
- Have access to internet and a personal email address, and
- Have the ability to enter responses into a web-based form themselves, or have a family member/friend/carer who could assist the participant complete the web-based data entry.

OR, where the recipient of the vaccine is less than 16 years of age:

- A parent or guardian who is capable of understanding the purposes and risks of the study and is capable of providing informed consent, and
- The parent or guardian who is willing and able to adhere to all protocol requirements, and the parent or guardian has access to the internet and a personal email address and has the ability to enter responses into a web-based form on behalf of the vaccine recipient.

Where applicable, participant assent will also be obtained if required by the applicable Independent Ethics Committee (IEC) / Institutional Review Board (IRB).

There are no exclusion criteria for this observational study.

## Variables

The table below summarises the types of variables collected for the study.

| **Investigator site participant data** | **Data variables collected** |
|---|---|
| Demographic and baseline characteristics | Age in years, gender, pregnancy status |
| Influenza vaccination information | Prior year influenza vaccination, bioCSL influenza vaccination date for each dose after 1 July 2015, vaccination site for each dose, bioCSL's influenza virus vaccine batch number for each dose after 1 July 2015. |
| Information on other vaccinations received on the same day as or in the 14 days before this year's seasonal influenza vaccine | Other vaccines received during the clinic visit or at previous clinic visits, and the site at which the vaccination was administered. |
| Clinical at-risk indications for complications from influenza | Relevant medical history of conditions placing participants at risk of complications from influenza infection^ |
| Medically attended adverse events | The date, nature of the adverse event, where attended, and outcome will be self-reported, with additional information about the medically attended adverse event to be recorded and/or followed up by the investigator site staff or bioCSL staff, as necessary. |
| **Participant data** | |
| Post-vaccination follow-up | Solicited local, systemic and allergic adverse events for 7 days after each vaccination, with intensity/severity grade |

^ immunocompromising conditions or other chronic illnesses, based on clinical risk groups as defined in the most recent version of The Green Book. Information for public health professionals on immunization. Influenza: The Green Book, chapter 19 [Public Health England, 2015].

## Data sources

Data collection will utilise a mix of investigator site data entry and participant (or parent/guardian) self-reported data entry into a web-accessed electronic database meeting appropriate observational research, regulatory and data protection standards.

## Study size

A total of up to 400 participants will be enrolled into the study, with a target of 100 participants in each age group:

- 5 to < 9 years,
- 9 to <18 years,
- 18 years to <65 years and
- ≥ 65 years.

Additionally, participants less than 5 years of age may be enrolled in the study, if they have inadvertently been administered bioCSL's influenza virus vaccine outside the licensed age indication (5 years and older), or if administered the vaccine deliberately 'off label' by their health care provider.

## Data analysis

### *Statistical Considerations*

A subset of key data will be listed by participant. More detail will be included in the Statistical Analysis Plan (SAP).

In general, summary descriptive statistics of continuous data will be presented as number of observations, mean, standard deviation (SD), median, minimum and maximum. For categorical variables, statistical summaries will include counts and percentages relative to the appropriate population. Two sided 95% confidence intervals will be provided for descriptive statistics, as warranted.

### *Analysis of Adverse Events*

Solicited AEs will be defined as those events specifically sought for and recorded by participants in the 7 day follow-up after the first and second vaccinations. Results will be presented by vaccine dose and by maximum intensity severity grade. The number and

percentage of participants experiencing at least one event for each solicited AE will be presented. In addition, the number of reported AEs will also be summarised.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 18.0) coding system to give a System Organ Class (SOC) and preferred term for each event.

The overall and age-stratified number and percentage of participants reporting solicited AEs (overall, and by severity grade) will be summarized. The 95% confidence intervals (based on the Exact Confidence Interval (CI) method) will also be presented.

Additionally, the frequency and severity of Medically attended (MAEs) occurring within 7 days after each influenza vaccination with bioCSL's influenza virus vaccine will be analysed.

The information outlined above will also be analysed for any instances of inadvertent use of bioCSL influenza virus vaccine in children less than 5 years of age, or 'off-label' administration of the vaccine in conflict with any aspect of the prescribing information contained in the vaccine's Summary of Product Characteristics.

## Milestones

An expedited summary safety report as per the EMA interim safety guidance [EMA/PRAC/222346/2014, Pharmacovigilance Risk Assessment Committee, EMA. April 2014], based on first dose data will be prepared for submission to regulatory agencies. The timing of the conduct of analyses for the expedited safety summary report will be determined in consultation between the Principal Investigator (PI), Sponsor and with regulatory agencies based on progress with recruitment each year. The expedited safety summary report may be based on a snapshot of study data, or a final locked dataset depending on the progress of study recruitment.

A final study report will be produced containing all study data at final database lock, and submitted to regulatory agencies. Additional interim reports may be conducted if requested by regulatory agencies if there is an identified need to review data between the expedited safety summary report and the expected timing of the final study report.