PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Post-authorisation passive enhanced safety surveillance of seasonal influenza vaccines: Protocol of a pilot study in England
AUTHORS	de Lusignan, Simon; Dos Santos, Gaël; Correa, Ana; Haguinet, François; Yonova, Ivelina; Lair, Florence; Byford, Rachel; Ferreira, Filipa; Stuttard, Karen; Chan, Tom

VERSION 1 - REVIEW

REVIEWER	Jorgen Bauwens Brighton Collaboration Foundation, Switzerland
REVIEW RETURNED	25-Jan-2017

GENERAL COMMENTS	* Secondary outcomes are only mentioned in the abstract but are missing in the article istelf. * Consider consistency in age strata: abstract refers to required number of participants according to EMA guidance, i.e. aga strata 18-64 and >=65, while analysis is described to be done in strata 18-65 and >65. * Page 3 line 15: reactionS * Page 3 line 16: (AEI)) * Page 6 line 21: remove bullet * Page 6 line 32: close ( )

REVIEWER	Pedro Moro CDC, USA
REVIEW RETURNED	17-Feb-2017

GENERAL COMMENTS	This protocol describes a pilot for passive enhanced surveillance of adverse events following seasonal influenza vaccines. In general I think the approach to conduct this vaccine safety surveillance project is sound and rational. The methods that would be used are very well explained. I believe it would be of interest to vaccine safety investigators and epidemiologists so I would recommend its publication in BMJ. I have a few questions or comments for the authors: The proposed system would be a passive surveillance system. Passive surveillance systems have several limitations. The authors mention some of the limitations with the proposed system however they need to provide more information on the limitations, some of which may be those typically encountered with passive systems. They also need to point out that with their system they won't be able to study rarer adverse events. The authors state they plan to collect data from EHR and also use a card-based reporting system. My question or comment is, why not collect all medically relevant data using EHR? At least those

	conditions requiring a physician visit? If they can collect all medical encounters or certain pre-specified conditions then you would not call it passive. The use of the card is important because it would enhance the collection of data specially for certain conditions such as injection site reactions, which may go unreported, especially the milder reactions not requiring a medical visit.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
1. Secondary outcomes are only mentioned in the abstract but are missing in the article itself.
R: We have amended this to only include the primary outcomes in the abstract, as is in the main text.

2. Consider consistency in age strata: abstract refers to required number of participants according to EMA guidance, i.e. age strata 18-64 and >=65, while analysis is described to be done in strata 18-65 and >65.
R: We have amended this throughout.

3. Page 3 line 15: reactionS
R: We have amended this.

4. Page 3 line 16: (AEI))
R: We have amended this.

5. Page 6 line 21: remove bullet
R: We have amended this.

6. Page 6 line 32: close ( )
R: We have amended this.

Reviewer 2
1. The proposed system would be a passive surveillance system. Passive surveillance systems have several limitations. The authors mention some of the limitations with the proposed system however they need to provide more information on the limitations, some of which may be those typically encountered with passive systems.
R: The proposed system is actually “Enhanced passive surveillance” as defined by the European Medicines Agency (EMA). This is passive surveillance plus adverse drug reaction (ADR) cards. We agree that more needs to be said about its limitations. Key strengths are:
1. The highly computerised medical records systems used in English primary care maximise the likelihood of reliably capturing the AEIs.
2. Also, Use of customized ADR cards
a. With cards pre-populated with possible AEI categories facilitating the report and coding of events
b. Specific tick box when no AEIs where experienced leading to a reasonably acceptable return rate (48% return rate)
We expect that by enhancing surveillance with a customised ADR card and encouraging patients to directly report their symptoms, we will more reliably detect a greater number of events. The proposed approach is not a standard passive surveillance study, but rather an enhanced approach using ADR cards which is a unique method for influenza safety surveillance. The key limitations are that we cannot detect: (1) Rare events; (2) Differences between brands.

We have updated the limitations to read:

This feasibility study has not been powered or designed to detect rare events or detect significant

statistical differences of adverse event rates across brands.

We have also modified the introduction to make it much clearer that enhanced passive surveillance includes use of ADR cards.

They also need to point out that with their system they won't be able to study rarer adverse events.
R: Whilst the proposed system is one step up from passive surveillance, as specified by EMA, our study is not powered or designed to collect rare adverse events. This is now acknowledged.

2. The authors state they plan to collect data from EHR and also use a card-based reporting system. My question or comment is, why not collect all medically relevant data using EHR? At least those conditions requiring a physician visit? If they can collect all medical encounters or certain pre-specified conditions then you would not call it passive. The use of the card is important because it would enhance the collection of data specially for certain conditions such as injection site reactions, which may go unreported, especially the milder reactions not requiring a medical visit.
R: We will be collecting all medically relevant data from the EHR, which includes the data from the adverse drug reaction reporting cards.

1. In the setting proposed, all information is computerised into the EHR, whether this comes from the medically attended visits or derived from the ADR cards
2. We thought passive surveillance using routine data would result in under-reporting for this vaccine surveillance study. The overarching goal was to use the customised ADR cards in order to improve the report of AEIs, especially for the less serious ones that may not require medical visit.

The comments already added in response to the peer review comments above have answered this point in the paper's text.

We feel this is an important protocol, which sets out the methods to rapidly detect adverse events following vaccination.

Thank you for considering our protocol.