CONFIDENTIAL

Protocol title: European Medicines Agency (EMA) post-authorisation safety study of influenza vaccine

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1. LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AEI	Adverse events of interest
CMR	Computerised Medical Record (system)
DHCMP	Department of Health Care Management and Policy, at University of Surrey
EMA	European Medicines Agency
GP	General Practitioner – A family physician providing NHS care to a registered list of patients
GPSoC	GP System of Choice, range of NHS approved computerised medical record systems that provide the required level of functionality to support primary care delivery
GSK	GlaxoSmithKline Biologicals
HSCIC	Health and Social Care information Centre (source of National data against which denominators and other population data can be checked)
HSCIC ODS	HSCIC Organisation Data Service – system that provides codes for all NHS bodies, including general practices and population data about these bodies
IGT	Information Governance Toolkit – standard set for holding health data
MAH	Marketing Authorisation Holders
NRES	National Research Ethics Service
NHS	National Health Service
PASS	Post Authorisation Safety study
PHE	Public Health England
QOF	Quality and Outcomes Framework
RCGP	Royal College of General Practitioners
RSC	Research and Surveillance Centre (part of RCGP)
REC	Research Ethics Committee
RES	Research and Enterprise Support
SLA	Service level agreement
Surrey	University of Surrey

2. RESPONSIBLE PARTIES

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3. ABSTRACT

Background:
The European Medicines Agency (EMA) has set out new requirements for influenza vaccine safety surveillance that all Marketing Authorisation Holders (MAHs) providing vaccines in the EU must address. The proposed study represents a pilot to explore the use of routinely collected data in the UK to provide timely and relevant information on influenza vaccine safety. UK primary care is highly computerised, though the major suppliers have different data models, coding systems, and methods of data access. Thus, a database approach may not be sufficient to meet the EMA commitment. As such, a sub-study will explore the utility of active solicitation of safety data from vaccinated subjects.

Objective:
To conduct a pilot assessing adverse event of interest (AEI) frequencies among flu-vaccinated subjects using routinely collected data in nine primary care practices. Our primary surveillance is of 7-day AEI, but we will not exclude events recorded outside this window, which will be analysed separately. Three practices will take part in the active surveillance sub-study.

Methods:
We will recruit nine practices representing urban and rural localities across England, and the three major computerised medical record (CMR) suppliers in the UK.

We will extract weekly data, using a method Surrey developed for use in the national surveillance system, to allow passive observation of data; refreshed weekly from participating practices. We will evaluate 7-day AEI frequencies from this data. In three of these nine practices, we will also utilize a more active data collection approach.

This protocol will be submitted to the NHS Research Ethics Committee (REC) for guidance on the necessary approvals for this surveillance, the consent required from patients and their carers, and the access to and use of data for this surveillance.

Expected outcomes:

- Weekly data flow that captures
    - Vaccination coverage by age strata and brand
    - Proportions of patients reporting pre-specified AEIs by age strata and brand
    - An assessment of data completeness and timeliness

This is a pilot study, the results of which will be used to assess the whether the data collected in the study meet the requirements of enhanced safety surveillance as stipulated in the interim guidance issued by EMA in April 2014.

4. PROJECT MILESTONES

Activity	2015											
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Protocol writing												
Contract writing												
Ethical process												
Information privacy process												
Practice recruitment												
Data extraction												
Reporting												

Milestones

Milestone 1
Protocol is completed.
March 2015

Milestone 2
Contract to deliver pilot study is signed.
April2015

Milestone 3
Ethics and information privacy processes are approved.
June 2015

Milestone 4
Practice recruitment is finalised.
September 2015

Milestone 5
Weekly data extraction begins.
September 2015

Milestone 6
Weekly reports are sent to GSK.
November 2015

5. RATIONALE AND BACKGROUND

The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU), located in London. The Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the EU. Part of this responsibility is to coordinate the EU's safety-monitoring or pharmacovigilance system for medicines, monitor the safety of medicines through the EU network, and take action, if information indicates that the benefit-risk balance of a medicine has changed since it was authorised.

In response to a recent expansion of national vaccination programmes in EU member states, the European Medicines Agency has released interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU.[i] This set out new standards for surveillance. The key objective of the EMA enhanced safety surveillance is to rapidly detect a significant increase in the frequency and/or severity of expected reactions (local, systemic or allergic reactions) that may indicate a potential or more serious risk, as exposure to the vaccine increases. The interim EMA guidance provides suggested surveillance methods, but formal communications between Marketing Authorisation Holders (MAHs) and the EMA indicate that there is flexibility around the specifications due to heterogeneity in vaccine coverage, brand distribution, and data collection options across member states.

The present proposed collaborative study between MAH GlaxoSmithKline Biologicals (GSK) and the University of Surrey, is a pilot study which reflects the recommendations of EMA for enhanced safety surveillance. The present study will be conducted by the Clinical Informatics Research Group at the University of Surrey. The primary purpose of the proposed pilot is to explore the potential of routine data to report what is required by EMA and what additional direct data may need to be collected. The results will inform decisions regarding future influenza vaccine safety surveillance activities in the UK.

The Clinical Informatics Research Group, in the Department of Health Care Management and Policy (DHCMP) at University of Surrey is the data and analysis hub for the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC), through a formal data sharing agreement. This work mainly comprises surveillance sponsored by Public Health England (PHE); the data processing, analysis capability, and leadership of the RCGP RSC is based at University of Surrey. The RCGP RSC is the gold standard sentinel network.[ii] The RCGP RSC network of practices has a membership designed to give national coverage of 1.5% of the population. The Surrey team have updated and modernised its information processes.

The most important work of the network is its influenza surveillance; many practices have been involved in this work for decades. Data are uploaded from the network weekly, to a secure sever with the option to switch to twice weekly uploads at time of epidemics. The methods developed

by the University of Surrey throughout its partnership with the RCGP RSC in influenza surveillance will be applied to this in-depth surveillance, with a focus on vaccine safety.

Seasonal influenza vaccines present several specific challenges for pharmacovigilance. These include immunisation in large population cohorts in a relatively short and fixed time period each year, and multiplicity of vaccine products on the market with the need for product-specific surveillance. There are also examples of batch-specific changes in manufacturing specifications during the product life-cycle, leading to unexpected new and emerging reactogenicity or other adverse immune response.

Pharmacovigilance systems for influenza vaccines need capability to rapidly detect and evaluate potential new safety concerns each influenza season. The aim is to mitigate risks before the peak period of seasonal immunisation. The main objective of enhanced safety surveillance is to detect and evaluate a potential increase in product and batch-specific reactogenicity and allergic events in near real-time in the earliest vaccinated cohorts. Enhanced surveillance must also be practicable in realistic clinical settings and administratively feasible every year.

The EMA Interim Guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU suggested that there are three options envisaged for enhanced surveillance:

- *Active surveillance:* Active follow-up of a cohort of children and adults for 7 days after immunisation for reactogenicity endpoints/adverse events.
- *Passive surveillance:* Rapidly estimate vaccine usage and facilitate passive adverse drug reaction (ADR) reporting, in order to derive reporting rate as a surrogate of incidence of the adverse events of interest (AEIs).
- *Data mining* or other use of electronic health record data.

In the UK, in response to the Chief Medical Office's letter published 25 May 2011[iii], the Department of Health recommended that seasonal influenza vaccine should be offered to the following eligible groups of GP patients including:

- All aged 65 years and over.
- All aged six months to 65 years falling in a clinical at-risk group (i.e. chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, diabetes, and immunosuppression).
- People who are in receipt of a carer's allowance, or those who are the main carer of an elderly or disabled person whose welfare may be at risk if the carer falls ill.
- All pregnant women.

Expansion of national vaccination has created a greater need for timely information and reassurance on the balance of risks and benefits for those receiving the vaccines. This

collaborative study is conceived in response to the EMA's call for enhanced safety surveillance. This study will not only formulate a framework for enhanced safety surveillance in the UK, but will also contribute to an EU-wider programme of enhanced safety surveillance for seasonal influenza vaccines.

6. OBJECTIVES AND ENDPOINTS

The proposed in-depth surveillance aims to report vaccine coverage and AEIs from routine data extracted using methods that Surrey now deploys to extract RCGP RSC surveillance data. Clinical data routinely collected as part of clinical consultations in primary care will be extracted from nine GP practices in order to estimate medically attended AEIs. The proposed study will also actively follow a cohort of patients who were exposed to seasonal influenza vaccination for 7 days in three of the nine GP practices using a customised card-based adverse drug reaction (ADR) or alternative data collection system. We will also provide data for use in determining whether or not these approaches are fit for enhanced surveillance of seasonal influenza vaccination by evaluating basic parameters of data completeness and timeliness.

Primary objectives:

- Weekly estimation of vaccine coverage, by age strata, CMO recommendation category, and brand
- Weekly reporting of AEI rates among subjects vaccinated against seasonal influenza, by age strata, co-morbidity and brand, from nine GP practices using CMR data
- Weekly reporting of AEI rates among subjects vaccinated against seasonal influenza, by age strata, co-morbidity and brand, from three GP practices using an active card-based ADR system

Secondary objectives:

- To assess the completeness of vaccination data in the CMR
- To assess the timeliness of vaccination data in the CMR
- To assess the completeness of AEI reporting in the CMR and through ADR card reporting
- To assess the timeliness of AEI reporting in the CMR and through ADR card reporting
- To assess whether the rates of the most frequently reported events are compatible with expectations from published rates in a comparable population

Primary endpoints:

- Patient counts and proportions of total registered patients vaccinated by age strata and co-morbidity, reported weekly and cumulatively by brand (also indicating those for whom brand data are unavailable)

- Patient counts and proportions of vaccinated patients with reported endpoints of interest by age strata and co-morbidity, reported weekly and cumulatively by brand (also indicating those for whom brand data are unavailable)
    - Presentation with fever or other febrile illness
    - Presentation related to local reaction
    - Presentation related to general reaction (fatigue, myalgia, etc.)
    - All other presentations that could plausibly be related to vaccination

Secondary endpoints:

- Proportion of those vaccinated for whom brand data and administration date are available in the CMR
- Mean (and standard deviation), median (and range) of the duration between vaccine administration and vaccination recording in the CMR
- Proportion of subjects, by age strata, given an ADR reporting card who return the completed card during the course of the study
- Proportion of subjects, by age strata, given an ADR reporting card who return the completed card within 14 days of vaccination
- Mean (and standard deviation), median (and range) of the time interval between vaccine administration and AEI reporting in the CMR and using the ADR card-based approach
- Mean (and standard deviation), median (and range) of the time interval between AEI reporting and recording in the CMR
- Incidence rates for the five most frequently reported AEs (where at least 5 cases are reported) reported alongside those available in the literature from a similar population (vaccinated or general population if vaccinated not available) within the same risk period and stratified by age when relevant and possible

7. RESEARCH METHODS

7.1.Study Design

Study setting and population

This pilot project will extract routinely collected primary care data from nine GP practices and an active surveillance approach in 3 of the 9 GP practices to estimate proportions of AEIs among influenza-vaccinated individuals.

The proposed pilot project will actively follow up a cohort of patients in three of the nine GP practices who were exposed to seasonal influenza vaccination in the months between 01/09/2015 and 30/11/2015, by using an existing card-based ADR reporting system, developed by the UK Medicines and Healthcare products Regulation Agency (MHRA). However, this will be customised to have fields that can be readily coded into the GP computerised medical record (CMR) system; and meet the requirements of the EMA. Patients will be issued with the appropriate ADR reporting card and invited to return the card to the GP surgeries after 7 days, but not later than 14 days post-vaccination.

We will look for practices ideally distributed across England (in London, a Northern city, and rural settings in the North and South) and aim to sample purposefully across these locations investigating the different brands of GP CMR systems. It is particularly important, in the first stages, to recruit large practices. We will rank practices based on our assessment of their potential compliance with the protocol requirements. Practices will be reimbursed for their involvement in this study, according to the National Institute of Health Research (NIHR) guidelines.

The average practice size in England and Wales is 7,034[iv], we estimate that data will be collected on a population of approximately 63,300 patients (across nine practices). In the period from September to December 2014, the seasonal influenza vaccine uptake for over 65 year olds was 71.5%; for those in a clinical risk group aged 6 months to 65 years old, the uptake was 48.5%; and for pregnant women, it was 43%. We have estimated influenza vaccine uptake using the coverage estimates published by Public Health England (PHE).[1]

There are a number of GP CMR systems in use; the systems eligible for use in English primary care must be part of GP System of Choice (GPSoC).[2] Practices have a single CMR system, which comprehensively contains data about their registered patients, their illnesses, therapy, and all the aspects of providing General Medical Services (GMS – the standard NHS

[1] Public Health England. Vaccine uptake guidance and the latest coverage data. https://www.gov.uk/government/collections/vaccine-uptake#seasonal-flu-vaccine-uptake

[2] Health and Social Care Information Centre. GP Systems of Choice (GPSoC)http://systems.hscic.gov.uk/gpsoc

primary care provision) or other primary care schema. There are predominantly 3 brands; the market leader is Egton Medical Information Systems (EMIS), followed by The Phoenix Partnership (TPP) SystmOne, and In Practice Systems (INPS) Vision.

These different systems have different data models, and our goal would be to be able to process data from all; in the first year, we would aim to have at least 2 out of these 3 data systems represented in our study, but this is dependent upon the practices that are willing to take part. These information systems broadly adopt 2 coding schemes (Read 2 and CTV3), but slightly different interfaces and preferred terms in the look-up tables. This may produce slightly different level of recording of codes, particularly non-QOF codes (Quality and Outcomes Framework

Ideally, GSK would monitor only GSK vaccines. However, as this pilot study will help inform safety surveillance activities in subsequent years, we will initially collect data on any influenza vaccine administered in the study population. We will then stratify the analysis based on vaccine brand (GSK, 'other', unknown).

Inclusion/Exclusion criteria

As this is a population-based safety surveillance project, all individuals who receive influenza vaccination in the 9 GP practices between 1 September and 30 November 2015 are eligible for inclusion in the analysis. The 30 November cut-off is because EMA is primarily interested in signal detection and safety reporting early in the annual vaccination period. In the 3 practices additionally using the ADR card, this will be given to all subjects vaccinated or, as appropriate, a parent or carer.

In the database analysis, only registered patients who have explicitly opted out of data sharing will be excluded from the analysis. We will identify those opted out in 2 ways: (1) look for opt-out codes within GP information systems where the patients have made an explicit choice to opt out; and (2) post project information in practice websites and waiting areas or GP surgeries to inform patients of the project to give them the opportunity to ask questions and to opt out. In the active surveillance component, AE reporting rates will be stratified by total number of subjects given a card and those who returned the card. All subjects given a card will be included in the denominator when assessing response rate.

Data extraction and management

The method and governance procedure is developed by the University of Surrey in partnership with RCGP RSC and PHE, using an approved provider, Apollo. Alternatively, we will use another approved data extraction supplier, or extract the relevant study data ourselves. Apollo extracts data using the Apollo automated extraction system. Communication is via a SOAP (Simple Object Access Protocol) web service, no special firewall configuration is needed.

Data extractions will be conducted in accordance with the Research Group's standard operating procedures in data extraction, pseudonymisation, and transfer. All data processing and analysis in the present proposed study will be conducted within the secure IT environment of the Clinical Informatics Research Group, at the University of Surrey. The information security policies and procedures of the Research Group have been approved by the NHS Health and Social Care Information Centre (HSCIC). Details of the departmental information governance policies and procedures can be found in:
http://www.clininf.eu/about/information-governance.html

We will only extract coded data, i.e. where the GP or other health professional codes a disease or symptom into the CMR system. The only exception to this are the regime and batch number fields of prescribing data. The latter may be important in identification of brand. The overwhelming majority of the large volume of research that has come out of UK primary care is based on coded data[3]. The richness of primary care data are such that we anticipate being able to detect important AEIs. At a future date, we may do free text analysis; however, ethical approval is difficult to obtain as it may contain personal details. It is not part of this protocol as the ethical approvals could not be obtained in time to begin data collection in 2015**.**

The following routinely collected patient data will be collected for the study:

- Demographic information: age, gender, ethnicity, registered date.
- Postcode: to understand any inequities in access according to level of social deprivation using Geographical Information System (GIS) methods. Full postcodes will be immediately transformed into deprivation scores, using the Index of Multiple Deprivation, within GP computer systems upon extraction.
- Primary care consultations following vaccination, any other markers of health care utilisation, and referral to further care.
- Reactogenicity outcomes of seasonal influenza vaccination as listed in the research literature and any contemporary EU guidance.
- Life-style/risk factors – e.g. BMI, smoking.
- Records of other diseases and long term conditions – e.g. chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, diabetes, immunosuppression, pneumonia, etc.
- Pregnancy.

Once the data are extracted, they are transferred to the custom built Data Warehouse located within the N3 (NHSnet) or for analysis in secure networks that meet the NHS

[3] Kousoulis AA, Rafi I, de Lusignan S. The CPRD and the RCGP: building on research success by enhancing benefits for patients and practices. Br J Gen Pract. 2015 Feb;65(631):54-5. doi: 10.3399/bjgp15X683353.

Information Governance toolkit level 2 standard. Hosting for this data warehouse is by Daisy Group and managed by an established third party provider, Concentra (though we are testing systems that will remove Concentra from the process – with instead these data coming to Surrey). These arrangements may change in the future in accordance with developments in technology.

At the point of the data drop, the data are filtered and proceed through a pseudonymisation package encrypting the NHS number. All data are strongly encrypted by a combination of symmetric and asymmetric encryption algorithms: Triple DES and RSA 1024 before transmission, and utilises public and private key pairs unique to each project. Pseudonymisation is applied at this stage to allow for backwards identification should there be a need to do so as part of an ethically approved study. However, the application of pseudonymisation at this stage also allows the same algorithm to be applied to additional data sources which may be linked data in future years, for example, enabling the linkage of patients' primary care and hospital data without a need to identify a person in the process of conducting this linkage.

A formal service level agreement (SLA) will be established with the volunteer practices, consenting to the use of their routinely collected data for the purposes of vaccine safety surveillance. This data will be extracted, stored, and processed by the team at the University of Surrey, and only aggregated tables will be made available in publications or to third parties.

Data analysis

R Studio within the secure analysis server is the analytical tool of choice for the Research Group. We will interpret coded data by the creation of ontologies that we will map to case-definitions, where available. However, we do not have the in depth descriptions required for case definition found, for example, in clinical trials. We will be inferring meaning from brief clinical coded information; though we have long experience of this and will have the opportunity to confirm with practices and practitioners how to interpret their clinical records.

Statistical analysis will consist primarily of reporting rates and proportions. Confidence intervals will be calculated; however, due to the effects of clustering and practice differences in this relatively small pilot these are likely to be wide.

Safety reporting, including routine pharmacovigilance

This study's primary endpoints are safety-related. However, it will be clearly communicated to participating practices that the study does not replace AEI reporting that would occur as part of routine practice; the reporting within this study is supplemental and their

participation should not alter routine safety reporting practices to either the appropriate authorities or MAHs in any way.

The team at Surrey will review the data submitted weekly as part of the study. If the team at Surrey becomes aware of a serious adverse event (SAE) experienced by a study participant, the SAE should be reported to GSK with 24 hours of awareness. If GSK deems additional information necessary, request of additional information will be sent through the team at Surrey. An SAE is defined as any untoward medical occurrence that:

- Results in death,
- Is life-threatening,
  NB: The term 'life-threatening' in the definition of 'serious' refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, had it been more severe.
- Requires hospitalization or prolongation of existing hospitalization,
- Results in disability/incapacity.
  NB: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza like illness, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Important medical events - events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

7.2 Project management

This study is conducted within the University of Surrey's formal frameworks for information and research governance. In addition, all externally funded projects and collaborative projects with external partners are supported and guided by the University's Research and Enterprise Support (RES) service. RES ensures that university-supported projects are financially viable, and that legal issues of knowledge transfer and intellectual properties are addressed. The project team is supported by IT services dedicated to the Faculty and to the Department of Health Care Management & Policy. Our secure analysis servers are optimised for routine healthcare data processing, to provide faster deliveries for our projects.

The project is accountable to the Project Steering Board, with the day-to-day operational issues managed by the Project Operational team.

Project Steering Board

The Steering Board will meet bi-annually to receive regular and exceptional reports, including reporting of adverse events, from the Operational Team, monitor progress against set milestones, and ensure that resources and support are available to enable the successful delivery of the project within the funding agreement. In the event of a report of adverse incidents, the Project Steering Board will co-ordinate an effective management of the adverse events in line with local and national guidance, and if appropriate, onward reporting to the University, GSK, external partners or external research and information governance authorities.

The Project Steering Board consists of senior academics from the University of Surrey and collaborating universities, a patient representative, senior practitioners involved in the domain of influenza vaccine, and a representative of the GSK of the study.

Steering Board Member (TBD)	Role and Organisation
Prof [redacted]	Principal Investigator, University of Surrey
	Research Representative, GSK
	Domain Expert, GSK
	GP/Practice representative
	Patient Representative
Dr [redacted]	Project Manager, University of Surrey

Project operational team

The operational team is responsible for the completion of the project objectives against set milestones (see Section 5: Project Milestones), and submit regular and ad-hoc reports to the

Project Steering Board. The Team will meet fortnightly in person and/or via teleconference, particularly in the early stages of the project, to ensure the project meets with the milestones agreed for the project.

The Operation Team consists of research staff, the project manager and the Principal Investigator of this project:

Team Member (TBD)	Lead responsibility in the project and organisation
Prof [redacted]	Senior Clinical Lead, University of Surrey
Dr [redacted]	Project Manager, University of Surrey
	Research Representative, GSK
[redacted]	Research Fellow, University of Surrey
[redacted] / [redacted]	Database developer, University of Surrey
Dr [redacted]	Senior Research Fellow, University of Surrey
[redacted]	Research Assistant, University of Surrey

These arrangements are standard University of Surrey research and surveillance governance requirements for projects.

Patient involvement

Patients will be involved in the protocol review from its completion. Their comments will be taken into consideration in the development of the protocol to help ensure its acceptability to patients. A patient representative will be part of the steering committee.

Practitioner involvement

Practices will be recruited from our existing research contacts and networks. We will look for practices purposefully to represent different social groups, brand of computerised medical record systems, and practice size (large practices may have more data extraction challenges).

Peer review of the study plan

The study plan will be sent for peer review by pharmacologists, general practitioners and lay advisors.

8. ETHICAL CONSIDERATIONS

The primary purpose of this study is to work with practitioners, governance experts, and a commercial MAH to develop robust process for the enhanced safety surveillance of seasonal influenza vaccines recommended by the EMA. The proposed study starts with an exploration of routinely collected primary care data from nine volunteer GP practices to assess if the data is fit for the purpose of supporting an enhanced EMA PASS of enhanced surveillance of seasonal influenza vaccination, and to draw conclusions if additional data collection in primary care is needed to meet EMA standards for enhanced surveillance of seasonal influenza vaccination.

The principal ethical issue is concerned with the protection and use of anonymised patient level information for the purpose of surveillance of safety of seasonal influenza vaccination as recommended by the EMA. NHS guidelines specify that a Section 251 approval is required when conducting research using anonymised patient level data, without individual level patient consent; approval is also dependent on the requesting institution meeting specific requirements on information governance, which the University of Surrey exceeds. The protection and use of anonymised patient level information is addressed more fully in the next section: information governance considerations.

The University of Surrey team will seek approval from the University Ethics Review Committee. In addition, the formal opinion of the Proportional Review System of the National Ethics Review Service will be sought regarding the need for NHS Research Ethics Committee (REC) approval. 'Defining Research' (http://www.hra.nhs.uk/documents/2013/09/defining-research.pdf), the National Research Ethics Service (NRES) guidance suggests that surveillance does not require formal review by a Research Ethics Committee. The research team will however seek an opinion from the NRES's Proportional Review system to check if formal approval from a NHS Research Ethics Committee (REC) is needed prior to the commencement of the study, as well as Section 251 approval.[4] If the proportional review suggests that a full NHS REC review is necessary, then applications will be submitted to the REC as well as the Clinical Research Network (CRN) and, if advised, the Confidential Advisory Group (CAG) for formal approval for Section 251 of NHS Act 2006 and Health Service (Control of Patient Information) Regulations 2002 exemptions.

Section 251 of the Health and Social Care Act 2001, allowed the Secretary of State to set aside the common law duty of confidentiality for defined medical purposes. Surveillance is generally taken to be one of the defined medical purposes for which data can be used. As it has not been tested whether the Health and Social Care Act is retrospective data are generally not extracted for periods prior to that Act, without a clear need generally approved by an ethics committee.

[4] Health and Social Care Act 2001. Section 251.
http://www.hra.nhs.uk/about-the-hra/our-committees/section-251/what-is-section-251/

Additionally, we will seek advice from NRES as to whether the individuals who are involved in the active surveillance portion of the study require formal taking of informed consent; or if collecting surveillance data in an anonymised form is acceptable.

9. INFORMATION GOVERNANCE CONSIDERATIONS

The Clinical Informatics Research Group at the University of Surrey has worked with routinely collected healthcare data in a number of research and evaluation projects over the last 15 years. The Research Group works within the research and Information Governance frameworks for health and social care in the United Kingdom, and is compliant with the University's best practice standards. The University of Surrey is registered with the Information Commissioner's Office Data Protection Register, and is compliant with the Data Protection Act, and other legislations.

In addition, the Research Group reviewed its departmental information governance policies and procedures, against the requirements of the NHS Information Governance Toolkit (IGT) for Hosted Secondary Use Team/ Project, Version 12.[5] The review was approved by the Health and Social Care Information Centre, and was deemed satisfactory to support application to Confidentiality Advisory Group or the Data Access Advisory Group.

In line with the principle of the Data Protection Act 1998, data subjects will be informed of the uses of their data in this study. Participating GP practices will be asked to display project information in their website, and project information posters in reception areas, from when the practice has consented to take part in the study and until the study is completed.

The project information will specifically refer to the right of the patients to opt out if they do not wish their data to be included in this study. We will respect the codes in the data indicating that a patient does not wish to have their record available for research; we will, however, seek to report the number of patients within a practice who have chosen to opt out.

No strong patient identifiers (NHS numbers, postcodes, dates of birth, etc.) will be available to GSK, third parties, or in publications. Additionally, no patient level data will be sent to GSK in a way that the individual patient can be re-identified. This may involve GSK being blind to practice identities, and the locality at which any AEI occurs.

[5] Department of Health. Information Governance Toolkit. https://www.igt.hscic.gov.uk/

10. DISSEMINATION AND PUBLIC REGISTER DISCLOSURE

The outputs from the research will be disseminated primarily through peer review papers in high impact journals within the domains of primary care, surveillance, vaccines, and infectious diseases. We will present findings at relevant seminars and conferences.

The University of Surrey, in accordance with GSK policy, will post a summary of the study protocol and results within 12 months of study completion and following review and comment by GSK on GSK's Clinical Study Register, accessible at http://www.gsk-clinicalstudyregister.com and at www.clinicaltrials.gov.

11. SIGN OFF PAGE

For and on behalf of

GLAXOSMITHKLINE BIOLOGICALS S.A.

Date :

Name :

Title :

For and on behalf of

UNIVERSITY OF SURREY

Date :

Name :

[redacted]

Title :
Professor of Primary Care and Clinical Informatics
Chair in Health Care Management, University of Surrey

12. REFERENCES

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13. APPENDIX

Appendix 1

Data extraction is by automated routine as detailed below:

Currently, data are extracted by weekly bulk upload. Apollo extracts data using the Apollo automated extraction system. Communication is via a SOAP (Simple Object Access Protocol) web service, no special firewall configuration is needed.

Once the data are extracted, they are transferred using the above methodology to the custom built Data Warehouse located within the N3 (NHSnet) or for analysis in secure networks that meet the NHS Information Governance toolkit level 2 standard. Hosting for this data warehouse is by Daisy Group and managed by an established third party provider, Concentra. These arrangements may change in the future in accordance with developments in technology.

At the point of the data drop the data are filtered and processed through a pseudonymisation package encrypting the NHS number. All data are strongly encrypted by a combination of symmetric and asymmetric encryption algorithms: Triple DES and RSA 1024 before transmission, and utilises public and private key pairs unique to each project.

Pseudonymisation is applied at this stage to allow for backwards identification should there be a need to do so as part of an ethically approved study. However, the application of pseudonymisation at this stage also allows the same algorithm to be applied to additional data sources which may be linked data in future years; for example, enabling the linkage of patients' primary care and hospital data without the need to identify a person in the process of conducting this linkage.