Study Protocol

Influenza A/H1N1v in pregnancy: An investigation of the characteristics and management of affected women, A/H1N1v vaccination in pregnancy and the relationship to pregnancy outcomes for mother and infant

1 Research Objectives

a) To conduct a systematic review to summarise existing evidence on the effects of influenza and its treatment, demographic and pregnancy characteristics and additional pregnancy management strategies on pregnancy outcomes.

b) To determine:

i) the incidence of influenza A/H1N1v in pregnancy

ii) the effect of H1N1 Influenza infection and/or treatment with neuraminidase antiviral drugs in pregnant women and /or H1N1 vaccination (timing of use, dose and agent) on pregnancy outcome, including specific adverse or beneficial effects of antiviral treatment or H1N1 vaccination on eventual maternal and fetal outcome

iii) the influence of demographic or pregnancy characteristics and additional aspects of pregnancy management on outcomes for mother and infant

c) To produce guidance on the management of H1N1v infection in pregnancy initially following systematic review updated subsequently by monthly review of emerging data from this study such that outcomes for women and infants are optimised during the current pandemic.

2 Existing Research

Influenza infection during pregnancy is associated with adverse maternal and fetal outcomes, including probable increases in the risk of maternal pneumonia and possible increases in risks of certain congenital malformations[1-6]. Recent US H1N1 pandemic experience as well as data from previous influenza pandemics indicates higher morbidity and mortality among pregnant women[7, 8], however, detailed epidemiological studies investigating risks in subgroups of pregnant women and the impact of pregnancy management strategies on outcomes are currently lacking

The neuraminidase inhibitors oseltamivir and zanamivir are effective for prophylaxis and treatment of H1N1 influenza. Neither is licensed for use in pregnancy, but current UK guidance recommends use in pregnancy when indicated. Oseltamivir is an oral treatment *with* limited transplacental bioavailability. Approximately 150 outcomes have been reported following oseltamivir exposure during pregnancy and provide no evidence of specific harms.[9, 10] Because of this, in the USA and Canada, oseltamivir is recommended as first line treatment in women with established H1N1 infection and for prophylaxis. Zanamivir is an inhaled treatment and the amount crossing the placenta is therefore small. For this reason it is preferred in the UK as the first line option in pregnancy, although experience of use in pregnancy is

limited, with only 4 cases published and a further 50 reported to regulatory authorities.[10-12] UK guidance also acknowledges that the benefits of oseltamivir outweigh potential risks during pregnancy.

This inconsistency in guidance between the UK and USA/Canada arises from the paucity of data on the safety of these antiviral drugs during pregnancy, especially relating to zanamivir. The data available are inadequate to exclude a clinically important increase in risk of congenital malformation or neonatal problems. This research is therefore designed to collect further experience of neuraminidase use in human pregnancy on which to base future guidance. The anticipated increase in numbers of cases of H1N1 in the second half of 2009 offers a unique opportunity to collect these data.

H1N1 influenza vaccination

There are currently two vaccines for H1N1 influenza available in the UK; Pandemrix® and Celvapan®. Pandemrix® is adjuvanted with AS03 (squalene, DL α tocopherol, polysorbate 80) and contains thiomersal (a mercury containing compound) as a preservative. Celvapan® is unadjuvanted and does not contain thiomersal. There are no specific safety data on the use of adjuvanted vaccines in pregnancy.

A study from 1973 of over 2000 pregnant women who received influenza vaccine demonstrated no associated adverse fetal effects.[13] There is no evidence of risk from vaccinating pregnant women, or those who are breast-feeding, with inactivated viral or bacterial vaccines or toxoids.[14] Expert scientific advice is clear that thiomersal-containing vaccines do not present a risk to pregnant women or their offspring, however published studies on the use of thiomersal containing vaccines in pregnancy are limited.

The Department of Health, UK has recommended that all pregnant women should be vaccinated as they are at increased risk of complications from swine flu. JCVI recommended that pregnant women should be given Pandemrix since a one-dose schedule with this vaccine appears to generate adequate levels of antibodies and thereby confer more rapid protection than would be afforded by a two-dose schedule. Once again, however, guidance as to which vaccine to recommend in pregnancy differs between countries, highlighting the lack of data regarding efficacy and safety of these vaccines in pregnant women.

2.1 Justification for research proposal

Preliminary data, particularly from the United States and Mexico, suggest that pregnant women are more susceptible to complications of influenza A/H1N1v infection[15, 16], and worldwide data suggest that younger people, including women of reproductive age are at increased risk of infection. This research will identify, through two existing reporting systems, the UK Teratology Information Service (UKTIS) and the UK Obstetric Surveillance System (UKOSS), all pregnant women hospitalised with confirmed influenza A/H1N1v in the UK, as well as pregnant women with the illness or requiring prophylactic antiviral therapy in the community. We will collect information on their demographic and pregnancy

characteristics as well as management, including use, mode and timing of any antiviral therapy. In addition, we will collect data on the incidence of complications of both influenza and pregnancy, and the outcomes for both women and their infants. We will investigate the relationship between demographic, pregnancy characteristics, management and outcomes in order to generate immediate recommendations for changes in practice to improve outcomes for this vulnerable group.

Data on pregnant women exposed to neuraminidase inhibitors is currently being collected by UKTIS as part of a routine surveillance program commissioned by the Health Protection Agency. Voluntary reporting is, however, known to under ascertain cases. Ascertainment of such cases is reliant on ad hoc reporting by busy health professionals who are primarily requesting advice. Studies using these data are therefore subject to case selection bias and are insufficient to enable scientifically valid conclusions to be drawn regarding the effects of H1N1 infection and/or neuraminidase inhibitor treatment in pregnancy on maternal and fetal outcome. At present, follow up of selected cases only is possible.

UKOSS is an existing network of collaborating obstetricians, midwives and obstetric anaesthetists in all 226 hospitals with consultant-led maternity units in the UK, through which selected studies of severe complications of pregnancy can be conducted[17]. The system has been used to conduct a number of studies of severe morbidities, resulting in improvements in the care of pregnant women throughout the UK[18-23]. The current paper-based system, however, does not allow a sufficiently rapid response to collect data for rapid analysis and production of guidance for clinical management of H1N1v infected women in the current pandemic.

We propose to extend these systems to allow rapid web-based reporting and analysis, together with conducting follow-up and testing of women with suspected influenza infection in pregnancy, to allow us to develop guidance on the management of H1N1v infection in pregnancy and hence improve outcomes for women and their infants.

Vaccination of pregnant women may significantly alter the impact of AH1N1v infection during pregnancy for the remainder of this pandemic, and hence our study period. Information about the AH1N1v and seasonal influenza vaccination status of pregnant women is thus paramount to interpreting the data collected on AH1N1v Influenza and antiviral use during this study. Furthermore, GSK and Baxter (manufacturers of the AH1N1v vaccines available in the UK) are under obligation to the EMEA (European Medicines Agency) to collect data on the effects of AH1N1v vaccination in pregnancy and have approached UKTIS to establish a registry of AH1N1v vaccination in pregnancy in order to collect this data. Given that we are already collecting information on swine flu and its treatment

in pregnancy, and that vaccination against swine flu may impact on the findings of our research, extension of the study to include collection of data on AH1N1v vaccination in pregnancy will enhance our study.

3 Methods – Systematic review

3.1 Research question

How is influenza H1N1v managed in pregnancy and what factors influence disease outcome for mother and infant?

3.2 Search strategy

A literature search will be performed to identify reports of influenza infection and/or treatment with the neuraminidase inhibitors oseltamivir or zanamavir during pregnancy using MEDLINE and EMBASE databases, as well as web search engines. Search terms will include pregnancy, influenza, neuraminidase inhibitors, oseltamivir and zanamavir in various permutations. Further data on H1N1 and neuraminidase inhibitor exposure in pregnancy will be ascertained by personal communication with manufacturers and non-UK teratology organisations including the European Network of Teratology Information Services (ENTIS), European Teratology Society (ETS), Organization of Teratology Information Specialists (OTIS, USA), and Motherisk (Canada).

Studies will be included if these include cases or case series of influenza or antiviral exposure in pregnancy and where data on maternal or fetal outcome has been collected prospectively.

3.3 Outputs

Included studies will be reviewed to identify factors influencing the outcomes of H1N1v infection in pregnancy for mother and infant. The results will be used to develop guidance for clinicians to improve the management and outcomes of infected pregnant women.

4 Methods – cohort study

4.1 Research design

This will be a prospective observational cohort study using several different sources to identify women in order to conduct a comprehensive national study. Information about pregnancy management and outcomes will be collected directly from heath professionals caring for infected women in secondary care settings and from health professionals as well as women themselves, with consent, where infection is managed in a primary care setting.

4.2 Identification of infected women

The cohort will be all pregnant women in the UK identified with confirmed or suspected influenza H1N1v , who have been offered treatment with antiviral medication (e.g. as prophylaxis) or who are offered immunisation against AH1N1v. The denominator population will be all women giving birth in the UK. The cohort will be identified through the following sources:

i. The UK Teratology Information Service (UKTIS). Women will be notified by health professionals when clinical advice is sought from the service, by means of a dedicated Swine Flu reporting line (0191 2606197) and also through a reporting form available for download from the UKTIS website (Appendix 1). Women will be asked for verbal consent for their contact details and initial clinical information to be provided to the research team. This information will then be passed to the research team by telephone, secure fax or where neither of these options is possible by post.

ii. Active notification with null reporting to UKTIS by research midwives through the Reproductive Medicine and Childbirth Research Network and a cohort of GP practices that have agreed to undertake pandemic flu research at short notice through the primary care network. It is anticipated that these practices will provide complete case ascertainment for the accurate estimation of incidence in their practice populations.

iii. The HPA Regional Microbiology Laboratory Network will alert clinicians who have sent specimens to the fact that the study is taking place and will ask them to seek consent for patient details to be provided to the research team

iv. Self reporting by patients to UKTIS via a dedicated patient reporting telephone line and a novel secure website that allows women to enter their details directly onto an online form designed to facilitate easy, rapid and accurate input of data into a database, hence reducing research staffing demands.

v. Active negative surveillance through the UKOSS collaboration of over 700 reporting obstetricians, midwives and anaesthetists in all 226 consultant-led maternity units in the UK through a new web-based reporting system.

Health professionals will be made aware of the study through the research networks, via information on the NPIS on-line database TOXBASE® and the UKTIS website and via advice provided on H1N1 influenza by the HPA. Eligible women will be made aware by information in antiviral distribution centres and via the UKTIS website.

4.3 Virological confirmation of H1N1

Details of pregnant women who have not been tested for H1N1v in a diagnostic setting will, with their consent, be forwarded to the HPA virology laboratory North East. Women recruited to the study who have not already had this will undergo H1N1 testing. This will be arranged by provision of a self administered swabbing kit by post from the UKTIS research team. This will be enclosed with the initial participant information sheet and consent forms. The self swabbing kit for H1N1v testing is already validated and is currently used by NHS Direct in conjunction with the HPA Centre for Infections (CFI). The kit comprises of 2 viral swabs, an instruction leaflet for patients explaining how to obtain optimal samples and a prepaid

envelope with the necessary transport tubes for return of the sample to the virology laboratory. This method of approach is important because reliability of identification of influenza viruses from nasal swabs is highest within 3 days of symptoms. Current routine practice in the UK entails collecting both a nasal and nasopharyngeal throat swab to optimise H1N1 diagnosis. Given the known difficulties of obtaining informative throat swabs by self testing, a nasal swab from each nostril will be requested instead. This is thought to achieve an equivalent diagnostic yield. Swabs returned through research testing will be processed immediately by the HPA virology lab in Newcastle to extract and store total nucleic acids. H1N1 testing will then be carried out at a later date in batched runs to minimise staffing and consumable costs. Testing including extraction, amplification and detection will be performed in accordance with the national standard operating procedures (SOP) for detection of H1N1v. Samples needing additional testing to clarify status will be referred to CFI, Colindale London.

It will be made clear to the patient that not all viral samples collected as part of this research will be analysed for H1N1 and that where testing is performed there is no guarantee that these results will be fed back to the patient or their referrer.

4.4 Data collection

1. Women identified by their health professionals or identifying themselves to the research team will be sent the participant information sheet and consent documentation, together with an initial data collection sheet that they are asked to complete if they agree to take part (Appendix 2). The GP/midwife reporting will be asked to alert the research team should the status of the patient change after initial notification, to avoid the small risk of contacting individuals who may have died. Four weeks after initial contact further information is sought from the participant (Appendix 3) and health professional (Appendix 4). If the patient has recovered, the next follow up will be of maternal and pregnancy outcome two weeks after birth, again collected from patient (Appendix 5) and health professional (Appendix 6). The final follow up questionnaire will be to request information on the baby's health at six months of age (Appendix 8). Patients who remain unwell from influenza will be followed up at four weekly intervals (using the forms in Appendices 3 and 4) until recovery and as above, four weeks after the estimated delivery date. The final follow up questionnaire will be to request information on the baby's health at six months of age (Appendix 8).

For practices that are not associated with a research network, the GP or midwife will identify participants and provide follow up information available from the medical records on two occasions (four weeks after the initial illness/exposure and after delivery). Consent and recruitment will be performed by the research team at UKTIS. For patients identified by the Primary Care Research Network or the Reproductive Medicine and Childbirth Research Networks, identification, recruitment, consent and follow-up may be delivered through GPs or research midwives. Anonymised details of patients declining participation will also be notified to UKTIS (Appendix 6) to allow accurate estimation of incidence. The details of research network involvement are currently being finalised.

Patients will be offered the opportunity to report additional illnesses, exposures or complications during their pregnancy at any point as well as at the planned follow up intervals through the a novel web-based reporting system, or by telephone. If a completed data collection form is not received back by UKTIS after three weeks, a further reminder will be sent out.

2. Nominated UKOSS reporting clinicians will be asked to report all pregnant women with confirmed or suspected H1N1v infection admitted to their unit. In view of the need for rapid and ongoing data analysis and production of guidance, we will set up a specific web-based rapid reporting and data collection system for this study to enable UKOSS nominated clinicians to report cases as they occur. In addition, nominated clinicians will be sent a standard UKOSS reporting card each month to further enhance case ascertainment. On receiving a case report, the central team will ask the clinician to complete an electronic data collection form, asking for further detailed information about diagnosis, management and outcomes. Women will be identified using a unique UKOSS number supplied by the central team. If a completed data collection form is not received back by the central team after three weeks, a further reminder will be sent out. If there is still no response after a further three weeks, the clinician will be contacted by telephone.

4.5 Identification of comparison women

Information about comparison women managed in hospitals will be obtained from previously collected UKOSS data. The UKOSS database contains detailed demographic, pregnancy and delivery information about a cohort of over 1200 women giving birth in the UK identified from the same hospitals as cohort women. Comparative information on several thousand women exposed to other medicines during pregnancy is available from the UKTIS pregnancy outcome register.

4.6 Monitoring ascertainment

The Confidential Enquiry into Maternal and Child Health (CEMACH) will be contacted at the end of the study and provided with information on cases of maternal or perinatal death in association with influenza in pregnancy, identifying the hospital and date of death. They will be asked to compare the cases they have identified with cases reported through UKTIS and UKOSS.

Ascertainment in primary care will be studied by comparing recruitment nationally with that achieved by network-associated practices reporting intensively.

4.7 Study Size

The primary objective of this study is to determine the incidence of H1N1v infection in pregnancy. The study size will therefore be dependent on the infection rate among pregnant women, together with the UK maternity rate (currently 760,000 maternities per year). With the limited available data, we anticipate

identifying 500-1000 affected pregnancies during the 6 month initial study period. Information on 1200 comparison women is available from existing UKOSS data. A study of this size will have 80% power at the 5% level to detect a doubling of the risk of any adverse outcome (severe maternal morbidity or mortality, preterm delivery, congenital malformation or perinatal death) in women with influenza or treated for influenza compared with comparison women.

4.8 Statistical Analysis

Incidence rates with 95% confidence intervals will be calculated and outcomes (maternal death, other major complication, preterm birth, congenital anomaly, perinatal death) compared between women with influenza and comparison women. Odds ratios with confidence intervals will be calculated and adjusted for confounders (age, parity, marital status, ethnicity, smoking status, socioeconomic status, previous preterm delivery, previous perinatal death) using logistic regression. In addition, outcomes will be explored in different subgroups according to demographic and pregnancy characteristics, timing, agent and dose of antiviral treatment, the use of additional treatments in pregnancy, timing and mode of delivery.

4.9 Outputs

The study data will be analysed on an ongoing basis in order to update guidance for management of women with H1N1v in pregnancy on a monthly basis.

4.10 Consent

4.10.1 UKTIS/UKOSS data collection from health professionals

All data collection will either involve anonymised information or will be performed with patient consent. In order to describe the incidence of H1N1v in pregnancy, some data must be collected on ALL cases occurring in the populations in which an accurate estimate of incidence is being made. These are (a) hospital inpatients and (b) people with swine flu infection or exposure identified in the community via specific research network practices. It is not practicable to obtain individual patient consent for all patients. Some potential participants will decline to participate, which may lead to a biased estimate of incidence. Therefore there is a need to pass some anonymised information to the research teams without consent.

Recruitment in the community (UKTIS):
For patients identified in the community, verbal consent will be sought by the responsible health professional for the provision of personal identifiable information to UKTIS, to allow an approach for written consent to participation. In practices where incidence is being measured (i.e. Sentinel Practices), anonymised information will be provided about patient characteristics for women who decline to give verbal consent. These practices will be expected to fax a report to UKTIS on a weekly basis, including ‘null

reporting' if no cases have been identified for that week. Subsequently, only women in the community providing written consent will be asked to provide further health information.

UKTIS is permitted to store patient data on the existing database under Section 60 of the Health and Social Care Act 2001 to enable surveillance and follow up of pregnancy outcomes of cases where exposure to a potential teratogen in has been reported. This data is obtained from health care professionals involved in the patient's care. UKTIS does not offer counselling or advice directly to members of the public.

Recruitment in hospitals (UKOSS):
The hospital based component of the research is a non-interventional (descriptive) study only. UKOSS collects only anonymised information and accordingly the central team will not seek to collect any names, addresses, dates of birth, hospital or NHS numbers in order that none of the participants are individually identifiable. Duplicate cases will be identified by comparing a woman's year of birth, reporting hospital and expected date of delivery and follow-up with reporting clinicians. Patients will be managed by their usual clinical team and will receive the usual management for their hospital of delivery. Information will be collected from the clinical team responsible for each patient after the initial diagnosis. The management of each woman participating will not be altered in any way by participation in the study. The anonymised information will be used to calculate incidence rates and identify means to further improve patient care. This UKOSS methodology has received the approval of the London Multi-centre Research Ethics Committee (study reference 04/MRE02/45). The National Information Governance Board (formerly Patient Information advisory Group, PIAG) has judged that collection of information only, for the purpose of studying incidence and identifying means to improve patient care, which is not individually identifiable and does not lead to any change in management for the individual patient is acceptable without requiring individual patient consent[24].

4.10.2 Patient testing and follow-up

Women self reporting or reported through their GPs will be provided with written information about the study, and will be given the opportunity to discuss any concerns they may have or to ask questions about the study. For most participants, these discussions will be by telephone with the research team at UKTIS. In some network-associated practices, informed consent may be obtained directly by local health professionals. Potential participants will be made aware that participation in the study is voluntary, that they may withdraw from the study at any point and that these decisions will not affect their routine clinical care. It will also be made clear at the point of enrolment that 1 in 7 pregnancies miscarry and 2 to 3 out of every 100 children are born with a birth defect, and that the study does not imply that influenza infection and/or antiviral treatment during pregnancy is causative of either of these outcomes.

The GP/midwife will be asked to alert the research team should the status of the patient change after initial notification, to avoid the small risk of contacting individuals who may have died. Similarly, pregnancy outcome will be confirmed through the GP practice or obstetric unit involved before contacting the patient regarding pregnancy outcome.

H1N1 testing will be offered on a research basis to women who have not been tested as part of their routine care. Women will be advised that not all swabs will be analysed, and that the test result will be used for research purposes only, and not to inform individual patient clinical care. There will be no guarantee that the result of these tests is fed back to the participating women or their referrer, or of a timescale within which testing will occur. Consent will be sought to store the sample for future tests to further characterise influenza viruses that may be present.

All advertising of the dedicated participant's telephone line will clearly state that the service is purely to enable women to self-report influenza or antiviral exposure in pregnancy and will not offer a medical assessment or give advice. A pre-recorded message at the start of the call will direct callers who are seeking medical advice to NHS Direct (England and Wales) or NHS 24 (Scotland).

5 Project timetable and milestones

5.1 Timetable

Aug-Sept 2009	Obtain necessary approvals, develop web-based reporting systems
Sept 2009	Systematic Literature Review
Sept 2009 −Jan 2010	Data collection.
Oct 2009−Feb 2010	Ongoing data analysis, production of management guidance and dissemination.
Nov 2009	Commence data collection on AH1N1v vaccination
Jan-Feb 2010	Report– outcomes of H1N1v infection in pregnancy
April 2010 – Feb 2011	Ongoing data collection on infant outcome at six months
Feb – April 2011	Data analysis and report of outcomes for A H1N1v vaccination in pregnancy

5.2 Milestones

Sept 2009	Approvals completed, data collection commenced
Oct 2009	Systematic Review completed, first guidance for clinicians
Nov 2009	First data analysis, revised guidance issued
Dec 2009	Ongoing data analysis, revised guidance issued
Feb 2010	Final report and guidance: Management and outcomes of H1N1v infection in pregnancy

6 Expertise

The research team has the necessary expertise to carry out this comprehensive national study, including clinical pharmacology and pharmacoepidemiology (SHLT), teratology (SHLT, LY, SS), public health (ELF, MK, JK), systematic reviewing (MK, JK, PB), congenital malformations (JK) perinatal epidemiology and statistics (MK, JK, PB), obstetric surveillance (MK), guideline development (JK, PB) and obstetrics (PB).

UKTIS is experienced in this type of research; it is actively providing information on antiviral use during the current H1N1 pandemic and has drafted national guidance for management of H1N1 infection or exposure during pregnancy. This guidance already prompts health professionals to report affected pregnancies to UKTIS. The infrastructure is thus already in place for recording pregnancy details and fetal outcomes collected by letter or telephone, as are the necessary ethical approvals for the relevant databases and current methods of data collection.

The National Perinatal Epidemiology Unit (NPEU) has a national and international reputation for conducting studies which change policy, influence practice and improve the care of women and their babies. MK developed and launched UKOSS and led the initiative from its inception; since its establishment in 2005, UKOSS has generated evidence to improve prevention and management of a range of severe pregnancy complications in the UK involving a network of over 700 collaborating clinicians at 226 hospitals throughout the UK. The infrastructure is thus in place to allow rapid identification of women hospitalized with H1N1 infection in pregnancy through an established active surveillance system.

In addition the project benefits from a wide range of collaborations. The study will be co-adopted by the Reproductive Health and Childbirth Network and the Primary Care Research Network. It has been discussed with both National leads of the Reproductive Health and Childbirth Network (Prof Steve Robson and Prof Steve Thornton) and Prof Wallace of the Primary Care Research Network. Each network will be involved in recruitment, and the subsequent consent and follow up of any patients accrued within the respective network. Collaboration with the HPA Virology Laboratory North East (Prof John McGee, Dr Manoj Valappil, Dr Andrew Sails) to undertake H1N1 testing on a research basis, provide expert virological opinion and act as lead laboratory of the HPA Regional Microbiology Laboratory Network (RMN) on this study has been agreed. The feasibility of a postal self testing system for H1N1 has been fully considered and discussed with the HPA laboratory in Colindale who are currently operating such a system for community influenza surveillance and who have agreed to share their expertise in this area. Links with the RMN will also ensure that any H1N1 positive samples are forwarded to Colindale for further analysis according to current surveillance practice, and that swabs for which an equivocal result is

obtained are also tested by one of the other HPA laboratories in order to ensure an accurate result and continue monitoring of possible viral mutation.

Dr Phillip Bryan of the Medicines and Healthcare Regulatory Agency (MRHA) will provide expertise on interpreting adverse reactions reported during this study, and assist with supplying information on adverse reactions associated with neuraminidase exposure in pregnancy reported via the MRHA.

Collaboration with non-UK Teratology organisations including the European Network of Teratology Information Services (ENTIS), European Teratology Society (ETS), Organization of Teratology Information Specialists (OTIS, USA), and Motherisk (Canada) will be formalised if the study is funded with a view to producing a meta analysis of the data collected by each of these centres.

Lastly, access to information on background congenital abnormality rates for the period of this study will be obtained from the British Isles Network of Congenital Anomalies Registers (BINOCAR) in collaboration with Dr Judith Rankin who also has extensive expertise in maternal and perinatal health.

We informed the manufacturers of both Oseltamivir (Roche) and Zanamivir (GSK) of our proposed study and are keen to work effectively with them on this project.

7 Service users

Within the timescale of the current pandemic, extensive consultation with service users has not been possible during the development of the project protocol. The planned project has been discussed with the NPEU advisory group, which includes both lay and professional representatives, and, if funded, lay representatives from UKOSS and UKTIS Steering Groups will be consulted about the development and acceptability of information and other materials.

8 Justification of support requested

The additional resource specified from the University of Newcastle is being sought for (a) additional information scientist/nursing staff for systematic review and to allow the logging and processing of data (1 wte, 6 months, £24k) (b) the development of a website to allow patients to enter and edit their own data directly (£14k), (c) funds to cover travel and administrative costs for collaborative work with other European Centres (£5k) and (d) Further publicity of the study with relevant health professionals (£5k) (e) statistical analysis costs (£5k). Note costs are approximate and include overheads.

At the time of submission of our expression of interest, H1N1 testing had been routinely carried out on all patients with suspected swine flu. As a result of the subsequent move from the containment to treatment phase by the Department of Health, diagnosis of H1N1 influenza is being made on clinical grounds. With the approach of autumn, it will become increasingly difficult to accurately differentiate between cases of

H1N1 and seasonal flu using clinical markers only. A further £30k is therefore being sought for H1N1 testing on a research basis.

Costs from the University of Oxford are sought to cover administration of UKOSS data collection (£4.5k), programming and database management (£3.5k) and website design (£3k). In addition, funds are sought to cover the data analysis and clinical guidance development and review (£15k) together with printing and mailing of monthly cards and data collection forms, telephone and stationery costs (£2k). Estates and indirect costs are sought at the standard University rate.

Please note that this proposal is the result of a collaboration formed after each organisation had submitted separate expressions of interest for the call for research, both of which were shortlisted for submission as full proposals. The costs included therefore reflect the combined costs of the two projects, and therefore show an increase over the amounts in both the individual expressions of interest (submitted by Prof Thomas and Dr Knight), although we have been able to make cost savings by combining the projects as well as enhancing the scope of the proposed research.

NHS Service support costs are requested to cover clinician time completing the data collection forms, providing women with study information and obtaining consent to participate.

No additional funding for the protocol amendments is being sought from the NIHR. GlaxoSmithKline (GSK) and Baxter have agreed to provide resources for the AH1N1v vaccination arm of the study via the Newcastle Hospitals NHS Foundation Trust. This additional funding will be used to employ an additional information scientist for processing of data and producing reports; a study administrator; funds to cover postage, administrative costs, further advertising of the study and stationary; statistical analysis costs and funding to update the database with the additional data fields and to produce six month infant follow-up forms.

The CLRN have agreed to provide the required NHS Service Support costs for the requested protocol amendment.

9 Research Ethics Committee Approval

The original proposal was given favourable opinion by the County Durham and Tees Valley 1 Research Ethics Committee.

The protocol amendment relating to AH1N1v vaccination in pregnancy has been submitted for ethical review.

10 Project Management

The overall conduct of the study will be monitored by a Management Group consisting of the Co-Applicants, Information Scientist, Researcher, Project Programmer, Statistician and other external members as considered necessary for the project.

11 Research Governance

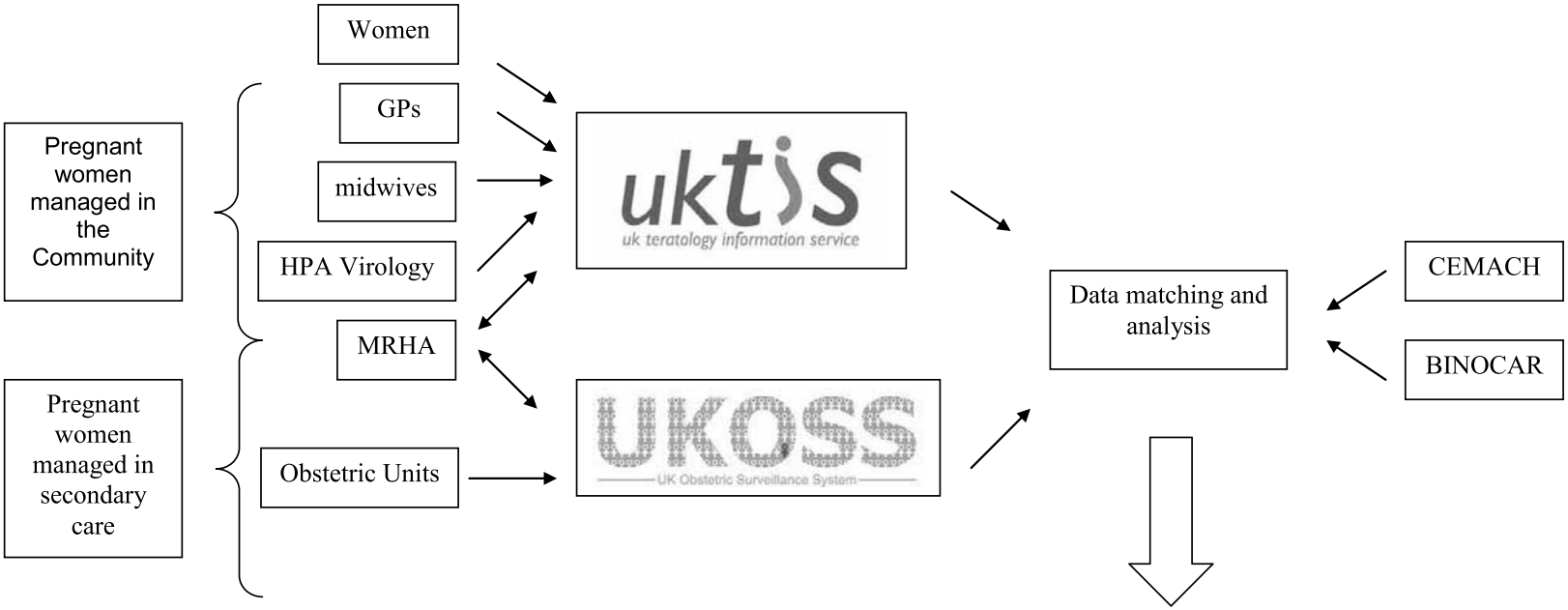
The Newcastle Upon Tyne Hospitals NHS Trust has agreed to sponsor the study.

12 Dissemination and publication

It will be important to feedback the outcomes of the study to the clinicians who participated in providing information. This will be done through monthly guidance for management and a final report. The results will also be reported to the Scientific Advisory Committee of the RCOG, the Royal College of Midwives, the Royal College of General Practitioners and the Obstetric Anaesthetists Association. In the academic arena, the findings will be presented at specialist conferences, such as the British Maternal and Fetal Medicine Society and the Annual Conference of the Faculty of Public Health. The findings of this study will also be submitted for publication in peer-reviewed journals such as the British Journal of Obstetrics and Gynaecology. The NPEU reports directly to the UK Department of Health and has a distinguished record for influencing health policy both in the UK and worldwide.

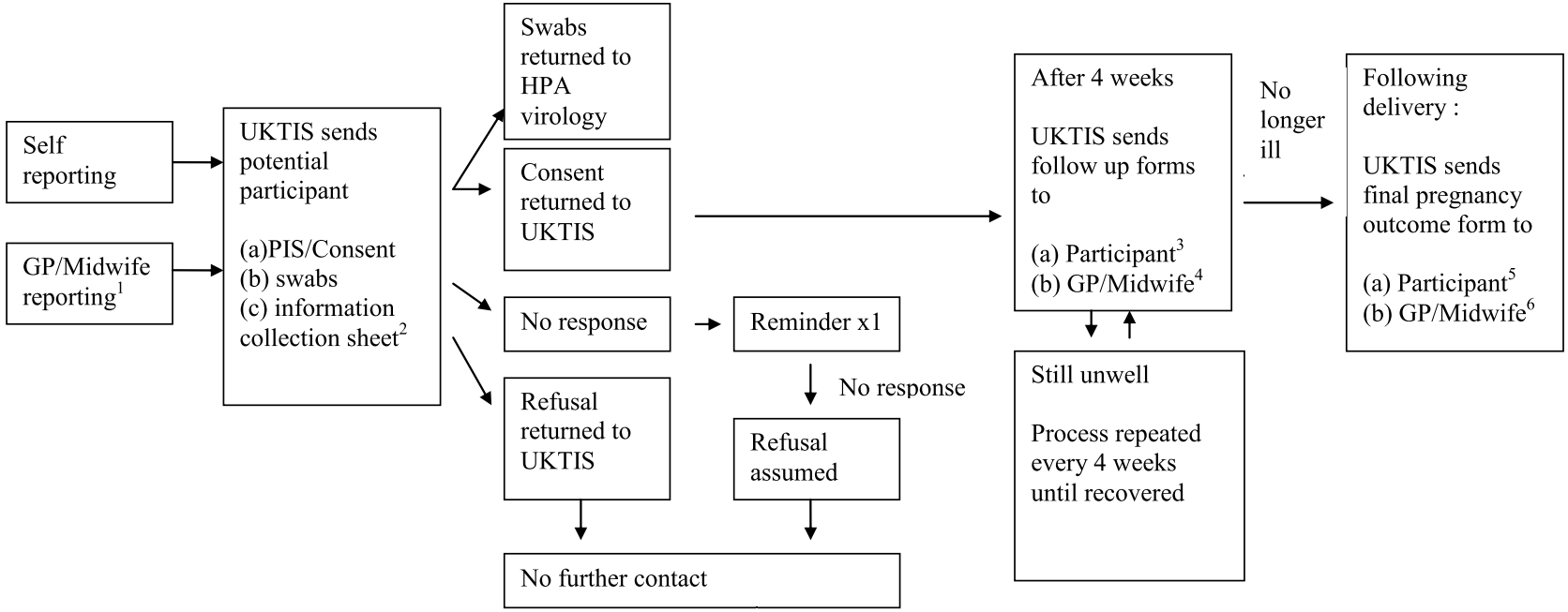
13 Flow Diagrams

(a) Overall study structure



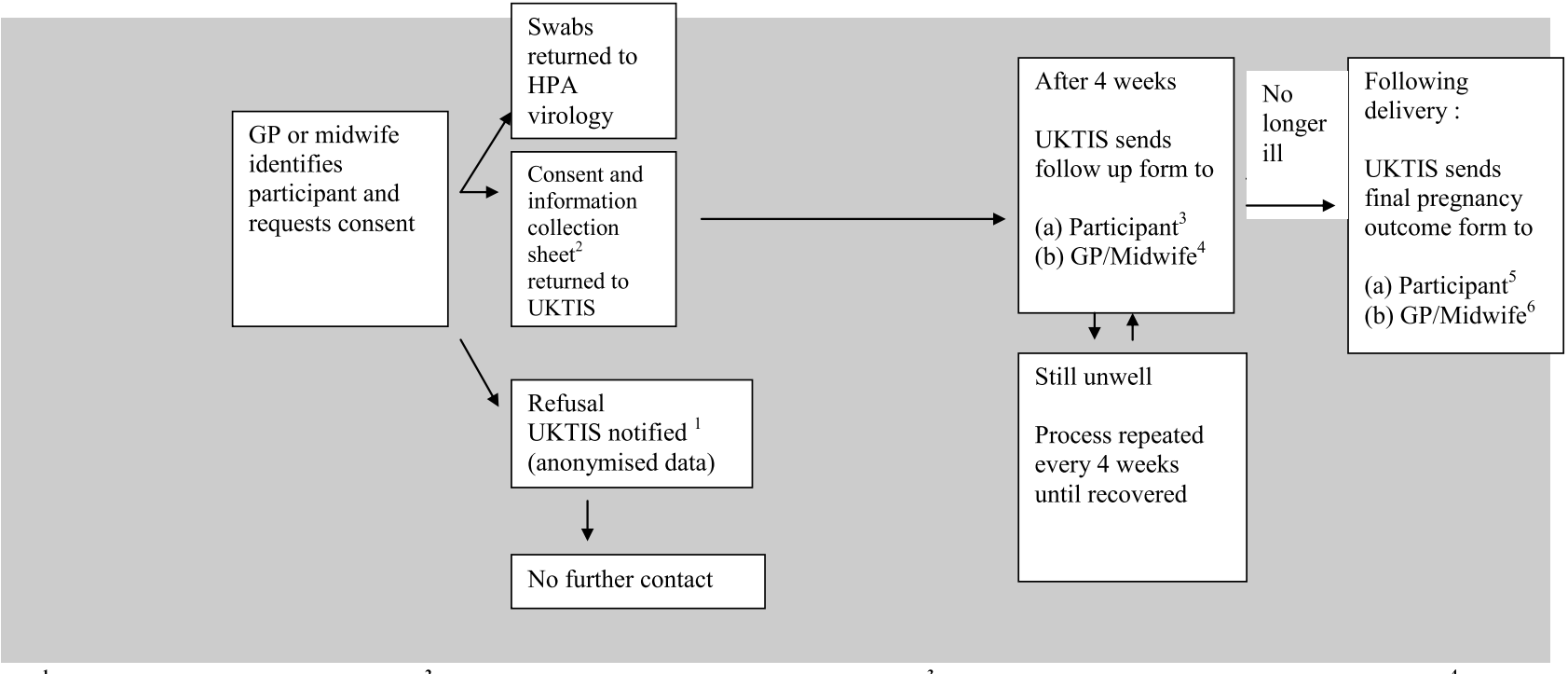
- **Oct 09 – Dec 09 Monthly review of emerging data to produce guidance on H1N1 management in pregnancy**
- **Feb 2010: Final report and guidance: Management and outcomes of H1N1v infection in pregnancy**

(b) Non-network recruiting in primary care



[1] Notification made using "UTKIS Antiviral Exposure in Pregnancy – Patient Reporting Form" (Appendix 1), [2] Initial information collection sheet - participant[Appendix 2], [3]Four week update form – participant [Appendix 3], [4] Four week update form – health professional [Appendix 4], [5] Final pregnancy outcome form – participant [Appendix 5], [6]Final pregnancy outcome form – health professional [Appendix 6]

(c) Network recruiting in primary care (provisional)



[1] Declined consent form (Appendix 7), [2] Initial information collection sheet [Appendix 2], [3]Four week update form – participant [Appendix 3], [4] Four week update form – health professional [Appendix 4], [4] Final pregnancy outcome form – participant [Appendix 5], [5] Final outcome form – health professional [Appendix 6]

14 References

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