

Influenza protocol vaccine amendment V3 07JAN2011**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 malformations¹⁻⁶. 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 conducted¹⁷. 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 UK¹⁸⁻²³. 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 health 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 **with a new participant recruitment covering letter. Before we initiate additional contact with participants, we will contact GPs to ask them to alert the research team**

to any women for whom additional contact may not be appropriate, for example those that might be unduly distressed by such an approach, ,e.g. due to adverse pregnancy outcomes . These women would not be contacted by the research team.

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 consent²⁴.

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 – Sept 2011	Ongoing data collection on infant outcome at six months
Aug 2011 – Oct 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

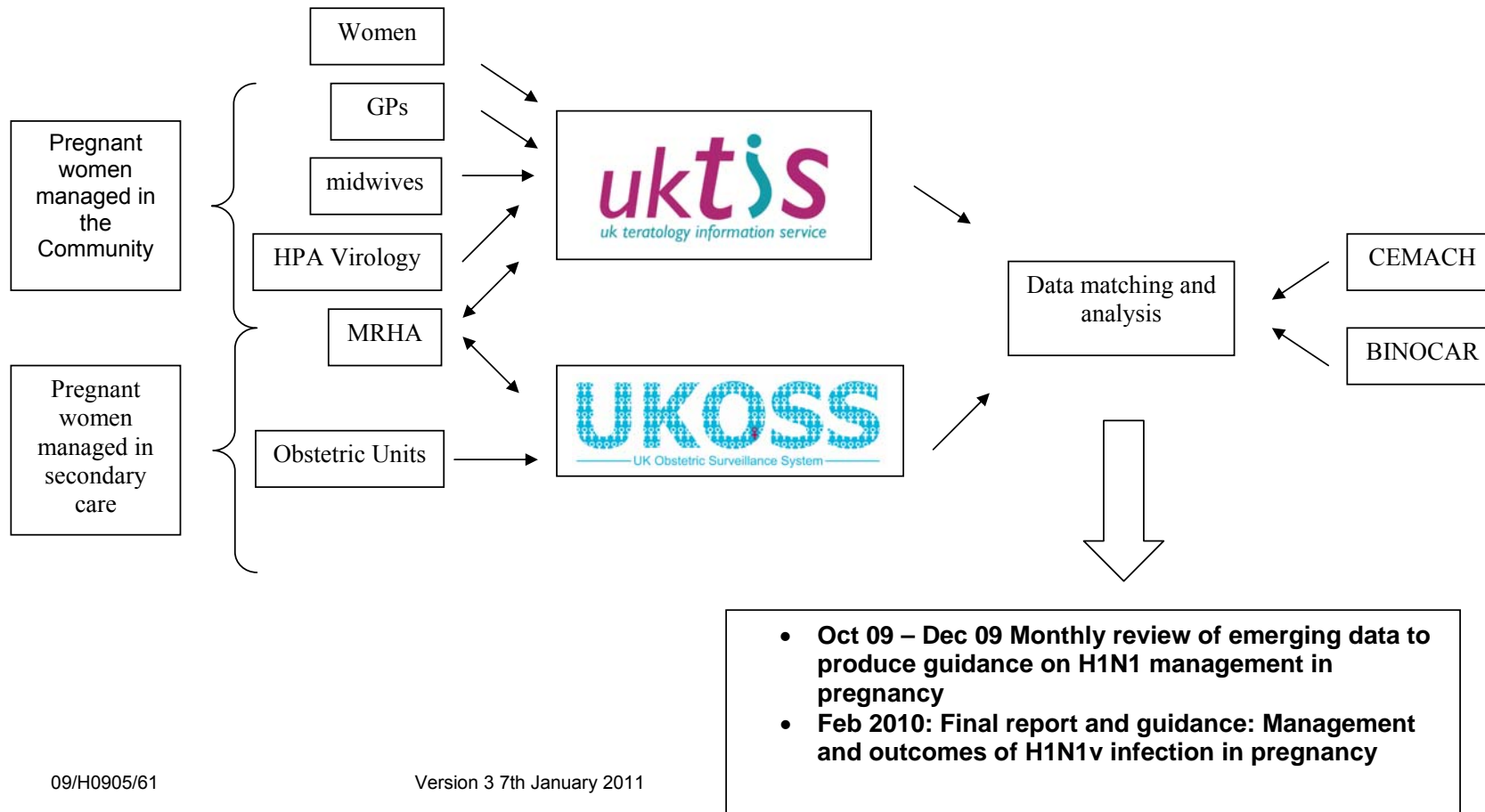
The Newcastle Upon Tyne Hospitals NHS Trust has agreed to sponsor the study.

12 Dissemination and publication

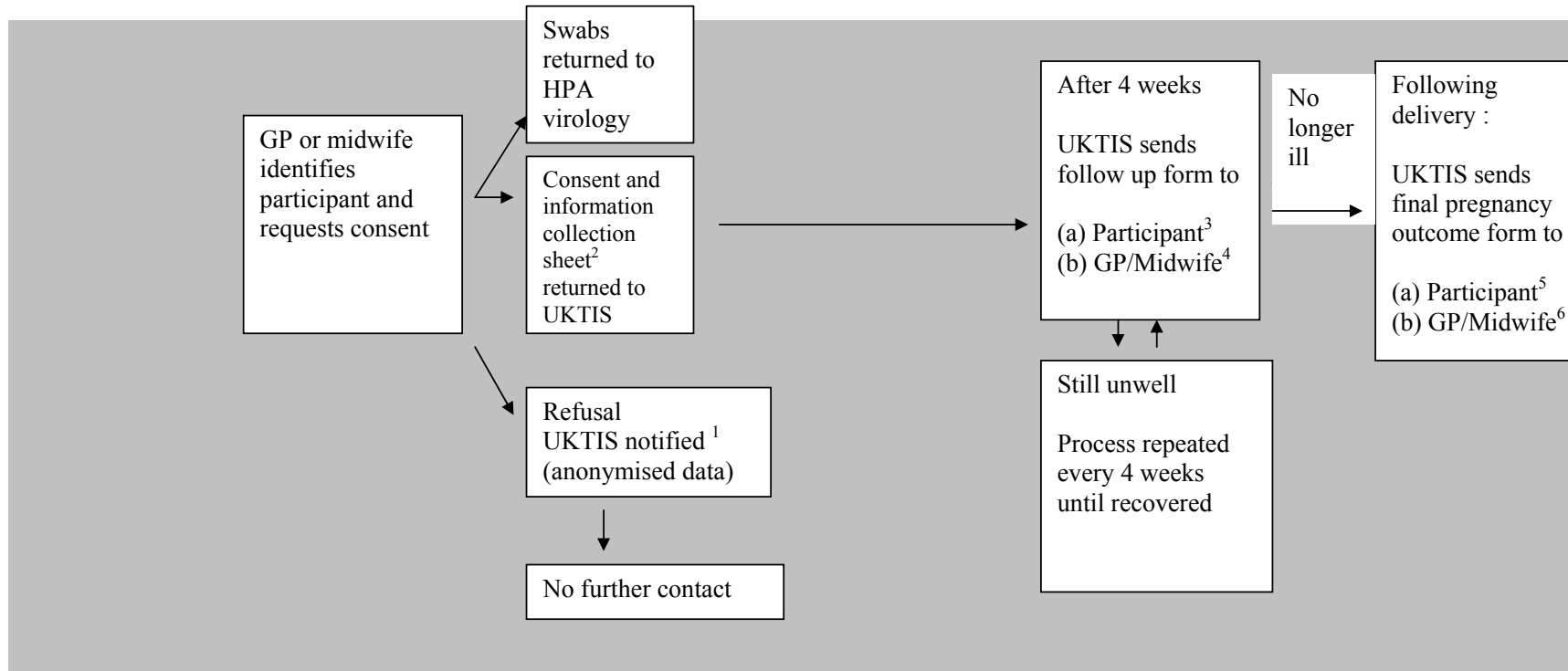
It will be important to feedback the outcomes of the study to the clinicians who participated in providing information. This will be done through monthly guidance for management and a final report. The results will also be reported to the Scientific Advisory Committee of the RCOG, the Royal College of 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



(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], ⁵ Final pregnancy outcome form – participant [Appendix 5], ⁶ Final outcome form – health professional [Appendix 6]

14 References

1. Leck I. Incidence of malformations following influenza epidemics. *Br J Prev Soc Med* 1963, 17:70-80.
2. Busby A., Dolk H., Armstrong B. Eye anomalies: seasonal variation and maternal viral infections. *Epidemiology* 2005, 16(3):317-322.
3. Doll R., Hill A. B., Sakula J. Asian influenza in pregnancy and congenital defects. *Br J Prev Soc Med* 1960, 14:167-172.
4. Coffey V. P., Jessop W. J. Maternal influenza and congenital deformities: a prospective study. *Lancet* 1959, 2(7109):935-938.
5. Hakosalo J., Saxen L. Influenza epidemic and congenital defects. *Lancet* 1971, 2(7738):1346-1347.
6. Acs N., Banhidy F., Puho E., Czeizel A. E. Maternal influenza during pregnancy and risk of congenital abnormalities in offspring. *Birth Defects Res A Clin Mol Teratol* 2005, 73(12):989-996.
7. Neuzil K. M., Reed G. W., Mitchel E. F., Simonsen L., Griffin M. R. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol* 1998, 148(11):1094-1102.
8. Greenberg M, Jacobziner H, Pakter J. Maternal mortality in the epidemic of Asian influenza, New York City, 1957. *Am J Obstet Gynecol* 1958, 76:897-902.
9. Ward P., Small I., Smith J., Suter P., Dutkowski R. Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. *J Antimicrob Chemother* 2005, 55 Suppl 1:i5-i21.
10. CHMP assessment report on novel influenza (H1N1) outbreak Tamiflu (oseltamivir) Relenza (zanamivir) EMEA/H/A-5.3/1172 [<http://www.emea.europa.eu/humandocs/PDFs/EPAR/tamiflu/28766209en.pdf>]
11. Freund B., Gravenstein S., Elliott M., Miller I. Zanamivir: a review of clinical safety. *Drug Saf* 1999, 21(4):267-281.
12. Tanaka T., Nakajima K., Murashima A., Garcia-Bourmissen F., Koren G., Ito S. Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnant and breastfeeding women. *Canadian Medical Association Journal* 2009, 181(1-2):55-58.
13. Heionen O, Slone D, Shapiro S: Birth Defects and Drugs in Pregnancy. In. Littleton, MA: Publishing Sciences Group; 1977.
14. Plotkin SA, Orenstein WA, Offit PA (eds.): Vaccines, 5 edn. Philadelphia: WB Saunders Company; 2008.
15. Hospitalized patients with novel influenza A (H1N1) virus infection - California, April-May, 2009. *MMWR Morb Mortal Wkly Rep* 2009, 58(19):536-541.
16. Novel influenza A (H1N1) virus infections in three pregnant women - United States, April-May 2009. *MMWR Morb Mortal Wkly Rep* 2009, 58(18):497-500.
17. Knight M., Kurinczuk J. J., Tuffnell D., Brocklehurst P. The UK Obstetric Surveillance System for rare disorders of pregnancy. *BJOG* 2005, 112(3):263-265.
18. Knight M. Peripartum hysterectomy in the UK: management and outcomes of the associated haemorrhage. *BJOG* 2007, 114(11):1380-1387.
19. Knight M. Eclampsia in the United Kingdom 2005. *BJOG* 2007, 114(9):1072-1078.
20. Knight M. Antenatal pulmonary embolism: risk factors, management and outcomes. *BJOG* 2008, 115(4):453-461.
21. Knight M., Kurinczuk J. J., Spark P., Brocklehurst P. Cesarean delivery and peripartum hysterectomy. *Obstet Gynecol* 2008, 111(1):97-105.
22. Knight M., Kurinczuk J. J., Spark P., Brocklehurst P. Inequalities in maternal health: national cohort study of ethnic variation in severe maternal morbidities. *BMJ* 2009, 338:b542.
23. Knight M., Nelson-Piercy C., Kurinczuk J. J., Spark P., Brocklehurst P. A prospective national study of acute fatty liver of pregnancy in the UK. *Gut* 2008, 57(7):951-956.
24. Guidance Notes: Section 60 of the Health and Social Care Act 2001 [<http://www.dh.gov.uk/assetRoot/04/06/63/84/04066384.pdf>]

Should you require further advice or clinical information on antiviral use in pregnancy please contact us on 0844 892 0909



UKTIS is a service commissioned by the HPA which has agreed to undertake the surveillance of pregnancy outcomes affected by the current H1N1 pandemic. UKTIS holds all information in strict confidence. The data protection aspects of this surveillance activity are covered by the HPA Section 60 approval, but health professionals are asked, where possible, to ensure that the women involved are aware that their personal information is being reviewed and that they are happy for it to be used in this way.

SWINE FLU IN PREGNANCY STUDY – PATIENT REPORTING FORM FOR HEALTHCARE PROFESSIONALS

To be completed by the midwife or GP DATE:.....

PARTICIPANT'S DETAILS:

Name Date of birth

NHS number Hospital number

Address

.....Postcode

Telephone number.....

LMP ____/____/____ Estimated date of delivery ____/____/____

Occupation.....

Ethnic group..... (please enter a code from the box)

Smoker? never gave up prior to pregnancy gave up during pregnancy current

Does the participant have any of the following? (please tick)

Asthma requiring drug treatment in the past three years

Chronic lung disease

Chronic heart disease

Chronic kidney disease

Chronic liver disease

Chronic neurological disease

Immunosuppression (whether caused by disease or treatment)

Diabetes mellitus

Any other serious medical condition.....

UK census coding for ethnic group	
WHITE	01. British
	02. Irish
	03. Any other white background
MIXED	04. White and black Caribbean
	05. White and black African
	06. White and Asian
	07. Any other mixed background
ASIAN OR ASIAN BRITISH	08. Indian
	09. Pakistani
	10. Bangladeshi
	11. Any other Asian background
BLACK OR BLACK BRITISH	12. Caribbean
	13. African
	14. Any other black background
CHINESE OR OTHER ETHNIC GROUP	15. Chinese
	16. Any other ethnic group

IMMUNISATION:

Has the participant been offered immunisation against AH1N1v ? Yes No don't know

Has the participant been vaccinated against AH1N1v ? Yes No don't know

If YES please provide the following details:

DETAILS OF FIRST AH1N1v VACCINATION:

Date: ____/____/____ Gestation at vaccination _____ weeks

Vaccine Name:.....

Manufacturer:.....

Batch / Lot no.

Adverse effects to vaccination ? Yes No

If yes, please select from the list below:

- headache
- arthralgia (joint pain)
- myalgia (muscle pain)
- reactions at the site of the injection (hardening, swelling, pain and redness)
- fever and fatigue (tiredness)
- other (please detail).....

Have these adverse effects been reported to the MHRA? Yes No don't know

DETAILS OF SECOND AH1N1v VACCINATION (where applicable):

Date: ____/____/____ Gestation at vaccination _____ weeks

Vaccine Name:.....

Manufacturer:.....

Batch / Lot no.

Adverse effects to vaccination ? Yes No

If yes, please select from the list below:

- headache
- arthralgia (joint pain)
- myalgia (muscle pain)
- reactions at the site of the injection (hardening, swelling, pain and redness)
- fever and fatigue (tiredness)
- other (please detail).....

Have these adverse effects been reported to the MHRA? Yes No don't know

OTHER VACCINATIONS:

Has the participant been vaccinated against Seasonal Flu? Yes No don't know

Date: ____/____/____ Gestation at vaccination _____ weeks

EXPOSURE DETAILS:

Antiviral medications prescribed? (Please tick):

Tamiflu® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prophylaxis Don't know

Relenza® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prophylaxis Don't know

Antiviral side effects or adverse drug reactions? No Yes Please detail.....

Please use the table below to indicate any influenza symptoms experienced by the participant:

Symptom	Tick if yes	If yes, give date of onset (dd/mm/yy)
Fever >38°		
Cough		
Sore throat		
Rhinorrhoea		
Loss of appetite		
Diarrhoea		
Tiredness		
Chills		
Aching muscles		
Breathlessness		
Limb or joint pain		
Headache		
Vomiting		
Sneezing		
Other (please state)		

INFLUENZA ILLNESS DIAGNOSIS

Virological confirmation of H1N1 influenza? Yes No Results pending

Don't know* Not tested*

If swabbed, please indicate details in the table below

Date when swab taken (dd/mm/yy)	Site (e.g. nasal, pharyngeal)	Result (negative/positive/pending)	Date of result (dd/mm/yy)

*** Where no diagnostic virological swab has been carried out, PLEASE TELEPHONE / FAX UKTIS IMMEDIATELY TO ENABLE A SELF SWAB KIT TO BE POSTED OUT TO PATIENTS WITH FLU-LIKE SYMPTOMS. ☎ 0191 260 6197 Fax: 0191 260 6193.**

Please note that we do *not* need to collect a swab sample from patients who have only been in contact with someone with Swine Flu, and who do not have any flu-like symptoms themselves.

Was the participant hospitalised? Yes No

If yes, what was the date of admission? ___/___/___ Date of discharge ___/___/___

What was the hospital name?


Name of hospital consultant:.....

Any additional comments?.....

.....
.....
.....


Your details (if not the GP): Profession.....Name.....

Address.....

..... 

GENERAL PRACTITIONER DETAILS: DrAddress.....

.....

Postcode 

Thank you for completing this form - "To submit this form:

- a) Telephone the Swine Flu Reporting Line on 0191 260 6197; *or*
- b) FAX to 0191 260 6193; *or*
- c) Post to: UK Teratology Information Service, Regional Drug & Therapeutics Centre, FREEPOST NEA1573, Newcastle upon Tyne, NE2 1BR

Note that the FREEPOST option should only be used as a last resort, where telephone or FAX is not available or appropriate"



SWINE FLU IN PREGNANCY – INITIAL INFORMATION COLLECTION- PARTICIPANTS

Thank you for taking part in our ‘Swine Flu in Pregnancy’ study. We would be grateful if you could please provide us with the following information about yourself. If anything on this form is unclear, or if you need help with filling it in please contact us on 0191 260 6197 and a member of our team will be glad to help.

YOUR DETAILS:

Please provide the following information about yourself:

Your name

Your date of birth

Your NHS number (if known).....

Your address.....

.....

Postcode Telephone number.....

What is your occupation?.....

What is your ethnic group?..... (please used the codes provided in the box)

What was the first day of your last menstrual period? ____/____/____

When is your baby due? ____/____/____

Do you have any of the following medical conditions? (Please tick any that apply)

Asthma in the past three years

Chronic lung disease

Chronic heart disease

Chronic kidney disease

Chronic liver disease

Chronic neurological disease

Immunosuppression (caused by disease or treatment)

Diabetes mellitus

Any other significant medical condition (please detail).....

Do you smoke? Yes No of cigarettes a day:.....

No (never)

I used to smoke but stopped before I became pregnant

I stopped smoking atweeks of this pregnancy

What was your weight before you were pregnant? _____

UK census coding for ethnic group	
WHITE	01. British
	02. Irish
	03. Any other white background
MIXED	04. White and black Caribbean
	05. White and black African
	06. White and Asian
	07. Any other mixed background
ASIAN OR ASIAN BRITISH	08. Indian
	09. Pakistani
	10. Bangladeshi
	11. Any other Asian background
BLACK OR BLACK BRITISH	12. Caribbean
	13. African
	14. Any other black background
CHINESE OR OTHER ETHNIC GROUP	15. Chinese
	16. Any other ethnic group

How tall are you? _____

VACCINATION (INJECTION)

Have you been offered vaccination for Swine Flu? Yes No

Did you have the vaccine? Yes No

And the name of the vaccine if known.....

If yes, please give the dates of when you were vaccinated (dd/mm/yy)

____/____/____ and ____/____/____

If 'no', what was the reason for not having the vaccine?

Vaccine not available yet Other please specify.....

Did you experience any side effects from the vaccination ? Yes No

If yes, please select from the list below:

- headache
- arthralgia (joint pain)
- myalgia (muscle pain)
- reactions at the site of the injection (hardening, swelling, pain and redness)
- fever and fatigue (tiredness)
- other (please detail).....

Have you had the seasonal flu vaccine this year? Yes No Date.....

INFLUENZA

Have you been in close contact with someone with suspected / confirmed Swine Flu?

Yes No

If 'yes', - please state your relationship to this person (eg. Husband / neighbour).....

- Do you live in the same home? Yes No
- Do you work together? Yes No
- Was this person diagnosed with swine flu on clinical symptoms?
Yes No don't know
- Did this person have a swab (nose or throat) to test for swine flu?
Yes No don't know

Have **you** had any flu-like symptoms? Yes No If 'yes', please fill in the table below

Symptom	Yes	Date symptom started
Fever (temperature $\geq 38^{\circ}\text{C}/100\text{F}$)		
Cough		
Sore throat		
Runny nose		
Loss of appetite		
Diarrhoea		
Tiredness		
Chills		
Aching muscles		
Limb or joint pain		
Headache		
Vomiting		
Sneezing		
Shortness of breath		
Other:		

Have you been diagnosed with swine flu? Yes No Don't know

If yes, was this diagnosis made on clinical symptoms alone (i.e. without a swab test)?

Yes No Don't know

How was the swine flu diagnosed?

By the GP at the surgery

By the GP over the telephone

Other (e.g. flu line, walk in centre, internet) Please provide details

On what date were you diagnosed with swine flu? ___/___/___ Not applicable

Have you been swabbed or tested for H1N1 influenza? Yes No* Don't know*

- **If you have any flu-like symptoms and have not already been tested for Swine Flu (H1N1) PLEASE telephone us or submit this form immediately online or by FAX to UKTIS TO ENABLE A SELF SWAB KIT TO BE POSTED OUT TO YOU (for research purposes) Fax: 0191 260 6193 ☎0191 260 6197**
- **Please note that we do *not* need to collect a swab sample from you if you have only been in contact with someone with Swine Flu, and you yourself do not have any flu-like symptoms.**

If you have already been swabbed for swine flu, what was the result?

Swine flu confirmed Swab did not detect swine flu I am still waiting for the result

How long had you felt unwell when the swab was taken?.....

What type of swab was taken? (eg. nose, throat).....

Were you hospitalised because of the flu? Yes No If yes, what was the hospital name?.....

ANTIVIRAL MEDICATION

Were you prescribed antiviral medication? (Please tick):

Tamiflu® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prevention Don't know

Relenza® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prevention Don't know

Did you experience any side effects / abnormal reactions to the antiviral medication? No Yes Please describe.....

YOUR CURRENT PREGNANCY

Have you had any complications during your pregnancy so far? Please detail below including when in your pregnancy they occurred:

.....
.....

Have you had any antenatal screening during this pregnancy? Yes No Don't know

If yes, were any of your antenatal screening tests abnormal? Please include information on blood tests and ultrasound scans.

.....

Did you take folic acid before pregnancy? Yes No

Are you currently taking folic acid during pregnancy? Yes No Dose (if known).....

If yes, how many weeks pregnant were you when you started taking folic acid? ___weeks

If you have stopped taking folic acid how many weeks pregnant were you when you stopped? ___weeks

Are you taking any medications (other than antivirals) during pregnancy? If yes, please provide details in the table below.

NAME OF MEDICATION TAKEN IN PREGNANCY	DOSE	NUMBER OF TIMES MEDICATION TAKEN IN 24 HOURS	ROUTE (E.G. TABLET BY MOUTH, INHALED, INJECTION)	STAGE OF PREGNANCY IN WEEKS WHEN MEDICATION STARTED (E.G. 10 WEEKS)	STAGE OF PREGNANCY IN WEEKS WHEN MEDICATION STOPPED

Are you taking any other medications or have you been exposed to any chemicals during pregnancy so far? This includes over the counter preparations, recreational drugs and alcohol. Please provide details below, including the doses and when in pregnancy you were exposed to them

.....

YOUR FAMILY

Did any of your blood relatives have a birth defect (eg. Missing fingers, heart abnormalities)? Yes No

Are any of your relatives affected with a genetic condition? Yes No

If so, please tell us more about the defect or condition and how this person is related to you.....

.....

YOUR PAST PREGNANCIES

Is this your first pregnancy? Yes No

If no, can you complete the following about your previous pregnancies

Numbers of:

Liveborn infants miscarriages....., terminations of pregnancy.....,

intrauterine deaths..... stillbirths..... neonatal deaths

Details of liveborn infants (please complete the table below)

Infant	Sex (M/F)	Date of birth (dd/mm/yy)	Number of weeks at birth (e.g. 40 weeks)	Birth weight (kg)	Any problems at birth eg. Respiratory distress, jaundice	Congenital malformations (birth defects)
1						
2						
3						
4						
5						

Is there anything else that you think might be important to tell us?

.....
.....

Please provide your GP and/or midwife's name, address and telephone number below

GP's name

Midwife's name

Address

.....

Postcode

GP's ☎

Midwife's ☎

Hospital Doctors details (name, hospital, specialty)

.....

Your Signature:**DATE:**

Thank you for completing this form – please return it to: UK Teratology Information Service, Regional Drug & Therapeutics Centre, FREEPOST NEA1573, Newcastle upon Tyne. NE2 1BR. ☎0191 260 6197 Fax: 0191 260 6193

SWINE FLU IN PREGNANCY – 4 WEEK FOLLOW UP FLU FORM - PARTICIPANTS

Thank you for taking part in our ‘Swine Flu in Pregnancy’ study. We would be grateful if you could please provide us with information about your recent suspected swine flu or treatment with antiviral drugs. If anything on this form is unclear, or if you need help with filling it in please contact us on 0191 260 6197 and a member of our team will be glad to help.

YOUR DETAILS:

Please provide the following information about yourself

Your name Your date of birth

Your telephone number.....

DETAILS OF ILLNESS

Have you fully recovered from the suspected episode of Swine-Flu Yes No N/A
 (if you are taking part in this study because you were offered antiviral medication, but were never unwell with flu please tick the N/A box and ignore any questions relating to flu symptoms)

What was the full duration of your influenza illness?.....days

Please provide as much detail about your symptoms as possible:

Symptom	Tick if yes	If yes, give date of onset (dd/mm/yy)
Fever (Temp > 38°C or 100.4° F)		
Cough		
Sore throat		
Runny nose		
Loss of appetite		
Diarrhoea		
Tiredness		
Chills		
Aching muscles		
Breathlessness		
Limb or joint pain		
Headache		
Vomiting		
Sneezing		
Other (please state)		

Were you tested for the Swine Flu virus (H1N1) by swab? Yes No Results pending Don't know

If swabbed, please indicate details in the table below

Date when swab taken (dd/mm/yy)	Site (e.g. nose, throat, both)	Result (virus detected / virus not detected/ still waiting for result)	Date of result (dd/mm/yy)

Were you prescribed antiviral medication? (Please tick):

Tamiflu® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prevention Don't know

Relenza® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prevention Don't know

Did you experience any side effects / abnormal reactions to the antiviral medication? No Yes Please describe.....

Did you take the antiviral medication (Tamiflu® or Relenza®) you were prescribed? Yes No

If 'no', please tell us why:

Side effects of drug (please detail).....

Swine flu swab did not detect H1N1 virus

Forgot

I started feeling better

Other.....

Did you receive any other treatment for flu (e.g. antibiotics)? Yes No Please provide details.....

COMPLICATIONS OF INFLUENZA

Were you admitted to hospital? Yes No

If yes, Hospital name

Date of admission : ___/___/___ Date of discharge : ___/___/___ Still in hospital

If you were under a hospital consultant please provide their name.....

Was your hospital stay related to influenza? Yes No

Did you develop pneumonia (i.e. a chest infection that required antibiotic treatment?) Yes No

Please provide a brief summary of your illness and how it progressed

Have you experienced any problems relating to your current pregnancy? Yes No

If yes, please detail.....

Are you still pregnant? Yes No

If you are no longer pregnant, please select the appropriate outcome from the options below:

Was your baby live born? Yes No

Was your baby stillborn? Yes No

Did this pregnancy end in a miscarriage? Yes No

Did you decide to terminate this pregnancy? Yes No

If yes, what was the reason for termination? (Please tick)

Personal Concerns about the effect of the influenza/antiviral medication in pregnancy

Abnormalities on scan or prenatal screening Other (please provide details below if you feel able)

If your pregnancy has ended, would you be willing for us to contact you if we require any further information? Yes No

GENERAL PRACTITIONER DETAILS: Dr Address.....

.....

Postcode ☎

Your Signature..... Date:.....

**Thank you for completing this form - please return it to: UK Teratology Information Service, Regional Drug & Therapeutics Centre, FREEPOST
NEA1573, Newcastle upon Tyne. NE2 1BR. Fax: 0191 260 6193**

Appendix 4 (Version2, 3rd November 2009)

Should you require further advice or clinical information on antiviral use in pregnancy please contact us on 0844 892 0909



UKTIS is a service commissioned by the HPA which has agreed to undertake the surveillance of pregnancy outcomes affected by the current H1N1 pandemic. UKTIS holds all information in strict confidence. The data protection aspects of this surveillance activity are covered by the HPA Section 60 approval, but health professionals are asked, where possible, to ensure that the women involved are aware that their personal information is being reviewed and that they are happy for it to be used in this way.

SWINE FLU IN PREGNANCY STUDY– FOUR WEEK UPDATE FORM – HEALTH PROFESSIONAL

To be completed by the midwife or GP

DATE:

PATIENT DETAILS:

Name Date of birth

NHS number Hospital number

Address.....

.....Postcode Telephone number.....

Patient status: Alive – prophylaxis only
 - recovered
 - still unwell
 Deceased (Date of death ___/___/___)

DETAILS OF ILLNESS

What was the full duration of flu-like illness?.....days Don't know

Please detail full symptom profile in the table below.

Symptom	Tick if yes	If yes, give date of onset (dd/mm/yy)
Fever T > 38C or 100.4 F		
Cough		
Sore throat		
Rhinorrhoea		
Loss of appetite		
Diarrhoea		
Tiredness		
Chills		
Aching muscles		
Breathlessness		
Limb or joint pain		
Headache		
Vomiting		
Sneezing		
Other (please state)		

Virological confirmation of H1N1 influenza? Yes No Results pending Don't know

If swabbed, please indicate details in the table below

Date when swab taken (dd/mm/yy)	Site (e.g. nasal, pharyngeal)	Result (negative/positive)	Date of result (dd/mm/yy)

Antiviral medications prescribed? (Please tick):

Tamiflu® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prophylaxis Don't know

Relenza® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prophylaxis Don't know

Were antivirals taken as prescribed? Yes No Don't know

If no, please detail length of course and reasons for discontinuing.....

Was any other treatment for flu administered eg antibiotics? (please detail).....

COMPLICATIONS OF INFLUENZA

Was the woman hospitalized? Yes No If yes, Hospital name

Date of admission ___/___/___

Date of discharge ___/___/___

If the woman was under a hospital consultant please provide their name.....

Was the admission due to the H1N1 influenza? Yes No

Did the participant develop a chest infection requiring antibiotic treatment? Yes No

Please provide brief summary of illness and clinical course

Have there been any pregnancy complications?.....

Is the pregnancy still ongoing? Yes No (If no please provide details).....

Your details (if not the GP): Profession.....Name

Address.....



GENERAL PRACTITIONER DETAILS: Dr Address.....

Postcode

Thank you for completing this form - please return it to UK Teratology Information Service By FAX to 0191 260 6193; or Post to: UK Teratology Information Service, Regional Drug & Therapeutics Centre, FREEPOST NEA1573, Newcastle upon Tyne, NE2 1BR

Note that the FREEPOST option should only be used as a last resort, where telephone or FAX is not available or appropriate"



SWINE FLU IN PREGNANCY – PREGNANCY OUTCOME FORM - PARTICIPANTS

Thank you for taking part in our ‘Swine Flu in Pregnancy’ study. We would be grateful if you could please provide us with **final information** about your pregnancy and your baby. If anything on this form is unclear, or if you need help with filling it in please contact us on **0191 260 6197** and a member of our team will be glad to help.

YOUR DETAILS:

Please provide the following information about yourself

Your name
Your date of birth
Your NHS number
Your address
.....Postcode.....
Your telephone number.....

VACCINATION (INJECTION)

Have you been offered vaccination for Swine Flu? Yes No

Did you have the vaccine? Yes No

If yes, please give the dates of when you were vaccinated (dd/mm/yy)

____/____/____ and ____/____/____

And the name of the vaccine if known.....

If ‘no’, what was the reason for not having the vaccine?

Vaccine not available yet Other please specify.....

Did you experience any side effects from the vaccination? Yes No

If yes, please select from the list below:

- headache
- arthralgia (joint pain)
- myalgia (muscle pain)
- reactions at the site of the injection (hardening, swelling, pain and redness)
- fever and fatigue (tiredness)
- other (please detail).....

Have you had the seasonal flu vaccine this year? Yes No Date.....

How many episodes of Flu-like illness or suspected Swine Flu have you had during this pregnancy?.....

How many courses of antiviral medications have you been prescribed.....

Please Note: If you have had more than one episode of suspected swine flu that we have not obtained information on please contact us.

DETAILS OF THIS PREGNANCY

Did you have any complications during your pregnancy? Please provide details below including when in your pregnancy they occurred

.....

.....

Were any abnormalities seen at your antenatal screening, including ultrasound?

.....

Did you take folic acid before pregnancy? Yes No

Did you take folic acid during pregnancy? Yes No Dose (if known).....

If yes, how many weeks pregnant were you when you started taking folic acid? ____/40

How many weeks pregnant were you when you stopped taking folic acid? ____/40

Did you take any other medication during pregnancy? If yes, please provide details in the table below.

NAME OF MEDICATION TAKEN IN PREGNANCY	DOSE	NUMBER OF TIMES MEDICATION TAKEN IN 24 HOURS	ROUTE (E.G. TABLET BY MOUTH, INHALED, INJECTION)	STAGE OF PREGNANCY IN WEEKS WHEN MEDICATION STARTED (E.G 10 WEEKS)	STAGE OF PREGNANCY IN WEEKS WHEN MEDICATION STOPPED

Did you take any other medications or were you exposed to any chemicals during pregnancy? This includes non-prescription medication, recreational drugs and alcohol. Please provide details below, including the doses and when in pregnancy you were exposed to them

.....

.....

YOUR PREGNANCY OUTCOME

Did you have any major problems during or soon after your delivery? Please provide us with details.....

.....

Were you transferred to the intensive care unit? Yes No

Was your baby live born Yes No

If Yes: please proceed to the section **‘YOUR BABY’**

If no, we would be grateful if you could provide us with the following information:

Did this pregnancy end in a miscarriage? Yes No

Did you decide to terminate this pregnancy? Yes No

If yes, what was the reason for termination? (Please tick)

Personal Concerns about the effect of the influenza/antivirals

Abnormalities on scan or prenatal screening Other (please provide details below if you feel able)

.....

Was your baby stillborn? Yes No

YOUR BABY

If you had a multiple birth please add the information about the babies alongside each question

Please complete the following about your baby/babies:

Was your baby: Male or Female

What was the delivery date? ____/____/____

What was the weight of your baby? _____ g What was the length of your baby? _____ cm

What was the head circumference of your baby? _____ cm

Does your baby have any **birth defects**? Yes No

If Yes, please give as many details as possible

.....

.....

Did your baby have **any problems in the first few days after birth**? Yes No

If Yes, please give as many details as possible (e.g. Was your baby admitted to the neonatal unit)

.....

.....

.....

Is there anything else about your baby that you think is important to tell us?

.....

.....

.....

GENERAL PRACTITIONER DETAILS:


Please provide the name and address of your GP and midwife:

Please provide details of any hospital doctors involved in the care of you or your baby:

Name

Address

.....



Thank you for completing this form - please return it in the FREEPOST envelope provided or return via FREEPOST to: UK
Teratology Information Service, Regional Drug & Therapeutics Centre, FREEPOST NEA1573, Newcastle upon Tyne. NE2 1BR.
Fax: 0191 260 6193

Appendix 6 (Version 3, 3rd November 2009)

Should you require further advice or clinical information on antiviral use in pregnancy please contact us on 0844 892 0909



UKTIS is a service commissioned by the HPA which has agreed to undertake the surveillance of pregnancy outcomes affected by the current H1N1 pandemic. UKTIS holds all information in strict confidence. The data protection aspects of this surveillance activity are covered by the HPA Section 60 approval, but health professionals are asked, where possible, to ensure that the women involved are aware that their personal information is being reviewed and that they are happy for it to be held for this purpose

SWINE FLU IN PREGNANCY STUDY- FINAL PREGNANCY OUTCOME FORM – HEALTH PROFESSIONAL

To be completed by the midwife or GP

DATE:

PARTICIPANT'S DETAILS:

Name Date of birth

NHS numberHospital number

Address.....

.....Postcode.....

Telephone number.....

Height at booking _____ cm

Weight at booking _____ kg

Patient status: Alive – prophylaxis only

- recovered

- still unwell

Deceased (Date of death ___/___/___)

IMMUNISATION

INFLUENZA ILLNESS DIAGNOSIS

Virological confirmation of H1N1 influenza? Yes No Results pending Don't know

If swabbed, please indicate details in the table below

Date when swab taken (dd/mm/yy)	Site (e.g. nasal, pharyngeal)	Result (negative/positive/pending)	Date of result (dd/mm/yy)

How many episodes of flu-like illness has the participant had during this pregnancy?.....

ANTIVIRAL MEDICATION

Antiviral medications prescribed? (Please tick):

Tamiflu® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prophylaxis

Relenza® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prophylaxis

Were antivirals taken as prescribed? Yes No Don't know

If no, please detail length of course and reasons for discontinuing.....

If any other treatment for flu (e.g. antibiotics) was administered please report this in the 'pregnancy details' section below

How many GP visits/consultations were needed *because of swine flu*?

Was the participant hospitalized? Yes No If yes, what was the date of admission? ____/____/____

Date of discharge? ____/____/____

What was the hospital name?

If the participant was under a hospital consultant please provide their name.....

Was this due to the H1N1 influenza? Yes No

If no please state the reason

If the participant was under a hospital consultant please provide their name.....

Was the participant admitted to ITU? Yes No

Did any other major maternal morbidity occur? Yes No

If yes, please specify.....

Did the participant die? Yes No

If yes, please state the date of death (dd/mm/yy) ____/____/____

What was the primary cause of death on the death certificate / post mortem findings?

PREGNANCY DETAILS

Were there any pregnancy complications? Please provide details below including the stage of pregnancy

.....
.....
.....

Please provide details of abnormalities on antenatal screening (including ultrasound).....

.....
.....

Did the participant take folic acid preconceptually? Yes No Date commenced.....

Is the participant currently taking folic acid during pregnancy? Yes No Dose (if known).....

Are you aware if the participant has taken any other medication before or during pregnancy? Yes No

If yes, please provide details in the table below.

NAME OF MEDICATION TAKEN IN PREGNANCY	DOSE	SCHEDULE	ROUTE	SOP (WEEKS) MEDICATION COMMENCED	SOP (WEEKS) MEDICATION CEASED

Are you aware if the participant has taken any other drugs or been exposed to chemicals during pregnancy?

Yes No If yes, please provide details including OTC preparations, illicit drugs, alcohol and treatment during labour. Please provide details below, inc. dose, route and timings of exposure.

.....

PAST OBSTETRIC HISTORY

Is there a family history of congenital malformations? Yes No

If yes, please specify which family member and the type of malformation.....

.....

Previous pregnancy outcomes: Numbers of

Liveborn infants miscarriages....., terminations of pregnancy.....,

intrauterine deaths..... stillbirths..... neonatal deaths

Details of liveborn infants (please complete the table below)

Infant	Sex (M/F)	Date of birth (dd/mm/yy)	Gestational age	Birth weight (kg)	Neonatal problems	Congenital malformations
1						
2						
3						
4						
5						

INFANT OUTCOME (this pregnancy)

For multiple births please photocopy this page and complete for each infant

What was the gestational age? ____/40 What was the delivery date? ____/____/____

What was the outcome? Please tick

Live born Details of delivery e.g. induced

Mode of delivery (please specify)

Spontaneous vaginal Ventouse Lift-out forceps Rotational forceps
Breech Pre-labour caesarean section Caesarean section after onset of labour

Miscarriage*

Termination of pregnancy* What was the reason for termination? Please tick

Personal Concerns r.e. the effect of the influenza/antivirals

Abnormalities on scan or prenatal screening Other (please provide details below) Don't know

.....

Intrauterine Death*

Stillborn*

Neonatal Death* Date of death ____/____/____

*Please provide post-mortem details or other relevant medical reports if available

.....

Please complete the following about the baby:

Gender: Male Female

Weight: _____ g Length: _____ cm Head circumference: _____ cm

APGAR 5 minutes: _____

Were there any **congenital malformations**? Yes No

If Yes, please give as many details as possible

.....

.....

Were there any **neonatal problems** affecting the child? Yes No

Was the infant admitted to a neonatal unit? Yes No

If Yes to either question, please give as many details as possible

.....

.....

.....

Please use this space to enter any other information you feel may be important

.....
.....
.....
.....
.....
.....

GENERAL PRACTITIONER DETAILS:

Please provide name and address:

Your details (if not the GP): Profession.....Name.....

Address

.....

..... ☎

Name of any other health professional involved in this woman's care.....

.....

Thank you for completing this form - please return it to UKTIS by: "To submit this form:

- a) FAX to 0191 260 6193; or
- b) Post to: UK Teratology Information Service, Regional Drug & Therapeutics Centre, FREEPOST NEA1573, Newcastle upon Tyne, NE2 1BR

Note that the FREEPOST option should only be used as a last resort, where telephone or FAX is not available or appropriate"



Any woman who is pregnant and has flu-like symptoms, prolonged contact with H1N1 or has been prescribed an antiviral should be asked for permission for her contact details to be passed on to UKTIS. UKTIS is a service commissioned by the HPA which has agreed to undertake the surveillance of pregnancy outcomes affected by the current H1N1 pandemic. It is important to collect information on the effects of influenza and its treatment in pregnancy as this helps us provide advice in the future.

H1N1 INFLUENZA IN PREGNANCY – NOTICE OF DECLINED CONSENT

To be completed by the midwife or GP

DATE:.....

PARTICIPANT'S DETAILS:

INITIALS: YEAR OF BIRTH..... POSTCODE.....

LMP ____/____/____ Estimated date of delivery ____/____/____

Occupation.....

Ethnic group..... (please enter a code from the box)

Smoker? never gave up prior to pregnancy gave up during pregnancy current

Does the participant have any of the following? (please tick)

- Asthma requiring drug treatment in the past three years
- Chronic lung disease
- Chronic heart disease
- Chronic kidney disease
- Chronic liver disease
- Chronic neurological disease
- Immunosuppression (whether caused by disease or treatment)
- Diabetes mellitus
- Any other serious medical condition.....

UK census coding for ethnic group	
WHITE	01. British
	02. Irish
	03. Any other white background
MIXED	04. White and black Caribbean
	05. White and black African
	06. White and Asian
	07. Any other mixed background
ASIAN OR ASIAN BRITISH	08. Indian
	09. Pakistani
	10. Bangladeshi
	11. Any other Asian background
BLACK OR BLACK BRITISH	12. Caribbean
	13. African
	14. Any other black background
CHINESE OR OTHER ETHNIC GROUP	15. Chinese
	16. Any other ethnic group

IMMUNISATION:

Has the participant been offered immunisation against AH1N1v ? Yes.....No..... Don't know.....

Has the participant been vaccinated against AH1N1v ? Yes.....No.....Don't know

If YES please provide the following details:

DETAILS OF FIRST AH1N1v VACCINATION:

Date:..... Gestation at vaccination.....weeks

Vaccine Name:.....

Manufacturer:.....

Batch / Lot no.

Adverse effects to vaccination ? Yes..... No.....

If yes, please select from the list below:

Have these adverse effects been reported to the MHRA? Yes..... No..... Don't know.....

DETAILS OF SECOND AH1N1v VACCINATION (where applicable):

Date:..... Gestation at vaccination.....weeks

Vaccine Name:.....

Manufacturer:.....

Batch / Lot no.

Adverse effects to vaccination ? Yes..... No.....

If yes, please select from the list below:

Have these adverse effects been reported to the MHRA? Yes..... No..... Don't know.....

Has the participant been vaccinated against Seasonal Flu? Yes..... No..... Don't know.....

Date:..... Gestation at vaccination.....weeks

EXPOSURE DETAILS:

Antiviral medications prescribed? (Please tick):

Tamiflu® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prophylaxis

Relenza® No Yes Start date ___/___/___ Stop date ___/___/___ for Treatment Prophylaxis

Any clinical features so far? Please indicate in the table below and add any additional symptoms

Symptom	Tick if yes	If yes, give date of onset (dd/mm/yy)
Fever >38°		
Cough		
Sore throat		
Rhinorrhoea		
Loss of appetite		
Diarrhoea		
Tiredness		
Chills		
Aching muscles		
Breathlessness		
Limb or joint pain		
Headache		
Vomiting		
Sneezing		
Other (please state)		

INFLUENZA ILLNESS DIAGNOSIS

Virological confirmation of H1N1 influenza? Yes No Results pending

Don't know* Not tested*

If swabbed, please indicate details in the table below

Date when swab taken (dd/mm/yy)	Site (e.g. nasal, pharyngeal)	Result (negative/positive/pending)	Date of result (dd/mm/yy)

Was the participant hospitalised? Yes No

If yes, what was the date of admission? ___/___/___ Date of discharge ___/___/___

What was the hospital name?

Any additional comments?.....


.....

Your details (if not the GP): Profession.....Name.....

Address.....



.....
GENERAL PRACTITIONER DETAILS: DrAddress.....
.....

Postcode 

Thank you for completing this form - please return it to UKTIS by:

- c) Telephone the Swine Flu Reporting Line on 0191 260 6197; *or*
- d) FAX to 0191 260 6193; *or*
- e) Post to: UK Teratology Information Service, Regional Drug & Therapeutics Centre, FREEPOST NEA1573, Newcastle upon Tyne, NE2 1BR

Note that the FREEPOST option should only be used as a last resort, where telephone or FAX is not available or appropriate"



**INFLUENZA A/H1N1v
IN PREGNANCY STUDY**

PRIVATE & CONFIDENTIAL

**SWINE FLU IN PREGNANCY STUDY: 6 MONTH INFANT OUTCOME FORM-
HEALTH PROFESSIONALS**

To be completed by the midwife or GP

DATE:

PARTICIPANT'S (mothers) DETAILS:

Name Date of birth

NHS number Hospital number

Address

..... Postcode

Telephone number

Please complete the following about the infant/s:

BABY'S NAME

BABY'S NHS NUMBER

Baby's date of birth ____/____/____

Gender: Male Female Indeterminate

Current Age ____ weeks

Current weight: _____ g Date ____/____/____

Current length: _____ cm Date ____/____/____

Current head circumference: _____ cm Date ____/____/____

Has the infant experienced any **illnesses** since birth? Yes No Don't know

If yes, please give as many details as possible

.....

.....

.....

Has the infant been diagnosed with any **congenital malformations**? Yes No Don't know

If yes, please give as many details as possible

.....

.....

.....

Has the infant experienced any **problems** since birth? Yes No Don't know

Was the infant admitted to a hospital? Yes No Don't know

If yes to either question, please give as many details as possible

.....
.....
.....

Has the infant been diagnosed with any **neurodevelopmental problems**? Yes No Don't know

If yes to either question, please give as many details as possible

.....
.....
.....

Please use this space to enter any other information you feel may be important

.....
.....
.....

GENERAL PRACTITIONER DETAILS:

Please provide name and address:

Your details (if not the GP):

Profession Name

Address

.....
..... ☎

Please copy us into any further correspondence regarding this pregnancy/child

Thank you for completing this form - please return it to UKTIS by: FAX to 0191 260 6193; *or* Post to: UK Teratology Information Service, Regional Drug & Therapeutics Centre, FREEPOST NEA1573, Newcastle upon Tyne, NE2 1BR

Note that the FREEPOST option should only be used as a last resort, where telephone or FAX is not available.



INFLUENZA A/H1N1v
IN PREGNANCY STUDY

PRIVATE & CONFIDENTIAL

SWINE FLU IN PREGNANCY STUDY: 6 MONTH INFANT OUTCOME FORM
PARTICIPANTS

DATE:

YOUR DETAILS:

Please provide the following information about yourself

Your name

Your date of birth ____/____/____

Your NHS number

Your address

.....Postcode.....

Your telephone number.....

Please complete the following about your baby/babies:

What is your baby's name/s?

What is your baby's NHS number?.....

What is your baby's date of birth? ____/____/____

Is your baby: Male or Female

What is the weight of your baby? _____ g Date ____/____/____

What is the length of your baby? _____ cm Date ____/____/____

What is the head circumference of your baby? _____ cm Date ____/____/____

Has your baby had any **illnesses** since birth? Yes No Don't know

If yes, please give as many details as possible

.....
.....
.....

Does your baby have any **birth defects**? Yes No

If Yes, please give as many details as possible

.....
.....

Did your baby have any **problems since birth**? Yes No Don't know

If Yes, please give as many details as possible (e.g. Was your baby admitted to hospital)

.....
.....
.....

Has your baby experienced any **delayed development** (i.e. are they meeting their developmental milestones?)

.....
.....
.....

Please use this space to enter any other information you feel may be important

.....
.....
.....
.....

GENERAL PRACTITIONER DETAILS:

Please provide name and address:

.....
.....

Your health visitor details :

Profession.....Name.....

Address

.....
..... ☎

Please copy us into any further correspondence regarding this pregnancy/child

Thank you for completing this form - please return it in the FREEPOST envelope provided or return via FREEPOST to: UK Teratology Information Service, Regional Drug & Therapeutics Centre, FREEPOST NEA1573, Newcastle upon Tyne. NE2 1BR.
Fax: 0191 260 6193