Study Title: Open Label, Randomized, Parallel-Group, Multi-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of Baxter H1N1 vaccine and GlaxoSmithKline H1N1 vaccine in children 6 months to 12 years of age.

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Investigators: Andrew Pollard (Oxford) (Chief Investigator)
Liz Miller (Health Protection Agency)
Paul Heath (St Georges, London)
Adam Finn (Bristol)
Saul Faust (Southampton)
Andrew Collinson (Devon and Exeter)
Matthew Snape (Oxford)

Sites/Centres: Oxford Vaccine Group,
Centre for Clinical Vaccinology and Tropical Medicine,
Churchill Hospital,
Oxford, OX3 7LJ
01865 857420

Health Protection Agency
Centre for Infections
61 Colindale Avenue
London
NW9 5EQ

St Georges Vaccine Institute
St Georges, University of London
Cranmer Terrace,
London SW17 ORE

Bristol Children's Vaccine Centre
UBHT Education Centre

Date and Version No:	25/09/2009, version 3
	Upper Maudlin Street Bristol BS2 8AE
	Royal Devon and Exeter NHS Foundation Trust Barrack Road Exeter EX2 5DW
	University of Southampton Wellcome Trust Clinical Research Facility, Southampton University Hospitals NHS Trust, Tremona Road, Southampton, SO16 6YD. 023 8079 4989
Sponsoring Institution	University of Oxford
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1. SYNOPSIS

Study Title	**Open Label, Randomized, Parallel-Group, Multi-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of Baxter H1N1 vaccine and GlaxoSmithKline H1N1 vaccine in children 6 months to 12 years of age.**
Internal ref. no.	2009/08 H1N1
Clinical Phase	Phase II
Trial Design	Open Label, Randomised
Trial Participants	Children aged 6 months to 12 years
Planned Sample Size	1000 participants
Follow-up duration	6 to 8 weeks
Planned Trial Period	12 weeks (for study visits)
Primary Objective	Immunogenicity • To compare the percentage of children aged 6 months to 12 years of age with a four fold rise in microneutralisation (MN) titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. Reactogenicity • To compare the percentage of children aged 6 months to 12 years of age experiencing fever and local reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine
Secondary Objectives	• To compare the percentage of children aged 6 months to 12 years of age with haemagglutination inhibition (HAI) titres of ≥ 1:32 three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To compare the percentage of children aged 6 months

	to 12 years of age with a four fold rise in HAI titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To determine the geometric mean fold rises in HAI titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To determine the geometric mean fold rises in MN titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To determine the geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To assess the percentage of children aged 6 months to 12 years of age experiencing non-febrile systemic reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine • To investigate the effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines in a given individual.
Primary Endpoint	Primary end points for the immunogenicity analysis will be defined as: • The percentage of children aged 6 months to 12 years of age with a four fold rise in microneutralisation (MN) titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. Primary endpoints for reactogenicity analysis

	• Percentage of participants experiencing each of fever (≥ 38°C per axilla), local tenderness, local swelling or local erythema within the 7 days following each immunisation with the study vaccines
Secondary Endpoints	• Percentage of subjects with an HAI titre ≥ 1 in 32 • The percentage of children aged 6 months to 12 years of age with a four fold rise in HAI titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • The geometric mean fold rises in HAI titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • The geometric mean fold rises in MN titres from baseline to after three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • The geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • Percentage of participants experiencing each of: reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds). • Percentage of participants experiencing each of: malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds). • The effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines.
Investigational	Baxter Novel Influenza A H1N1 Whole Virus Vaccine

Medicinal Products	(Celvapan) GlaxoSmithKline Novel Influenza A H1N1 Split Virion Vaccine (Pandemrix)

2. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CFI	Centre for Infections
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials & Research Governance, University of Oxford
EMEA	European Medicines Agency
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GP	General Practitioner
HAI	Haemaglutination Inhibition
HPA	Health Protection Agency
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
MN	Microneutralisation
NRES	National Research Ethics Service
OVG	Oxford Vaccine Group

PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RVU	Respiratory Virus Unit
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunisation
SAR	Serious Adverse Reaction
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSG	Oxford Radcliffe Hospitals Trust / University of Oxford Trials Safety Group
VRD	Virus Reference Department
WHO	World Health Organisation

3. BACKGROUND AND RATIONALE

Two manufacturers, Baxter and GlaxoSmithKline, have gained marketing authorisation approval from the EMEA for a pandemic strain vaccine under the "mock-up" dossier route based on limited clinical trial data for a candidate H5N1 vaccine. These vaccines have now been modified to cover the novel influenza A H1N1 strain. The proposed study aims to assess the safety and immunogenicity of these two H1N1 vaccines when administered as two doses three weeks apart to children aged 6 months to 12 years of age.

The first illness caused by a new influenza A virus was confirmed in the United Kingdom on 27 April 2009. Since then the virus has become much more common in both the UK and across the world, and the World Health Organization (WHO) declared a pandemic on 11 June 2009. Internationally, human infections with the new virus have occurred in 120 countries including the UK (WHO). There have been more than 77,000 laboratory confirmed cases and 332 deaths globally. The actual number of cases of people infected with the new virus is likely to be much higher than these numbers suggest, as most cases are not tested. There have been 11,159 laboratory confirmed cases of new influenza A H1N1v in the United Kingdom, and 840 hospitalisations as of the 23rd July 2009[1].

In response to this pandemic the WHO's Strategic Advisory Group of Experts on Immunisation (SAGE), held an extraordinary meeting on 7th July 2009 to consider the role for immunisation in the prevention of this disease[2]. The full report is included as appendix A of this protocol, however the key recommendations were

- All countries should immunize their health-care workers as a first priority to protect the essential health infrastructure. As vaccines available initially will not be sufficient, a step-wise approach to vaccinate particular groups may be considered. SAGE suggested the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions: pregnant women; those aged above 6 months with one of several chronic medical conditions; healthy young adults of 15 to 49 years of age; healthy children; healthy adults of 50 to 64 years of age; and healthy adults of 65 years of age and above.
- Since new technologies are involved in the production of some pandemic vaccines, which have not yet been extensively evaluated for their safety in certain population groups, it is very important to implement post-marketing surveillance of the highest possible quality. In addition, rapid sharing of the results of immunogenicity and

post-marketing safety and effectiveness studies among the international community will be essential for allowing countries to make necessary adjustments to their vaccination policies.

- In view of the anticipated limited vaccine availability at global level and the potential need to protect against "drifted" strains of virus, SAGE recommended that promoting production and use of vaccines such as those that are formulated with oil-in-water adjuvants and live attenuated influenza vaccines was important.
- As most of the production of the seasonal vaccine for the 2009-2010 influenza season in the northern hemisphere is almost complete and is therefore unlikely to affect production of pandemic vaccine, SAGE did not consider that there was a need to recommend a "switch" from seasonal to pandemic vaccine production.

As children are recognised as being a high risk group for pandemic influenza, it is imperative to conduct a study comparing the immunogenicity and reactogenicity of the two vaccines likely to be available for use in the UK.

One vaccine, Celvapan, (manufactured by Baxter Vaccines) is a whole virus unadjuvanted vaccine, and the other, Pandemrix, (from GlaxoSmithKline vaccines (GSK)) is a split virion vaccine adjuvanted with an oil in water emulsion (ASO3) containing Squalene, Vitamin E- as immunostimulant and Tween 80 as surfactant. Both manufacturers have gained marketing authorisation approval from the EMEA for a pandemic strain vaccine under the “mock-up” dossier route based on limited clinical trial data for a candidate H5N1 vaccine. As the influenza strain on which these vaccines are based has changed from H5N1 to H1N1, vaccine manufacturers have had to apply for a ‘variation’ to the marketing authorisation for these vaccines. There are however limited data on safety and immunogenicity in children.

Previous studies have suggested that whole virus vaccine may be better at inducing a protective immune response in children following a single dose than a subunit or split virion vaccine. Reactogenicity may also vary between the two vaccines. There are, however, limited data on the immunogenicity and reactogenicity of these vaccines in a paediatric population, particularly in children under 3 years of age. The need for comparative immunogenicity and reactogenicity data for these two products in children has therefore been identified by the UK Scientific Advisory Group for Emergencies (SAGE) as a high priority to help guide national recommendations on which to use in a paediatric population.

Information that is available on the immunogenicity and reactogenicity of the H5N1 version of the GSK pandemic influenza vaccine in children between the ages of 3 and 9 years suggests that initial seroconversion rates following immunisation with 2 doses of a half adult dose of vaccine (0.25 mL) are comparable to those observed after immunisation with 2 doses of the full 'adult' dose (0.5mL). As fever rates were higher in the full dose than half dose group (for 3 to 5 year olds 36% versus 16%, respectively, had temperatures above 37.5 °C), consideration has been given to using the half dose of GSK vaccine in this study. However it has been decided to use a full dose in all age groups. This decision has been made on the basis of:

- evidence that in the 3 to 5 year age group the full dose of the H5N1 vaccine resulted in better persistence of protective antibodies to 6 months post-immunisation than the half dose
- evidence that the full dose also provides better cross-protection against antigenically drifted versions of the H5N1 vaccine than the half dose
- the suggestion that the higher fever rates were predominantly seen in the 6 to 9 year old age groups rather than the 3 to 5 year old age groups, suggesting that this may be more of a feature with increasing, rather than decreasing, age
- advice from the Department of Health that, based on the above evidence, they would anticipate using a full dose of Pandemrix in all age groups in the event of mass immunisation of children against 'swine flu', as this would be more likely to protect against a 'second wave' of pandemic influenza with an antigenically drifted virus. Therefore evidence on the full dose of vaccine would be most relevant to immunisation policy.

If, however, it became apparent prior to the start of this study that a half dose of either vaccine were to be recommended for routine use in children, then we would use a half dose of the relevant vaccine in this study.

Cases of Guillian-Barré syndrome, characterised by symmetric paralysis, have previously been attributed to influenza vaccination. The possible association with the influenza vaccine was initially suggested following the 1976-1977 A/ New Jersey (Swine 'flu) season, when relative risks between 4.0 and 7.6 in the 6 or 8 week period post vaccination were seen. Variation in the number of cases of Guillian-Barré syndrome from year to year and season to season are well recognised. An extensive study of all cases of Guillian-Barré syndrome recorded on the General Practice Research Database (total cases 989) in the period 1990-

2005 found no association of Guillian-Barré syndrome with influenza vaccination. In the 90 day period after vaccination the relative risk of Guillian-Barré syndrome was calculated as 0.76. This is in contrast to the relative risk following an influenza-like illness, calculated at 7.35. The occurrence of Guillian-Barré syndrome related to vaccination as part of this study is considered very unlikely and indeed the vaccine may well protect against Guillian-Barré syndrome by preventing influenza itself.

This study aims to compare the immunogenicity, reactogenicity and safety of the two H1N1 vaccines in children aged 6 months to 12 years in a multi centre, open label, randomised head to head trial. Immunogenicity will be assessed by both Haemagglutination inhibition and microneutralisation. Although EMEA guidelines for licensure of influenza vaccine are based on HAI assays, the primary objective for this study is to determine the percentage of subjects with seroconversions (i.e., fourfold or greater increases in antibody titre) by MN, while determination of the proportion of subjects which show seroconversion by HI will be a secondary objective. The decision for the preference of MN titres over HI titres was made based on recently published observations by CDC[3] and results from the Health Protection Agency's own analysis, which showed that the MN assay generally yields higher titres and detected more seroconversions (i.e., fourfold or greater increases in antibody titres) to A/California/04/2009 than the HI assay (although both generally show high correlation).

In addition to the collection of serum samples for analysis of vaccine immunogenicity, with specific consent the cellular 'plug' remaining after centrifugation from participants in Oxford, London, and Southampton will be stored and sent (as applicable) to the Oxford Vaccine Group for DNA extraction. The DNA samples obtained in this study can then contribute to a DNA bank pooling samples from multiple different Oxford Vaccine Group studies. These DNA samples can be used for genome wide analysis of the genetic factors influencing the host response (immunogenicity and reactogenicity) to the vaccines received in the relevant studies. This DNA extraction and storage will only occur with the specific consent of participants, and DNA will not be analysed for any other purpose than to assess factors influencing the response to vaccines. Funding for the DNA analysis is independent to funding for this influenza immunogenicity and reactogenicity study. Similarly, where appropriate consent is given by Bristol and Exeter participants, genetic samples will be stored in the Bristol Research in Infection & Immunity Collaboration Tissue Bank and aliquots made available for genetic analysis relating to this and potentially other future studies.

With appropriate consent, serum samples remaining after the analyses required for this study will be stored for use in future infection and immunity related research studies at the relevant study sites.

4. OBJECTIVES

4.1 Primary Objective

Immunogenicity

- To compare the percentage of children aged 6 months to 12 years of age with a four fold rise in microneutralisation (MN) titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.

Reactogenicity

- To compare the percentage of children aged 6 months to 12 years of age experiencing fever and local reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine

4.2 Secondary Objectives

- To compare the percentage of children aged 6 months to 12 years of age with Haemagglutination Inhibition (HAI) titres of ≥ 1:32 three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- To compare the percentage of children aged 6 months to 12 years of age with a four fold rise in HAI titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- The geometric mean fold rise in HAI titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- The geometric mean fold rise in MN titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.

- The geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- To assess the percentage of children aged 6 months to 12 years of age experiencing non-febrile systemic reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine
- To investigate the effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines in a given individual.

5. TRIAL DESIGN

5.1 Summary of Trial Design

This is a multi centre, open-label, randomised, controlled study in 1000 children aged 6 months to 12 years.

A summary of the trial can be seen in table one:

Table One: Trial summary

	Day 0	Day 21 (3 weeks)	Day 42 (6 weeks)
Group A1 (N~250) 6mths - <3 yrs Baxter vaccine	Vaccination 1 Blood A	Vaccination 2	 Blood B
Group B1 (N~250) 6mths - <3 yrs GSK vaccine	Vaccination 1 Blood A	Vaccination 2	 Blood B
Group A2 (N~250) ≥3 yrs – 12 yrs Baxter vaccine	Vaccination 1 Blood A	Vaccination 2	 Blood B
Group B2 (N~250) ≥3 yrs – 12 yrs	Vaccination 1	Vaccination 2	

GSK vaccine	Blood A		Blood B

5.2 Study Procedures

It is predicted that 1000 total participants will be recruited across the UK, 500 in each of 2 age categories (6 months to <3 years and ≥3 years to 12 years). 250 participants within each age group will be randomly allocated to receive two doses of either the Baxter vaccine or the GlaxoSmithKline vaccine. A baseline blood test will be taken at enrolment and a further blood test at 6 weeks (3 weeks after the second vaccine dose) to determine immunogenicity of the vaccine. A diary card detailing local and systemic effects of the vaccine and any AEs, medications used to treat these AEs and SAEs will be completed by parents/ guardians for the first week after each immunisation, as will a memory aid card used to record solicited adverse events persisting after the first week following immunisation and any medically significant adverse events occurring

5.3 Primary and Secondary Endpoints/Outcome Measures

Primary end points for the immunogenicity analysis will be defined as:

- Percentage of subjects with a 4 fold rise in MN titre between the pre-vaccination sample and sample taken 3 weeks after the second dose

Primary endpoints for reactogenicity analysis

- Percentage of participants experiencing each of fever (≥ 38°C per axilla), local tenderness, local swelling or local erythema within the 7 days following each immunisation with the study vaccines

Secondary endpoints:

- Percentage of subjects with an HAI titre ≥ 1 in 32
- Percentage of subjects with a 4 fold rise in HAI titre between the pre-vaccination sample and sample taken 3 weeks after the second dose
- The geometric mean fold rises in HAI titres from baseline to after three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- The geometric mean fold rises in MN titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.

- The geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- Percentage of participants experiencing each of: reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds).
- Percentage of participants experiencing each of: malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds).
- The effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines.

5.4 Trial Participants

5.4.1 Overall Description of Trial Participants

We intend to recruit 1000 total participants from across the UK, 500 in each of 2 age categories, 6 months to <3 years (i.e. to day before 3rd birthday) and ≥ 3 years to 12 years. 250 participants within each age group will be randomly allocated to receive the Baxter vaccine and 250 the GSK vaccine.

5.4.2 Inclusion Criteria

The participant must satisfy all the following criteria to be eligible for the study:

- baby or child aged between 6 months to 12 years of age (i.e. to day before 13th birthday).
- for whom a parent/legal guardian has given written informed consent after the nature of the study has been explained;
- available for all the visits scheduled in the study
- willingness to complete all study procedures

5.4.3 Exclusion Criteria

The potential participants may not enter the study if ANY of the following apply:

- History of any vaccine against novel influenza A strain H1N1 (based on verbal confirmation from parent/guardian);

- Previous laboratory confirmed case of novel influenza A strain H1N1 or treatment with oseltamivir or zanamivir for novel influenza A strain H1N1 (n.b. a child commenced on treatment with oseltamivir or zanamivir for novel influenza A strain H1N1 whose treatment was stopped following negative microbiological tests for H1N1 on nasals swabs would be allowed to enrol in the study].
- History of severe allergic reaction after previous vaccinations or hypersensitivity to any H1N1 vaccine component;
- Current egg allergy
- Known or suspected impairment/alteration of the immune system
- Disorders of coagulation
- Immunosuppressive therapy, use of systemic corticosteroids for more than 1 week within the 3 months prior to enrolment
- Receipt of blood, blood products and/or plasma derivatives or any immunoglobulin preparation within 3 months prior to enrolment;
- Intent to immunize with any other vaccine(s) against novel influenza A strain H1N1 throughout the study period;
- Participation in another clinical trial of an investigational medical product
- Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives. Children with chronic, stable medical illnesses that do not result in immunosuppression (e.g. cerebral palsy, epilepsy, cystic fibrosis, congenital heart disease) will be allowed to participate in the study, unless these conditions will in some way interfere with the completion of study procedures. Children with conditions that may alter the immune response to vaccines (e.g. Trisomy 21) or will affect the ability to accurately describe adverse events (e.g. children over 5 years of age but with severe learning difficulties) will be excluded.

5.4.4 Temporary Exclusion Criteria

- Participants who have experienced fever (>38.0°C) within the previous 24 hours.
- Participants receiving another immunisation within 3 days prior to enrolment (21 days for any live vaccine), or planning to receive another vaccine within 7 days of enrolment.

5.5 Expenses and Benefits

All participants will be reimbursed £10 for each study visit to cover travel expenses. These payments will be provided to participants at the conclusion of the third and final study visit (or following the scheduled date for this visit if this were not to be completed).

5.6 Study Procedures

5.6.1 Recruitment and pre screening

In order to recruit the required cohort of 1000 participants, several strategies may be employed:

Direct mail-out: This will involve obtaining names and addresses of children via the Child Health Computer database or sending information home from schools with other school mailings.

Direct email and web newsletter advertising via local school parent email databases

Direct email and web newsletter advertising the study in Hospitals and Universities in participating regions

Radio and local newspaper advertisement campaign: adverts will be placed on local radio/newspapers with brief details of the study and contact details for further information.

Radio/television interviews: Regional radio and television stations will be contacted to arrange an interview opportunity with one of the study investigators.

Display of posters advertising the study in hospitals, at doctor's surgery, schools and other public places.

Presentation of relevant information at suitable locations, e.g. information sessions in schools and nurseries.

Description of study and copy of information booklet on study site websites.

Once an expression of interest has been received by the study centres an appointment would be made for them to attend at the designated recruitment centre where informed consent would be taken and the first study visit would be carried out. In schools, separate informed consent sessions may be arranged for parents where this is required. Due to the number of participants to be enrolled within a short time frame, some study centres may choose not to have a formal pre-screening process. Instead, the inclusion and exclusion criteria will be made clear in the information letter made available to all families interested in

participating in this study, and families will be encouraged to make an appointment only if their child has no exclusion criteria.

5.6.2 Informed consent

At Visit 1, written and verbal versions of the participant information and informed consent will be presented to the participants' parent or legal guardian detailing no less than:

the exact nature of the study;

the implications and constraints of the protocol;

the known side effects and any risks involved in taking part.

It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant's parent or legal guardian will be allowed as much time as required to consider the information, and the opportunity to question the researcher, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will be obtained by means of a dated signature of the person legally responsible for the participant and signature of the person who presented informed consent. A copy of the signed Informed Consent will be given to the participant's parent or legal guardian. The original signed form will be retained at the study site. The informed consent discussion will be conducted by a nurse or doctor who has been trained in the consent process. The written informed consent form and any other written information will be revised whenever important new information becomes available that may be relevant to the consent. Any revised written informed consent form and written study information will be submitted to an ethics committee for approval before use.

The participant's parent or legal guardian will be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information will be documented.

5.6.3 Screening and eligibility assessment

Following the attainment of informed consent, potential participants will be assessed by a study doctor to determine whether the candidate satisfies the inclusion/ exclusion criteria and to aid in the analysis of data. This assessment will include:

- Demographics: The date of birth, ethnicity and gender.
- Medical History: Details of any significant medical history based on parental recall

(including previous seasonal influenza vaccination, atopy and a personal or family history of seizures).

- Gestational age at birth (for participants under 1 year of age only).
- Concomitant Medication: All immunosuppressive medication and non-steroidal anti-inflammatory medications.
- Physical Examination
- Axillary temperature.

The details of this assessment will be recorded in the CRF. If the inclusion/ exclusion criteria are satisfied (including willingness to have a blood sample taken) and the informed written consent has been obtained the participant will be randomised to receive either the Baxter or the GlaxoSmithKline vaccine

5.6.4 Randomisation

Envelope randomisation will be generated by Nick Andrews or another statistician at the Health Protection Agency. The randomisation envelope will only be opened once the participant has demonstrated their willingness to have a blood test; at the point of randomisation the child will be considered enrolled into the study. The study will be open label, however the group to which they have been randomised will be concealed until after the point of enrolment.

5.6.5 Baseline assessments

1. Perform blood draw collecting up to 6 ml in the 6 month to 3 year age groups and10ml in the 3 – 12 year age groups.
2. Randomise participant to receive either the Baxter or GSK vaccine
3. Administer vaccination, as per randomisation group.
4. Record vaccination details in participant's 'red book' and/or the study vaccination card.
5. Observe the participant for at least 20 minutes after vaccination for any immediate reactions.
6. Fill out an 'unscheduled vaccination' form for the participant's Primary Care Trust.
7. Fill out a notification to the participant's GP of the vaccine administered.
8. Provide participant with study centre contact details (including 24 hour telephone advice line contact details for study staff member).
9. Instruct participant on notifying study centre of any serious adverse events/reactions.
10. Instruct participants to use antipyretics only to treat fever or other adverse reactions, rather than prophylactically.

11. Provide participant's parent or legal guardian with a Diary Card to detail local and systemic effects and AEs in first seven days after immunisation and Memory Card to record any ongoing solicited reactions or doctor's visit/visit to Emergency Department from day 8 to the next visit.
12. Schedule Visit 2, 21 days after Visit 1.

5.6.6 Subsequent assessments

Eligibility Check

The on-going eligibility of the participant will be reviewed at each visit. The participant's medical status will be assessed to detect:

1. any serious reaction related to the investigational vaccine
2. any further condition occurring which in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Follow-up Phone Call

5-7 days after Visit 1

1. A follow-up phone call will be made to the participant's parent or legal guardian 7 days after the first administration of the study vaccine. This phone call will establish whether an SAE has occurred during the last 7 days.
2. Where an SAE has occurred that is deemed to need further review the information will be passed on to a nurse or medic from the study team who will phone the participant's parent or legal guardian to discuss further.
3. The phone call will also serve as a reminder to return the diary card and complete the memory card as appropriate.

Visit 2

21 days (+/-7 days) after visit 1 date.

1. Obtain interim history and check eligibility criteria, specifically assessing for:
    a. serious adverse events
    b. adverse events requiring a visit to a physician or emergency department or potentially leading to the withdrawal of the participant
    c. newly prescribed vaccines
    d. any solicited AEs continuing on after day 7 post-immunisation or any medically significant AEs (as recorded in the memory aid card).

2. Measure axillary temperature immediately prior to vaccination and record on CRF.
3. If the participant is still suitable for inclusion in the study, administer vaccination with either Baxter or GSK vaccine as per randomisation group.
4. Record vaccination details in participant's 'red book' and/or study vaccination card.
5. Observe the participant for at least 20 minutes after vaccination for any immediate reactions.
6. Fill out an 'unscheduled vaccination' form for the participant's Primary Care Trust.
7. Fill out a notification to the participant's GP of the vaccine administered.
8. Ensure participant has study site contact details (including 24 hour emergency contact details for study staff member).
9. Instruct participant on notifying study site of any serious adverse events/reactions.
10. Provide participant's parent or legal guardian with a Diary Card to detail local and systemic effects and AEs in first seven days after immunisation and Memory Card to record ongoing solicited reactions or doctor's visit/visit to Emergency Department from day 8 to the next visit.
11. Schedule Visit 3, 21 days after Visit 2.

Follow-up Phone Call

5-7 days after Visit 2

1. A follow-up phone call will be made to the participant's parent or legal guardian 7 days after the second administration of the study vaccine. This phone call will establish whether an SAE has occurred during the last 7 days.
2. Where an SAE has occurred that is deemed to need further review the information will be passed on to a nurse or medic from the study team who will phone the participant's parent or legal guardian to discuss further.
3. The phone call will also serve as a reminder to return the diary card and complete the memory card as appropriate.

Visit 3

21 days (- 7 days to + 14 days) after Visit 2

1. Obtain interim history, specifically assessing for:
    a. serious adverse events
    b. adverse events requiring a visit to a physician or emergency department or potentially leading to the withdrawal of the participant

c. newly prescribed vaccines
d. any solicited AEs continuing on after day 7 post-immunisation or any medically significant AEs (as recorded in the memory aid card).

2. Perform blood draw collecting up to 6 ms in the 6 month to 3 year age groups and 10 mls in the 3 – 12 year age groups.

Every endeavour should be made to respect the timelines indicated above, however if a participant is not able to undertake a study visit within these timelines (e.g. due to intercurrent illness) then as long as the visit is able to be done in a reasonably timely manner they will not be excluded from the study. In particular, every effort should be made to complete the immunisation course once this has been commenced.

5.6.7 Blood sampling

The volume of blood samples obtained from infants less than 3 years of age will be up to 6 mL, the volume after 3 years of age will be up to 10 mL. If the initial attempt at venepuncture is unsuccessful, (i.e. less than 4 ml obtained), then, depending on the judgment of the staff member, assent will be sought from the parents and child (as appropriate according to age) to have a further attempt. Following the initial attempt at venepuncture, a parent may decline any of these further attempts and their child will still be eligible to remain in the study. A local anaesthetic cream (Ametop or Emla according to local practice at each site) or cold spray (ethyl chloride) will be applied for an appropriate period of time prior to each venepuncture. The parent/guardian will be provided with the anaesthetic cream and instructions for use prior to Visit 3 so that they can apply it to the child's skin in the appropriate amount of time prior to the visit.

5.6.8 Diary card for recording local and systemic side effects

The participant's parent or guardian will be instructed to complete a diary card to record daily temperatures and describe local and systemic symptoms, all adverse events (AEs), and usage of analgesic/antipyretic medication for seven days following each vaccination starting on the day of administration.

Upon completion of the diary cards (i.e. 7 days after administration of the study vaccine) they will be mailed by the participant's parent or guardian directly to the Health Protection Agency. Data Clarification Forms or annotated photocopies of the diary card will be sent to the study site by the Health Protection Agency when queries arise from the participant's diary card.

These data queries will be resolved with the participant's parent or guardian when the participant attends for the second (V2) visit and the third (V3) visit.

5.6.9 Memory Card for recording visits to doctors and emergency departments

The participant's parent or guardian will be instructed to complete a memory card to record any visits to a doctor or emergency department from the eighth day after vaccination until the next study visit and any adverse events recorded in the diary card that are ongoing after day 7.

The memory card will be returned to the study site at the following study visit at which point the study staff will review the recorded information with the participant's parent or guardian and record this in the CRF.

5.7 Laboratory methods

Blood samples taken from participants will be stored at room temperature for up to 60 minutes, and then stored at between 2 to 8°C. Samples collected at each study site will be centrifuged at 3000 rpm for 10 minutes within 24 hours at the study site and separated into at least 2 aliquots for storage at or below -30°C. Aliquots will be shipped separately to the Centre for Infections Virus Reference Department (VRD) for testing. All samples will be analysed by microneutralisation (MN) and haemagglutination inhibition (HAI) with the NIBRG121 virus (rg virus based on ACalifornia/7/2009 (vH1N1) and A/Puerto Rico/8/34). Pre and post vaccination sera will be tested in parallel.

Microneutralisation (MN)

The microneutralisation assay will be performed in 96- well format according to previously described protocols and SOPs developed at the Respiratory Virus Unit (RVU).

Serum Pre-treatment

Elimination of complement (e.g. from Foetal Calf Serum in culture medium) will be achieved by incubation of study sera and appropriate quality control sera (provided and chosen according to test virus by the RVU; usually serum of ferret, sheep or human, with/without neutralization activity) at +56°C / 30min. This step will be performed simultaneously for all study samples and control sera.

MN Test

The MN analysis with the NIBRG121 virus will be performed as follows: a 6-step, two-fold dilution series (covering titres 20 to 640) will be set up for each of the samples and control sera. After addition of a pre-titred virus (usually around 100x$TCID_{50}$ per well or 0.1-1 virus particle per cell) neutralisation will be performed by incubation of the virus/serum mixture at room temperature for 1h.

After neutralization, a suspension of MDCK cells will be added and the plates will be incubated for 16h at 37°C in a CO2 incubator. The remaining infectivity of virus after neutralisation is determined in an EIA format using a mAb to detect expression of viral nucleoprotein. The amount of nucleoprotein expression is determined photometrically (OD450) using a plate reader.

Reading

An Optical Density reading for each dilution step for each sample will be used to calculate the titre. The titre will be reported as the reciprocal dilution at which 50% of the virus is neutralized (e.g. titre of 100). The microneutralisation analysis will be performed in duplicate (in separate runs on 2 days) for each sample.

The two titres for each sample must not differ by more than a two-fold serial dilution. In cases, where samples don't fall within this limit, a third analysis is performed and the two closest titres (which must be within a two-fold serial dilution) will be reported.

Haemagglutination Inhibition (HAI)

The principle of the HAI test is based on the ability of specific anti-influenza antibodies to inhibit haemagglutination of red blood cells (RBC) by influenza virus haemagglutinin antigen (HA). The sera to be tested have to be previously treated to eliminate the non-specific inhibitors and the anti-species HAs. The experiment will be performed in accordance to protocols and SOPs established by RVU.

Serum Pre-treatment

Elimination of non-specific inhibitors will be achieved by incubation of the unknown serum samples and quality control sera (serum of ferret or human immunized with influenza virus) with neuraminidase (RDE II; 18 h / +36°C followed by heat-inactivation 1h / +56°C).

All samples (sera pre- and post-vaccination and controls) will be prepared simultaneously.

HAI Test

For the HI analysis with the NIBRG121 virus samples and controls will be titrated in an 8-step, two-fold dilution series (covering titres 8 to 1024) and incubated with the haemagglutinin antigen suspension (previously titrated to adjust the dilution at 4 haemagglutination units/25 µL; 50% endpoint). The haemagglutinin antigen is not added to the well dedicated to the RDE quality control.

The mixture is incubated for 1 hour at room temperature and 25 µL of the 0.5% RBC suspension (turkey blood) are added. The reaction is left for 1/2 hour at room temperature before reading.

Reading

The serum titre is equal to the highest reciprocal dilution, which induces a complete inhibition of haemagglutination. The titre of each quality control serum is close to the previously assigned value (within one serial two-fold dilution limits).

The RBC controls (red blood cell suspension without antigen) and the RDE controls do not produce any agglutination.

Each serum sample is titrated in duplicate and individual titres will be reported (two for each sample). These must not differ by more than a two-fold serial dilution. In cases, where samples don't fall within this limit, a third analysis is performed and the two closest titres (which must be within a two-fold serial dilution) will be reported.

5.8 Definition of End of Trial

The end of trial is the date at which the processing of samples for the purposes of this study has been completed.

5.9 Discontinuation/ Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Consent withdrawn
- Lost to follow up

Withdrawn participants will not be replaced.
Data generated from participants that later withdraw will still be included in the analysis on an intention to treat basis.
The reason for withdrawal will be recorded in the end of study CRF if the participant offers an explanation.
If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

5.10 Source Data

Source documents are original documents and records from which participants' data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, and correspondence.
CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data).
All documents will be stored safely in confidential conditions. With the exception of the study diary card (where the participant's first name only will be listed) and correspondence sent to the relevant child health computer department and general practitioner all documents leaving the study sites will refer to the participant by the study participant number/code, not by name.

6. TREATMENT OF TRIAL PARTICIPANTS

6.1 Description of Study Treatment

Baxter H1N1 vaccine
The novel Influenza A H1N1 Vaccine produced by Baxter Vaccines is a whole virus unadjuvanted vaccine with 7.5 µg of H1N1 virus per 0.5 ml dose. The H1N1 virus is grown in a vero cell culture. The vaccine is presented as a multidose vial (10 doses per vial).

GSK H1N1 vaccine
The novel Influenza A H1N1 Vaccine produced by GSK Vaccines is a split virion vaccine adjuvanted with an oil in water emulsion (ASO3) containing Squalene, Vitamin E- as immunostimulant and Tween 80 as surfactant. The vaccine also contains the preservative thiomersal. Each 0.5 ml dose contains 3.75 µg of H1N1 virus. The H1N1 virus is grown in an

egg cell culture and is presented in a multidose vial (10 doses per vial) to be reconstituted with the adjuvant (also in a multi-dose vial, 10 doses per vial) prior to administration.

If at the start of the trial there is clinical data or a recommendation from JCVI that supports the use of a half dose of either vaccine in children this will be used, however in the absence of any specific directive of this nature a full dose will be used (see section 3, background and rationale).

Both vaccines are to be administered intramuscularly via a 23 gauge, 25 mm needle into either the upper arm or thigh (if muscle bulk of the upper arm is insufficient). Vaccines should be administered into the non-dominant arm or thigh, ensuring consistency of limb administration between both doses of vaccine.

6.2 Storage of Study Vaccine

Prior to the commencement of the trial the Department of Health will supply the Baxter vaccine (Celvapan) to the Centre for Infections (CFI) which holds a GMP licence for re-labelling of IMPs. At CFI this vaccine will be relabelled for use in this clinical trial. They will then be shipped via cold chain to the trial sites using accredited couriers.
The GSK vaccine (Pandemrix) will be labelled for use in this clinical trial by GSK and shipped directly to the trial sites using accredited couriers.
The labels applied to these vaccines will include information on the study name/code, the CI and for 'clinical trial use only' and vial number.
The investigator (or delegate) will make an inventory and acknowledge receipt of all shipments of study medication/vaccine.
All vaccine supplies must be stored between +2 and +8°C. Vaccines that have been stored differently from the sponsor's recommendations must not be used unless the sponsor provides written authorization for use. In the event that the use cannot be authorized, vaccine supply must be replaced with fresh stock supplied by the sponsor.

6.3 Vaccine administration

The investigator will be responsible for the administration of the vaccine to subjects enrolled into the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.
The vaccine must be visually inspected before use.

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Any axillary temperature ≥ 38°C or serious active infection is reason for delaying vaccination.

Standard immunization practices should be observed and care should be taken to administer the injection intramuscularly. A 23 gauge, 25 mm needle is to be used for administration. As with all injectable vaccines, appropriate medical treatment and supervision should be readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 should be available in case of any anaphylactic reactions. Care must be taken to ensure the vaccine is not injected into a blood vessel.

6.4 Vaccine compliance

The investigator will be responsible for adequate and accurate accounting of vaccine usage. The investigator or designee will administer the study vaccines only to individuals included in this study following the procedures set out in this study protocol. The date, dosage, and time of the vaccinations will be recorded. The investigator will track vaccines received, used and wasted and will retain all unused or expired products until the sponsor is satisfied that the vaccine accountability records are correct. Thereafter, all unused vaccines are to be destroyed at the investigational site. An overall summary of vaccines supplied, received, wasted, used and returned will be prepared at the conclusion of the study.

6.5 Adherence to randomisation list

The investigator or his designate will administer the vaccine as indicated on the randomization list for the individual subject. Adherence to the randomization will be verified by the Study Monitor by checking the vaccination records maintained in the investigator's study file.

6.6 Accountability of the Study Treatment

All vaccine doses will be accounted for within an accountability log. Unused vaccine at the end of the trial will be disposed of with written documentation describing this process.

6.7 Concomitant medication

Any immunosuppressant or non-steroidal anti-inflammatory medication taken at the time of enrolment into the study is to be recorded on the CRF.

7. SAFETY REPORTING

7.1 Definitions

7.1.1 Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation participants administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment (the study medication).

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

7.1.2 Adverse Reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose.

The phrase "responses to a medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

7.1.3 Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.1.4 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death,

- Is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events. NOTE: Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.1.5 Serious Adverse Reaction (SAR)

An adverse event (expected or unexpected) that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.

7.1.6 Expected Serious Adverse Events/Reactions

No serious adverse events or reactions are expected. Extensive study of Guillian-Barré syndrome has demonstrated that there is no association between influenza vaccines and Guillian-Barré syndrome, and therefore Guillian-Barré syndrome is not expected to occur in this study.

7.1.7 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information.

7.1.8 Adverse event of special interest (AESI)

Adverse events of special interest are those AEs recommended by the CHMP for inclusion as part of Risk Management Plans to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/359381/2009) and include: neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's palsy, demyelinating disorders, and vaccination failure.

7.1.9 Potentially Immune Mediated Diseases or pIMDs

Adverse events that constitute pIMDs are those diseases and conditions listed in Appendix E.

7.2 Reporting Procedures for All Adverse Events

In the seven days following vaccine administration the following solicited symptoms will be recorded by the participants parents/guardian in their study diary:

- injection site reactions (local tenderness, swelling or erythema)
- Fever ((≥ 38°C per axilla)
- Non febrile systemic reactions, i.e:
- reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds).
- malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds).

In addition parents/ guardians will be requested to record any other general symptoms in the 7 days post vaccination in the diary card.

These study diaries will be sent directly to the HPA for review by medical staff prior to transciption of the data to the study database. If clarification of any adverse events is required then the study staff at the relevant study site will be contacted.

At visit 2 and 3 medically significant adverse events (as recorded on the memory aid card) that have occurred in the period between the seven days after vaccination and the subsequent study visit (visit 2 or 3) will be recorded on the CRF, whether or not these are attributed to the study medication. Medically significant AEs will be defined as AEs requiring a physician visit, Emergency Department visit, or leading to a subject's withdrawal (with the exclusion of pre-planned visits and GP or emergency department visits for routine medical care). Adverse events solicited in the diary card that are ongoing after day 7 (as recorded in the memory aid card) will similarly be recorded in the CRF.

The following information will be recorded for medically significant AEs: description, date of onset and end date, severity, assessment of relatedness to study medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship of medically significant AEs to the study medication will be assessed by a medically qualified investigator according to the following criteria:

- Related - If the causal relationship between the IMP and the SAE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- Not related - If there is no causal relationship between the IMP and the SAE i.e. the event is caused by something other that the IMP e.g. underlying disease, a concomitant medication.

Verbal consent will be sought from participants to follow up all AEs considered related to the study medication, AEs leading to the participant's withdrawal from the study, AESIs, pIMD and pregnancies until resolution or the event is considered stable. If obtained this verbal consent will be documented in participant's case report form (CRF).

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment (see section 6.6). A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.
The rates of adverse events experienced by participants will be reviewed by a data monitoring committee (see section 10 below).

7.3 Reporting Procedures for Serious Adverse Events

All SAEs must be reported to the chief investigator or delegate for review within one working day of discovery or notification of the event. The chief investigator or delegate will then forward these on to CTRG and to the relevant vaccine manufacturer within 24 hours of receipt. All SAE information must be recorded on a signed SAE form and relayed to the chief investigator by fax or email. Additional information received for a case (follow-up or

corrections to the original case) need to be detailed on a new SAE form and faxed to the chief investigator or delegate for review and forwarding to the CTRG.

All serious adverse reactions (SAR's), AESIs and pIMDs will be reported on CIOMS 1 forms to the relevant manufacturer within 24 hours of any study staff becoming aware of these events. These events should also be reported as SAE's using the appropriate forms.

The CI will report all SUSARs to the MHRA, the Research Ethics Committee concerned and Host NHS Trusts. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.
In addition to the expedited reporting above, the CI shall submit once a year throughout the clinical trial or on request a safety report to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and sponsor.

The CTRG will ensure that all SAEs are reviewed by medical monitors on a weekly basis and at the next meeting of the Oxford Radcliffe Hospitals Trust / University of Oxford Trials Safety Group (TSG), who will meet at regular intervals and consider:

- Occurrence and nature of adverse events
- Whether additional information on adverse events is required
- Consider taking appropriate action where necessary to halt trials
- Act / advise on incidents occurring between meetings that require rapid assessment (e.g. SUSARs)

If deemed appropriate, the TSG will refer the SAEs experienced in the study to the data monitoring committee for review.

7.4 Reporting of Pregnancy

Although pregnancy tests will not be performed in this study due to the age range of the participants, if the investigators were to become aware of a study participant receiving a study vaccine within 30 days prior to pregnancy or during pregnancy, then they would inform the chief investigator or delegate, who will inform the sponsor, the ethics committee, the MHRA and the vaccine manufacturer of this occurrence.

8. STATISTICS

8.1 Description of Statistical Methods

Immunogenicity

The following statistical parameters will be determined for each study group:

- Percentage of subjects with an HAI titre ≥ 1 in 32
- Percentage of subjects with a 4 fold rise in HAI titre between the pre-vaccination sample and sample taken 3 weeks after the second dose
- Percentage of subjects with a 4 fold rise in MN titre between the pre-vaccination sample and sample taken 3 weeks after the second dose
- Geometric mean of pre-vaccination serum HAI titres
- Geometric mean of post-vaccination serum HAI titres
- Geometric mean of pre-vaccination serum MN titres
- Geometric mean of post-vaccination serum MN titres
- Geometric mean of the rise in HAI titres from pre- to post-immunisation
- Geometric mean of the rise in MN titres from pre- to post-immunisation

The above analyses will be performed on all participants in the Per-protocol (PP) immunogenicity population (see section 8.8). In addition, a sub-analysis will be performed on the participants in the PP population who were seronegative by for the relevant assay (MN or HAI) at enrolment.

In the event of HAI titres being negative at the initial dilution (1:8) an arbitrary value of 4 will be assigned for calculation of fold rise and GMTs, while for the MN assay (initial dilution 1:20) this value will be 10.

Reactogenicity

- Percentage of participants experiencing each of fever (≥ 38°C per axilla), local tenderness, local swelling or local erythema within the 7 days following each immunisation with the study vaccines
- Percentage of participants experiencing each of: reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds).

- Percentage of participants experiencing each of: malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds).

In children aged under 5 years the severity of solicited systemic reactions will be graded according to the following criteria:

Reduced Feeding:

0 None	
1 Mild	Eating less than normal for 1-2 feeds
2 Moderate	Missed 1-2 feeds completely
3 Severe	Refused most or all feeds

Reduced Activity

0 None	
1 Mild	Less interested in surroundings, toys etc
2 Moderate	No interest in above and sleeping through feeds
3 Severe	Sleeping most of the time

Increased Irritability

0 None	
1 Mild	Continuously irritable for less than 1 hour
2 Moderate	Continuously irritable for 1 to less than 3 hours
3 Severe	Continuously irritable for 3 or more hours

Persistent Crying

0 None	
1 Mild	Cried continuously for less than 1 hour
2 Moderate	Cried continuously for 1 to less than 3 hours
3 Severe	Cried continuously for 3 or more hours

Vomiting

0 None	
1 Mild	1-2 episodes without interfering with routine

2 Moderate Several episodes & cannot keep any food down
3 Severe: Frequent episodes & taking nothing by mouth

Diarrhoea
0 None
1 Mild More loose stools than usual
2 Moderate Frequent runny stools without much solid material
3 Severe Multiple liquid stools without much solid material

In children aged 5 years or above the severity of solicited systemic events will be assessed on the following scale:

Generally unwell (malaise)
0 = No
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

Headache
0 = None
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

Vomiting
0 None
1 Mild 1-2 episodes without interfering with routine
2 Moderate Several episodes & cannot keep any food down
3 Severe: Frequent episodes & taking nothing by mouth

Diarrhoea
0 None
1 Mild More loose stools than usual
2 Moderate Frequent runny stools without much solid material

3 Severe Multiple liquid stools without much solid material

Reduced feeding

0 None

1 Mild Eating less than normal for 1-2 meals

2 Moderate Missed 1-2 meals completely

3 Severe Refused most or all meals

Myalgia

0 = None

1 = Mild (transient with no limitation on normal activity)

2 = Moderate (some limitation in daily activity)

3 = Severe (unable to perform normal daily activity).

Arthralgia

0 = None

1 = Mild (transient with no limitation on normal activity)

2 = Moderate (some limitation in daily activity)

3 = Severe (unable to perform normal daily activity).

In both age groups, local erythema and swelling will be classified as absent, less than 2.5 cm and greater than or equal to 2.5 cm, while local tenderness will be assessed on the following scale:

0 = None

1 = Mild (transient with no limitation on normal activity)

2 = Moderate (some limitation in daily activity)

3 = Severe (unable to perform normal daily activity).

Reactogenicity will be assessed by calculating the percentage of participants with solicited local reactions and fever in each group (i.e. the percentage of participants within each age group receiving each vaccine experiencing these reactions).The percentage of participants in

each group experiencing each of these reactions after each vaccine will be calculated, as will the percentage of participants in each group experiencing each reaction during the immunisation course. The percentage of participants experiencing any solicited local reaction or fever may also be calculated, both after each immunisation and during the whole vaccine course. As well as being calculated for each group, these percentages may also be calculated for all recipients of each vaccine (regardless of age group).

The percentage of participants experiencing non-febrile solicited adverse events (e.g. irritability or vomiting) will be calculated for recipients of each vaccine aged less than 5 years and for those aged 5 years and over. This will be calculated for participants experiencing each non-febrile solicited adverse event after each vaccine dose and during the whole immunisation course, and the percentage of participants experiencing any solicited local reaction or fever may also be calculated, both after each immunisation and during the whole vaccine course.

The number of subjects with reported serious adverse events up to 7 days after each vaccination and during the whole study will also be calculated, as will the number of participants with any adverse event in the first week after immunisation and any medically significant adverse event during the study.

In the event of one of the vaccines not being available at the start of this study, an alternative enrolment strategy will be conducted, in which participants are initially recruited to receive the available vaccine alone. This could be done at all sites or a selection of sites as appropriate, and enrolment for this phase would continue until one half of the participants due to receive that vaccine had been recruited (i.e. 125 in each age group). Recruitment to the study will then cease until both vaccines are available, at which time a revised randomisation (2:1) scheme will be employed, so that equal numbers of participants will have received each vaccine by the study's end.

8.2 The Number of Participants

With a sample size of 100-200 in each of two age groups for each vaccine the precision (95% CI) of estimates of percentages with adverse reactions or responding to vaccination is shown in the table below.

	N=100	N=150	N=200
Observed %	95% CI*	95% CI	95%CI
0	0 to 4	0 to 2	0 to 2
10	5 to 18	6 to 16	6 to 15
20	13 to 29	14 to 27	15 to 26
30	21 to 40	23 to 38	24 to 37
40	30 to 50	32 to 48	33 to 47
50	40 to 60	42 to 58	43 to 57
60	50 to 70	52 to 68	53 to 67
70	60 to 79	62 to 77	63 to 76
80	71 to 87	73 to 86	74 to 85
90	82 to 95	84 to 94	85 to 94

*exact 95% CIs are shown

So precision is within +/- 10% for N=100, +/- 8% for N=150 and +/- 7% for N=200

Detectable differences in percentages between vaccines or age groups will be as follows (80% power, 5% significance level, N=100-200 per group compared)

	N=100		N=150		N=200	
True % in first group	% in second group detectable (below)	% in second group detectable (above)	% in second group detectable (below)	% in second group detectable (above)	% in second group detectable (below)	% in second group detectable (above)

0	-	9	-	6	-	5
10	0	26	2	22	3	21
20	6	39	8	35	10	33
30	13	50	16	46	18	44
40	21	61	24	57	26	54
50	30	70	33	67	36	64
60	39	79	43	76	46	74
70	50	87	54	84	56	82
80	61	94	65	92	67	90
90	74	100	77	98	79	97

So, for example, if one vaccine has a true local reaction rate of 10% in a given age group then a rate of 26% is detectable as different for the other vaccine with N=100 down to 21% for N=200. Similarly if one vaccine had a seroconversion rate of 70%, then it would be possible to detect a difference in seroconversion rates to the other vaccine if this value was below 56% or greater than 82%.

For comparison of geometric mean HI fold rises between vaccines or ages, the sample size of 200 will allow 1.34 fold differences to be detectable with 80% power at 5% significance. This uses an estimate of 0.45 for the log10 scale SD of post vaccination fold rises as seen with other influenza vaccines. For N=100 1.51 fold differences are detectable and for N=150 1.40 fold differences.

Based on these calculations a sample size of 200 per group has been chosen to optimise the power to detect a difference in the immunogenicity and reactogenicity of the two vaccines in the two age groups. Specifically, it was felt that a difference in seroconversion or local reaction/ fever rates of -14% and +12% around a (hypothetical) rate of 70% would be of

clinical importance, and that it would not be possible to this degree of variance with a smaller sample size.

In order to account for about 25% of participants not completing the study or not having blood samples obtained, the overall number of participants is therefore 1000. Due to the rapid nature of recruitment across multiple sites that is required for this study, it may not be possible to precisely match the number of participants to 1000; the actual figure enrolled may therefore be slightly higher or lower than this target figure. Recruitment is provisionally expected to be approximately 250 participants at 3 sites (Oxford, Southampton, and St. George's) and approximately 250 participants at 2 sites combined (Bristol and Exeter), however should it be required to optimise recruitment then it will be possible for any site to recruit more than the provisional number of participants.

If recruitment were to be lower than expected then the above calculations suggest that the immunogenicity and reactogenicity of the individual vaccines could still be assessed with reasonably narrow confidence intervals (e.g. +/- 10% for 100 participants in each group), however the ability to detect differences between the two groups would be reduced.

Withdrawn participants will not be replaced.

It is anticipated that some potential participants who will be allocated a participant number after completion of informed consent will not subsequently be enrolled or randomised (e.g. if an exclusion criterion is identified at medical assessment or the child is unwilling to have a blood sample taken). An excess of participant numbers will therefore be allocated for each study site to allow for this.

8.3 Interim analysis

An interim analysis may be performed when results of laboratory assays or adverse event rates are available on about 250 participants for each vaccine (i.e. half-way through). This analysis will consist of a descriptive analysis (proportions and 95% CI's) of the primary immunogenicity end point and a subset of safety end points (fever ≥ 38°C, local redness and swelling ≥ 2.5 cm). Continuation of recruitment will not be dependent on the results of this analysis, which is being performed due to the need for rapid data on these vaccines in children. An additional interim analysis, in which adverse event rates after the first dose of

vaccine are evaluated by study statistician's and/or the data monitoring committee, may be performed.

8.4 The Level of Statistical Significance

The level of statistical significance will be taken as 5%.

8.5 Criteria for the Termination of the Trial.

The study uses two vaccines produced by Baxter and GlaxoSmithKline. Both manufacturers have gained marketing authorisation approval from the EMEA for a pandemic strain vaccine under the "mock-up" dossier route based on limited clinical trial data for a candidate H5N1 vaccine. Trials of the mock up vaccines have been conducted in adults and there is some safety data of the use of the GSK H5N1 vaccine in children over 3 years of age. These trials have not reported significant safety concerns. The vaccines are similar to other influenza vaccines that have been licensed and used in children. It is unlikely that any safety issues should lead to termination of the trial, however the data monitoring committee will have the authority to recommend termination of the trial or for immunisation with either of the vaccines to be discontinued. In addition, the investigator has the right to discontinue this study at any time. If the clinical study is prematurely terminated, the investigator is to promptly inform the participants and should assure appropriate therapy and follow-up for the participants.

8.6 Procedure for Accounting for Missing, Unused, and Spurious Data.

The reason for missing data (consent withdrawn, lost to follow-up, removed from study due to serious side effects, death, or unable to obtain any laboratory results) will be indicated but missing data will not be imputed. Amount of missing data between the 2 groups and other demographic characteristics will be compared.

8.7 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any additional analysis or deviation(s) from the analysis plan will be documented and updated according to the statistical standard operating procedure.

8.8 Inclusion in Analysis

The primary immunogenicity analyses will be conducted on a per-protocol (PP) population, consisting of all participants who completed the study and did not experience any significant protocol deviations. All participants in the PP population providing a blood sample following immunisation will be included in the PP immunogenicity analyses, with the exception of

analyses related to the fold rises from baselines, in which all participants in the PP population providing blood samples both before and after baseline will be included in the PP immunogenicity analyses.

An intention to treat (ITT) immunogenicity population will also be defined, consisting of all participants receiving an immunisation and providing a blood sample after immunisation. If the ITT immunogenicity population differs from the PP population by more than 10% then the measures of immunogenicity will also be calculated for the ITT immunogenicity population.

All data will be included up until the time that a participant is withdrawn from the study.

The population for safety analysis will include all those that received a study vaccine and provided any safety/reactogenicity data.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

10. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and the study sites standard operating procedures.

Regular monitoring will be performed according to ICH GCP. Monitoring of this study will be conducted by freelance monitors in collaboration with the quality assurance manager of the Oxford Vaccine Group and local staff at each study centre. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures and an approved monitoring plan, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

A trial steering committee will be formed that will include, but not be limited to, the chief investigator, a statistician, a quality assurance manager and project manager.

A Data Monitoring Committee (DMC) will be convened that will primarily have responsibility for reviewing the adverse event rates and serious adverse events experienced by participants in this study. Due to the rapid nature of recruitment intended for this study, it is not anticipated that the DMC will be able to review immunogenicity data during the study itself. The DMC will be independent of the study team and will report to the trial steering

committee. The DMC will include, but not be limited to, a paediatric infectious disease specialist, a statistician and a consultant with expertise in public health.
This committee will be in addition to the trial safety group (TSG), who will provide review of serious adverse events as part of routine procedures for the CTRG.

11. ETHICS

11.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

11.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

11.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.
The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

11.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. With the exception of the study diary card (where the participant's first name only will be listed) and correspondence sent to the relevant child health computer department and general practitioner all documents leaving the study sites will refer to the participant by the study participant number/code, not by name. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

11.5 Compensation for harm

As study sponsor the University of Oxford will provide indemnity for harm arising as a result of the study protocol.

The Government has already provided an indemnity to Baxter and GSK in relation to any claims arising out of the use of the vaccines purchased under the Advance Purchase Agreements (APA) with those companies, other than where the harm is due to a defect in manufacture. That indemnity covers the use of the vaccine in research projects, as the contractual indemnity provisions are not limited by reference to the circumstances in which the vaccines are used.

In relation to the liability of the sponsors and investigators taking part in the research projects, the usual insurance or indemnity arrangements will apply (for example, in relation to NHS bodies and staff, the NHS Indemnity and Clinical Negligence Scheme arrangements apply).

Exceptionally, given the nature of this study, as part of a wider government response to a major public health emergency, the Department will also offer a “no fault” compensation scheme to trial participants, in relation to serious injury of an enduring and disabling character caused by the vaccines which are the subject of the trials

12. DATA HANDLING AND RECORD KEEPING

Information on study participants will be recorded on hard copy case report forms (CRFs) held locally. CRFs will be supplied by CFI in packs and will include the following:

i. Subject contact details (to be retained locally)
ii. Inclusion and exclusion criteria
iii. Medical history
iv. Immunosuppressive or non-steroidal medication at study start
v. Each vaccination and each blood
vi. Post vaccination follow up at 3 weeks
vii. Study termination record for subjects completing per protocol and for earlier withdrawals
viii. Age specific diary cards for completion by parents
ix. Memory aid card for completion by parents

Each study site will be responsible for generating and retaining their own source documents if required.

Each study participant will have a unique study number which will be allocated following the taking of informed consent. For each participant, sufficient labels with the same study number will be generated at CFI to label all CRFs, diary cards, vaccine vials and blood sample tubes.

In order to identify study staff who have completed each CRF, each site will have a signature sheet, including full name and initials a copy of which will be provided to CFI.

12.1 Data entry at CFI

The CRFs from each trial site will be photocopied locally and the copy sent to CFI with the original retained at the local site. The diary cards will be sent directly to CFI by the participant's parent or legal guardian. The diary cards will be photocopied at CFI and a copy will be sent to the local site to retain in the participant's study file. The only patient identifying information on the CRFs sent to CFI will be study number and participant initials. The only patient identifying information on the diary cards sent to CFI will be the participant's first name on the front page to aid parents who may have more than one child enrolled in the study, and the study number and participant initials. A study database will be constructed at CFI to record the information collected in the CRFs and diary cards. As the data is being entered, the CRFs and diary cards will be monitored. Study diaries will be reviewed by medical staff at the HPA prior to transciption of the data to the study database. If clarification of any adverse events is required or completion errors or omissions are noted then the study staff at the relevant study site will be contacted.

When completion errors or omissions are noted the study site will be notified of the entries requiring correction or clarification. The local investigator will make the correction on the CRFs, crossing out any incorrect information with a single line, and will sign and date the change on the original CRF which will be photocopied again and sent to CFI. On return of the photocopy to CFI the database will be updated accordingly and the photocopy filed with the initial photocopy. Corrections to the diary cards will be made via data clarification forms that will be sent to the study sites to resolve with the participant's parent or guardian on the subsequent study visit.

If diaries have not been returned to CFI at the specified time, the local site will contact the parent and advise CFI of any outstanding diaries weekly by a spreadsheet return. This return will also list by subject number and initials any subject who has withdrawn from the study and complete the “end of study” CRF as appropriate.

Information from the CRFs will be double entered onto the data base at CFI by two independent data-entry staff. Verification routine will be done weekly and data inputting errors corrected.

12.2 Data locking

At the end of the study, the database will be locked and a data extract provided to the study statistician for analysis according to a pre-defined statistical analysis plan. Should an interim analysis be conducted then a dated copy of the database will be made and locked and the analysis conducted on a data extract of that locked database.

13. FINANCE AND INSURANCE

The involved parties will be insured, in accordance with the Clinical Trials regulations, against financial loss resulting from personal injury and/or other damages, which may arise as a consequence of this study. For details see contract agreements.

14. PUBLICATION POLICY

The Investigator will co-ordinate dissemination of data from this study. All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study will be reviewed by each sub-investigator prior to submission.

15. REFERENCES

1. Health Protection Agency Weekly National Influenza Report 23rd July 2009.
2. World Health Organisation Pandemic (H1N1) 2009 briefing note 2: WHO recommendations on pandemic (H1N1) 2009 vaccines, 2009.
3. Katz J, Hancock K, Veguilla V, Zhong W, Lu X, Sun H, et al. Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine. *Morbidity and Mortality Weekly Review* 2009;58(19):521 - 524.

APPENDIX A: PANDEMIC (H1N1) 2009 BRIEFING NOTE 2. WHO RECOMMENDATIONS ON PANDEMIC (H1N1) 2009 VACCINES

13 JULY 2009 | GENEVA -- On 7 July 2009, the Strategic Advisory Group of Experts (SAGE) on Immunization held an extraordinary meeting in Geneva to discuss issues and make recommendations related to vaccine for the pandemic (H1N1) 2009.

SAGE reviewed the current pandemic situation, the current status of seasonal vaccine production and potential A (H1N1) vaccine production capacity, and considered potential options for vaccine use.

The experts identified three different objectives that countries could adopt as part of their pandemic vaccination strategy:

- protect the integrity of the health-care system and the country's critical infrastructure;
- reduce morbidity and mortality; and
- reduce transmission of the pandemic virus within communities.

Countries could use a variety of vaccine deployment strategies to reach these objectives but any strategy should reflect the country’s epidemiological situation, resources and ability to access vaccine, to implement vaccination campaigns in the targeted groups, and to use other non-vaccine mitigation measures.

Although the severity of the pandemic is currently considered to be moderate with most patients experiencing uncomplicated, self-limited illness, some groups such as pregnant women and persons with asthma and other chronic conditions such as morbid obesity appear to be at increased risk for severe disease and death from infection.

Since the spread of the pandemic virus is considered unstoppable, vaccine will be needed in all countries. SAGE emphasized the importance of striving to achieve equity among countries to access vaccines developed in response to the pandemic (H1N1) 2009.

The following recommendations were provided to the WHO Director-General:

- All countries should immunize their health-care workers as a first priority to protect the essential health infrastructure. As vaccines available initially will not be

sufficient, a step-wise approach to vaccinate particular groups may be considered. SAGE suggested the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions: pregnant women; those aged above 6 months with one of several chronic medical conditions; healthy young adults of 15 to 49 years of age; healthy children; healthy adults of 50 to 64 years of age; and healthy adults of 65 years of age and above.

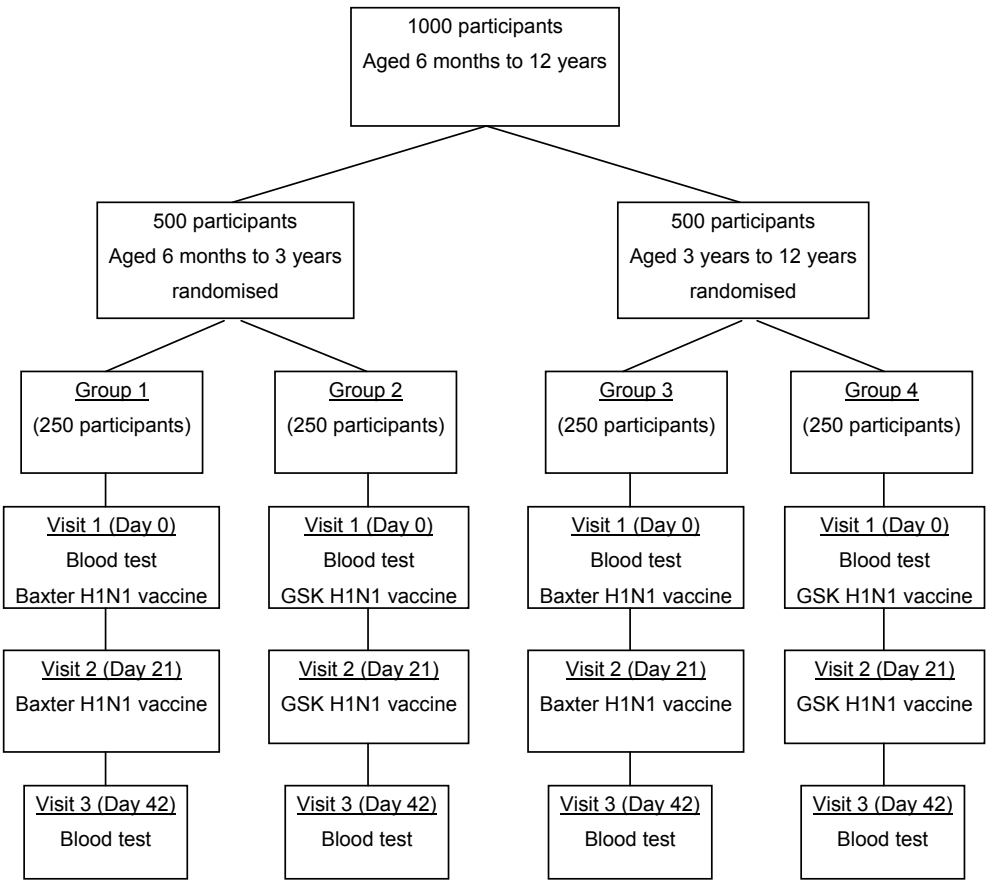
- Since new technologies are involved in the production of some pandemic vaccines, which have not yet been extensively evaluated for their safety in certain population groups, it is very important to implement post-marketing surveillance of the highest possible quality. In addition, rapid sharing of the results of immunogenicity and post-marketing safety and effectiveness studies among the international community will be essential for allowing countries to make necessary adjustments to their vaccination policies.
- In view of the anticipated limited vaccine availability at a global level and the potential need to protect against "drifted" strains of virus, SAGE recommended that promoting production and use of vaccines such as those that are formulated with oil-in-water adjuvants and live attenuated influenza vaccines was important.
- As most of the production of the seasonal vaccine for the 2009-2010 influenza season in the northern hemisphere is almost complete and is therefore unlikely to affect production of pandemic vaccine, SAGE did not consider that there was a need to recommend a "switch" from seasonal to pandemic vaccine production.

WHO Director-General Dr Margaret Chan endorsed the above recommendations on 11 July 2009, recognizing that they were well adapted to the current pandemic situation. She also noted that the recommendations will need to be changed if and when new evidence becomes available.

SAGE was established by the WHO Director-General in 1999 as the principal advisory group to WHO for vaccines and immunization. It comprises 15 members who serve in their personal capacity and represent a broad range of disciplines from around the world in the fields such as epidemiology, public health, vaccinology, paediatrics, internal medicine, infectious diseases, immunology, drug regulation, programme management, immunisation delivery, and health-care administration.

Additional participants in the SAGE meeting included members of the ad hoc policy advisory working group on influenza A (H1N1) vaccine, chairs of the regional technical advisory groups and external experts. Observers included industry representatives and regulators who did not take part in the recommendation process in order to avoid conflicts of interest.

APPENDIX B: STUDY FLOW CHART



APPENDIX C: STUDY TIMELINES

Stage	Timing (Planned start date 8th September, depending on vaccine availability and regulatory approval)
Visit 1	Week 1 to 3
Visit 2	Weeks 4 to 7
Visit 3	Weeks 7 to 12
Laboratory testing	Weeks 12 to 14
Analysis and initial report	Week 15
Completion of study for initial reporting	Week 15 (Week beginning 17th December if commence 8th September)

APPENDIX D: STAFF PERSONNEL

CFI

Professor Elizabeth Miller:	Principal investigator for CFI site and overall trial co-ordinator
Nick Andrews:	Trial statistician
Liz Sheasby:	Quality Assurance at the CFI site
Pauline Kaye:	Trial data manager
Dr. Katja Hoschler:	Responsible for overseeing serological testing for the trial
Teresa Gibbs:	Senior administrator responsible for overseeing data entry and verification

OVG

Professor Andrew Pollard:	Chief investigator of study
Dr Matthew Snape:	Principal investigator for OVG site
Tessa John:	Clinical Team Leader at OVG site
Simon Kerridge:	Quality Assurance at the OVG site
Amanda Reiner:	Project Manager at OVG site

St George's Vaccine Institute

Dr Paul Heath:	Principal investigator at St George's site.
Dr Clarissa Oeser.	Research fellow
Dr Shamez Ladhani.	Consultant Paediatrician
Dr Ifeanyichukwu Okike:	Research Fellow

Bristol Children's Vaccine Centre

Professor Adam Finn:	Principal investigator at Bristol site
Dr Jolanta Bernatoniene:	Consultant paediatrician
Dr Edward Clarke:	Clinical Lecturer in Paediatric Infectious Diseases
Dr Ruth Allen:	Manager, Medicines for Children South West
Natalie Fineman:	MCRN Research Nurse team leader

Royal Devon and Exeter Hospital

Dr Andrew Collinson:	Principal Investigator at Royal Devon and Exeter

University of Southampton Wellcome Trust Clinical Research Facility

Dr Saul Faust:	Principal investigator at Southampton site

APPENDIX E:

Immune Mediated Disorders (IMD)

Event Category	Immune-Mediated Disorder	MedDRA PT
Neuroinflammatory disorders	Cranial nerve disorders	Optic neuritis
		III nerve paralysis
		III nerve paresis
		IV nerve paralysis
		IV nerve paresis
		VI nerve paralysis
		Facial palsy
		Facial paresis
		VII nerve paralysis
		XI nerve paralysis
		Vagus nerve paralysis
		Acoustic nerve neuritis
		Glossopharyngeal nerve paralysis
		Trigeminal palsy
		Trigeminal nerve paresis
		Tongue paralysis
		Hypoglossal nerve paresis
		Anosmia
		Neuritis cranial
		Cranial neuropathy
		Paresis cranial nerve
		Cranial nerve paralysis
		Cranial nerve palsies multiple
	Multiple sclerosis	Multiple sclerosis
		Primary progressive multiple sclerosis
		Progressive multiple sclerosis
		Marburg's variant multiple sclerosis
		Secondary progressive multiple sclerosis
		Multiple sclerosis relapse
		Progressive relapsing multiple sclerosis
		Relapsing-remitting multiple sclerosis
	Demyelinating disease	Demyelination
		Leukoencephalomyelitis
		Acute disseminated encephalomyelitis
		Concentric sclerosis
		Neuromyelitis optica
		Chronic inflammatory demyelinating polyradiculoneuropathy
		Demyelinating polyneuropathy
	Transverse myelitis	Myelitis transverse
		Myelitis
	Guillain-Barré syndrome	Guillain-Barré syndrome
		Miller Fisher syndrome
	Myasthenia gravis	Myasthenia gravis
		Ocular myasthenia
	Encephalitis	Encephalitis
		Encephalomyelitis
		Encephalitis post immunisation

Event Category	Immune-Mediated Disorder	MedDRA PT
		Encephalitis toxic
	Neuritis	Neuritis
		Cervical neuritis
		Mononeuritis
		Mononeuropathy multiplex
		Brachial plexopathy
		Radiculopathy
		Radiculitis
		Radiculitis brachial
		Radiculitis cervical
Musculoskeletal disorders	Systemic lupus erythematosus	Systemic lupus erythematosus
	Cutaneous lupus	Cutaneous lupus
	Sjogren's syndrome	Sjogren's syndrome
	Scleroderma	Scleroderma
		Systemic sclerosis
		CREST syndrome
		Morphoea
	Dermatomyositis	Dermatomyositis
	Polymyositis	Polymyositis
	Rheumatoid arthritis	Rheumatoid arthritis
		Juvenile arthritis
	Polymyalgia rheumatica	Polymyalgia rheumatica
	Reactive arthritis	Arthritis reactive
		Reiter's syndrome
	Psoriatic arthritis	Psoriatic arthropathy
	Ankylosing spondylitis	Ankylosing spondylitis
	Undifferentiated spondyloarthropathy	Spondyloarthropathy
	Mixed connective tissue disease	Mixed connective tissue disease
Gastrointestinal disorders	Crohn's disease	Crohn's disease
	Ulcerative colitis	Colitis ulcerative
	Ulcerative proctitis	Proctitis ulcerative
	Celiac disease	Coeliac disease
Metabolic disorders	Autoimmune thyroiditis	Autoimmune thyroiditis
	Hashimoto's thyroiditis	
	Grave's or Basedow's disease	Basedow's disease
	Insulin-dependent diabetes mellitus	Type 1 diabetes mellitus
	Addison's disease	Addison's disease
Skin disorders	Psoriasis	Psoriasis
	Vitiligo	Vitiligo
	Raynaud's phenomenon	Raynaud's phenomenon
	Erythema nodosum	Erythema nodosum
	Autoimmune bullous skin diseases	Pemphigus
		Pemphigoid
		Dermatitis herpetiformis
Other	Stevens-Johnson syndrome	Stevens-Johnson syndrome
		Erythema multiforme
		Toxic epidermal necrolysis

Event Category	Immune-Mediated Disorder	MedDRA PT
	Autoimmune hemolytic anemia	Anemia heamolytic autoimmune
	Thrombocytopenias	Thrombocytopenia
		Autoimmune thrombocytopenia
		Idiopathic thrombocytopenic purpura
		Thrombocytopenic purpura
		Thrombotic thrombocytopenic purpura
	Antiphospholipid syndrome	Antiphospholipid syndrome
	Vasculitis	Vasculitis
		Diffuse vasculitis
		Leukocytoclastic vasculitis
		Behcet's syndrome
		Temporal arteritis
		Takayasu's arteritis
		Microscopic polyangiitis
		Polysrteritis nodosa
		Wegener's granulomatosis
		Allergic granulomatous angiitis
		Henoch-Schonlein purpura
		Kawasaki's disease
	Pernicious anemia	Pernicious anaemia
	Autoimmune hepatitis	Autoimmune hepatitis
	Primary biliary cirrhosis	Biliary cirrhosis primary
	Primary slerosisng cholangitis	Cholangitis sclerosing
	Autoimmune glomerulonephritis	Glomerulonephritis
	Autoimmune uveitis	Uveitis
	Autoimmune myocarditis	Autoimmune myocarditis
	Sarcoidosis	Sarcoidosis