Trial Title: Immunogenicity and reactogenicity of concomitantly administered hexavalent and group B meningococcal vaccines in infancy.

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Funder: MCM

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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY TRIAL CONTACTS

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2. SYNOPSIS

Trial Title	Immunogenicity and reactogenicity of concomitantly administered hexavalent and group B meningococcal vaccines in infancy	
Internal ref. no. (or short title)	The 6-in-1 vaccine study	
Clinical Phase	Phase IV: Post licensure	
Trial Design	Open label, non-inferiority randomised clinical trial	
Trial Participants	Infants aged 8 – 13 weeks at enrolment	
Planned Sample Size	240 healthy infants aged 8 – 13 weeks at enrolment	
Adjusted Sample Size	194	
Treatment duration	10 months	
Follow up duration	1 month following final vaccination	
Planned Trial Period	Approximately 19 months	
	Objectives	Outcome Measures
Primary	Compare the immunogenicity of the *Haemophilus influenza* type B (Hib) component of 6 in 1(IH) (Infanrix hexa) and 6 in 1(V) (Vaxelis) when co-administered with 4CMenB in the UK routine immunisation schedule at 5 months of age	Assess the anti-PRP (Hib) IgG concentrations at 5 months of age as measured by ELISA.

Secondary	Compare the anti-PRP (Hib) IgG concentrations at 13 months of age (1 month after administration of Hib-MenC at 12 months of age) in participants primed with 6 in 1(IH) and 6 in 1(V) Compare the immunogenicity of the other antigens in the routine UK infant immunisation schedule at 5 and 13 months of age in participants receiving 6 in 1(IH) and 6 in 1(V)	Assess the anti-PRP (Hib) IgG concentrations at 13 months of age as measured by ELISA. Assess the IgG concentrations at 5 and 13 months of: a. Diphtheria toxoid b. Tetanus toxoid c. Hepatitis B d. Vaccine-serotype pneumococcal capsule antigens e. Pertussis antigens f. Poliovirus neutralising antibodies Assess serum bactericidal titres at 5 and 13 months of age of: a. 3 reference serogroup B meningococcal strains b. Serogroup C meningococcus
	Reactogenicity of 6 in 1(IH) and 6 in 1(V) when administered in the routine UK immunisation schedule	Solicited local and systemic adverse events within 5 days of immunisation
Investigational Medicinal Product(s)	6 in 1(IH) (Infanrix hexa) 6 in 1 (V) (Vaxelis)	
Formulation, Dose, Route of Administration	6 in 1(IH) – a licensed hexavalent vaccine for DTaP/IPV/Hib/HepB. It is available as a powder and suspension for intramuscular injection with a volume of 0.5ml. It can be given as a 3 dose primary series on the current UK immunisation schedule (1). 6 in 1(V) – another licensed hexavalent vaccine for DTaP/IPV/Hib/HepB. It is available in a pre-filled syringe as a suspension for intramuscular injection with a volume of 0.5ml. It is given as a 3 dose primary series at least 1 month apart (2).	

3. ABBREVIATIONS

6 in 1(IH)	Infanrix hexa
6 in 1(V)	Vaxelis
AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
EMA	European Medicines Agency
GCP	Good Clinical Practice
GMC	Geometric Mean Concentration
GP	General Practitioner
GTAC	Gene Therapy Advisory Committee
Hib	*Haemophilus influenza* type B
HRA	Health Research Authority
HBV	Hepatitis B virus
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MCM	Merck Connaught Merieux (partnership between Merck, Sharp and Dohme (MSD) and Sanofi Pasteur)
MenB	Meningococcal B vaccine

MenC	Meningococcal C vaccine
MHRA	Medicines and Healthcare products Regulatory Agency
MMR	Measles, Mumps and Rubella vaccine
NHS	National Health Service
NRES	National Research Ethics Service
OMPC	Outer membrane protein complex
OVG	Oxford Vaccine Group
PCV13	Pneumococcal conjugate vaccine for 13 serotypes
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SBA	Serum bactericidal activity
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSG	Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group
UKPVG	United Kingdom Paediatric Vaccine Group
WHO	World Health Organisation

4. BACKGROUND AND RATIONALE

Hepatitis B virus (HBV) is a viral illness that results in inflammation of the liver. It causes significant morbidity and mortality worldwide and is the most common chronic viral infection in the world. It is estimated that up to 30% of the world's population has serological evidence of a current or past HBV infection (3). HBV can manifest either as an acute illness causing nausea, malaise, abdominal pain and jaundice or as an often asymptomatic chronic infection. Chronic HBV infection can lead to liver cirrhosis and hepatocellular carcinoma (4).

HBV is blood borne and transmitted via exposure to infected blood or bodily fluids contaminated by blood. One of the most common forms of transmission is vertical or perinatal transmission of HBV from infected mothers to neonates. Low and middle-income countries have disproportionally higher rates of HBV thus there is a high prevalence in immigrants to higher-income countries. Of those who develop an acute HBV infection, 95% of babies, 20-30% of children and less than 5% of adults will go on to have a chronic infection. There is no available treatment for an acute HBV infection whilst antivirals such as Tenofovir can improve chronic HBV infections by slowing cirrhosis and reducing the risk of liver cancer (3).

Given the complications associated with HBV, prevention of transmission is the best method for controlling this infection. Prevention includes avoidance of transmission from infected people via counselling against high risk behaviours, screening of blood products and more stringent infection control in healthcare settings through universal precautions. By far the most effective way of controlling HBV is through vaccination (3).

The first HBV vaccine was developed in 1982 and is in widespread use. Most vaccines for HBV were developed using recombinant DNA to express a protein (antigen) against hepatitis (HBsAg). HBV vaccines are available in monovalent (single), combination (with Hepatitis A) and multivalent forms (with multiple other vaccines). Routine immunisation of neonates is a common practice worldwide with the WHO recommending a dose of HBV at birth followed by either a 2 or 3 dose schedule. Completion of either of these programmes induces protective antibody levels in up to 95% of infants, children and adolescents (3).

The burden of HBV in the UK reflects that of other high-income countries. In 2016 there were 453 cases of acute HBV reported and an annual incidence of 0.82 per 100,000 people. During the same period 11,901 cases of HBV were recorded, the remainder being chronic infections (4). The UK added a vaccine for HBV to the routine childhood immunisation schedule in 2017 as part of a multivalent vaccine. Multivalent vaccines are cost effective on a population level. They reduce the number of needles that need to be administered thus reducing the risk of complications, they minimise the number of vaccine healthcare visits needed and associated costs and they improve compliance and vaccine coverage (5).

Characteristics of licensed vaccines

6 in 1(IH) (Infanrix hexa)

Developed by GlaxoSmithKline, 6 in 1(IH) is a multivalent vaccine that protects against diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenza* type B (Hib) and hepatitis B virus (HBV). It is licensed in Europe and has been widely used internationally with data to support its efficacy and safety. It is available in a powder and suspension for injection form. 6 in 1(IH) has been included in the UK's routine

immunisation schedule at 2, 3 and 4 months of age since 2017. It is made up of diphtheria and tetanus toxoid, Bordetella pertussis antigens (pertussis toxoid, filamentous haemagglutinin and pertactin), inactivated poliovirus (type 1 – 3), Hib polysaccharide conjugated to tetanus toxoid as the carrier protein and hepatitis B surface antigen (1).

6 in 1(V) *(Vaxelis)*

One of the other multivalent vaccines that contains Hepatitis B currently licensed in Europe is 6 in 1(V). Developed jointly by Merck/MSD and Sanofi Pasteur, 6 in 1(V) is available as a fully liquid and ready to use injection and protects against the same organisms as 6 in 1(IH) however the structure of some components differs. 6 in 1(V) contains diphtheria and tetanus toxoid, *Bordetella pertussis* antigens (including pertussis toxoid, filamentous haemagglutinin, pertactin and fimbriae types 2 and 3), inactivated poliovirus (including type 1 – 3), Hib polysaccharide conjugated to a meningococcal outer membrane complex (OMPC) and hepatitis B surface antigen (2). It is the structure of the Hib component that may be relevant to the use of 6 in 1(V) in the UK. 4CMenB is the meningococcal B vaccine currently in use in the UK's routine immunisation schedule at 2, 4 and 12 months of age. The structure of 4CMenB includes meningococcal outer membrane vesicles which carries with it a theoretical risk of a carrier induced epitopic suppression of the Hib responses of 6 in 1(V) when given concurrently with 4CMenB. This interaction has the potential to lead to the creation of a birth cohort with sub-optimal responses to the Hib antigen of 6 in 1(V) and thus risk a re-emergence of Hib as was seen in the UK in 1999 – 2003. (6)

There is also the possibility that the combination of the OMPC from 6 in 1(V) and 4CMenB could cause increased systemic and local vaccine adverse reactions when co-administered (as compared to adverse reactions that can occur using the existing schedule). In the absence of any evidence to show that these concerns are unfounded, it is possible that the use of 6 in 1(V) in the UK immunisation schedule would be seen as inappropriate. This could limit the flexibility of vaccine procurement for the UK government.

We plan to conduct a head-to-head unblinded open randomised trial comparing the immunogenicity and reactogenicity at 5 and 13 months of both licensed DTaP-Hib-IPV-HepB vaccines when administered at 2, 3 and 4 months of age alongside the current UK vaccination schedule (including 4CMenB).

Known potential risks and benefits to participants

Potential risks to participants

Participants in this trial will be receiving licensed vaccines, which are either the same as, or similar to, those already included in the routine UK immunisation schedule. The risks to participants include the common side effects of vaccination with 6 in 1(IH) and 6 in 1(V) and the risks of blood sampling. These include swelling, redness and pain at the injection site, fever, irritability, crying, tiredness, reduced appetite and vomiting (7, 8).

As with all vaccines, there is a small chance of an allergic reaction including severe reactions such as anaphylaxis (risk is less than 1 in a million doses for existing vaccines) (7). The risks associated with blood sampling include pain at the injection site, bruising, bleeding and infection. Anaesthetic cream is offered to minimise any pain during venepuncture. Additionally, the volume of blood taken during the study period does not exceed the recommended European limits for infants (8).

There is also a potential for reduced Hib immunogenicity in the group that receives 6 in 1(V). If any participants (in either group) have a sub-optimal response to the Hib component of the immunisation

schedule (i.e. anti-PRP IgG < 1.0 µg/ml at 13 months of age), their GP will be contacted and advised that the participant requires an additional dose of the Hib-MenC combination vaccine.

As outlined above, there is also a theoretical risk of increased reactogenicity in 6 in 1(V) group when coadministered with 4CMenB. 4CMenB has been shown to have an increased risk of fever when given with other vaccines and paracetamol administration is advised to ameliorate this (9). The practice of giving prophylactic paracetamol will be continued in this study and parents will be asked to give the three recommended doses of paracetamol after vaccination with 4CMenB as per guidance from Public Health England (10).

Potential benefits to participants

The benefits to participants is the administration of their routine vaccines in their own home or in a suitable and convenient location and telephone access to an on-call study team member for urgent clinical queries related to the study.

Route of administration, dosage, dosage regimen and treatment period

Both 6 in 1(IH) and 6 in 1(V) are administered intramuscularly and will be given as per the UK immunisation schedule for hexavalent vaccines at 2, 3 and 4 months of age. The study period will be over 11 months therefore routine vaccines will be administered until 12 months of age with the last study visit at 13 months.

Description of population to be studied

This study will recruit healthy infants born at ≥ 37 weeks in the UK in the local geographic areas of study sites. They will be aged between 8 and 13 weeks at enrolment and have no significant medical problems or known allergies to 6 in 1(IH), 6 in 1(V) or the routine immunisations given in the UK schedule or their components.

5. OUTCOME AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective Compare the immunogenicity of the Hib component of 6 in 1(IH) and 6 in 1(V) when co-administered with 4CMenB in the UK routine immunisation schedule at 5 months of age.	Measurement of anti-PRP (Hib) IgG concentrations at 5 months of age as measured by ELISA.	At 5 months of age (at least 4 weeks after administration of the last dose of either 6 in 1(IH) and 6 in 1(V) primary immunisations).
Secondary Objectives Compare the anti-PRP (Hib) IgG concentrations at 13 months of age (1 month after administration of Hib-MenC at 12 months of age) in participants primed with 6 in 1(IH) and 6 in 1(V) .	Assess the anti-PRP (Hib) IgG concentrations at 13 months of age as measured by ELISA.	At 13 months of age (at least 4 weeks after the Hib-MenC vaccination at 12 months of age).
The immunogenicity of the other antigens in the routine immunisation schedule incorporating either 6 in 1(IH) or 6 in 1(V) .	Assess the IgG concentrations at 5 and 13 months of: a.Diphtheria-toxoid b.Tetanus toxoid c.Hepatitis B virus d.Vaccine-serotype pneumococcal capsule antigens e.Pertussis antigens f.Poliovirus neutralising antibodies Assess serum bactericidal titres at 5 and 13 months of age of: a. 3 reference serogroup B meningococcal strains b. Serogroup C meningococcus	At 5 and 13 months of age (approximately 4 weeks after completion of the primary routine immunisations and approximately 4 weeks after the booster doses in the routine immunisation schedule).
The reactogenicity of 6 in 1(IH) and 6 in 1(V) when administered in the routine UK immunisation schedule	Solicited local and systemic adverse events within 5 days of immunisations	In the 5 days post immunisation in participant diaries

6. TRIAL DESIGN

6.1 Study design

This study will be an open label, non-inferiority 1:1 randomised clinical trial conducted by the UKPVG sites led by the Oxford Vaccine Group (OVG). We will enrol healthy infants who reside in the UK aged between 8 and 13+0 weeks. There will be 6 visits in total throughout this study including two blood tests. These visits will take place in participant's homes or a suitable, convenient location. Participants will expect to be involved in the study for approximately 11 months (from enrolment at 8 weeks minimum to the last blood test at 13 months of age).

Participants will only be enrolled after written informed consent is obtained from a parent or legal guardian. Study visits will be made up of four visits for vaccination and two visits for blood sampling as shown in Table 1.

Table 1: Study design

Group	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Age of participant	2 months	3 months	4 months	5 months	12 months	13 months
Visit windows	8 – 13 weeks of age	4-6 weeks after visit 1	4-6 weeks after visit 2	4-6 weeks after visit 3	12 months of age (+28 days)	4-6 weeks after visit 5
Visit description	Enrolment Vaccination	Vaccination	Vaccination	Blood sampling	Vaccination	Blood sampling
Group 1 6 in 1(IH) arm (n=120)	6 in 1(IH) MenB Rotavirus	6 in 1(IH) Rotavirus PCV13*	6 in 1(IH) MenB		Hib-MenC PCV13 MMR MenB	
Group 2 6 in 1(V) arm (n=120)	6 in 1(V) MenB Rotavirus	6 in 1(V) Rotavirus PCV13*	6 in 1(V) MenB			

* PCV13 will be administered at 3 and 12 months. This reflects the change in the routine UK infant immunisation schedule for infants born on or after 1 January 2020.

Table 2: Vaccine products

Vaccines to be used	Commercial name
6 in 1(IH)	Infanrix hexa
6 in 1(V)	Vaxelis
PCV13	Prevenar13
MenB	Bexsero
Rotavirus	Rotarix
Hib/MenC	Menitorix
MMR	MMR VaxPRO or Priorix

6.2 Study outcomes

Immunogenicity

Blood samples will be tested for immunogenicity of the vaccines administered in the routine UK schedule and the two vaccines under investigation in this study (6 in 1(IH) and 6 in 1(V)). The primary outcome is to determine immunogenicity to Hib through anti-PRP Hib IgG concentrations at 5 months of age. The secondary outcomes are to determine immunogenicity to Hib through anti-PRP Hib IgG concentrations at 13 months of age, the IgG concentrations against diphtheria-toxoid, tetanus-toxoid, Hepatitis B, vaccine serotype pneumococcal capsule, pertussis antigens and poliovirus neutralising antibodies and SBA titres against 3 reference serogroup B meningococcal strains at 5 and 13 months of age and serogroup C meningococcus at 13 months of age.

Reactogencity

Reactogenicity will be measured after each vaccination visit through the collection of information from participant diaries. The parents/legal guardians of participants will be asked to maintain an electronic/paper diary card detailing all (solicited and unsolicited) reactions in the 5 days following vaccination after each vaccination visit for both groups (Visit 1, Visit 2, Visit 3 and Visit 5). Comparison of reactogenicity data between the two study groups will allow us to determine if one schedule is more reactogenic than the other. We will ask parents to measure participant's temperature daily using axillary thermometers supplied by the study team.

For participants in both groups, parents/legal guardians will be asked to record:

- For 5 days post vaccination; details of any illnesses, and any medicines including prescription medications given to treat these.
- Any illness considered serious (i.e. those that would be classified as a serious adverse event) for the duration of the study.

7. PARTICIPANT IDENTIFICATION

7.1. Trial Participants

Healthy infants aged 8 to 13+0 weeks who are yet to receive their routine 2 month immunisations.

7.2. Inclusion Criteria

For recruitment to all study groups, participants MUST FULFILL each of the below criterion:

- Parents/legal guardians are over 16 years of age, and are willing and able to consent to enrol their child/children in the study
- Parents/legal guardians able to comply with the requirements of the trial protocol and have internet access for the duration of the study
- Parents/legal guardians are willing to allow their General Practitioner, health visitor and consultant, if appropriate, to be notified of participation in the trial.
- Participants born at ≥ 37 weeks gestation
- Participants are due to receive their primary immunisations, aged 8 to 13 weeks (i.e. the day the child turns 13 weeks of age) at enrolment

7.3. Exclusion Criteria

The participant may not enter the trial IF ANY of the following apply:

- Parents/legal guardians of children are on the delegation log of this study
- Confirmed or suspected immunodeficiency
- Fulfil any of the contraindications to vaccination as specified in The Green Book (11)
- Confirmed anaphylactic reaction/s to any constituent/s or excipient/s of the vaccine(s)
- Confirmed anaphylactic reaction to neomycin, streptomycin or polymyxin B (which may be present in trace amounts in the tetanus vaccine), kanamycin, histidine, sodium chloride or sucrose (which may be present in trace amounts in the Meningococcal B vaccine) or to gelatin (which may be present in trace amounts in the MMR vaccine)
- Latex hypersensitivity (the syringe cap of the Meningococcal B vaccine Bexsero may contain natural rubber latex)
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.

- Child is currently participating in another interventional clinical trial

7.4 Temporary exclusions for all groups

For a vaccination visit only (visit 1, 2, 3, and 5)

- Administration of any other vaccine within 14 days prior to study vaccines.
- Scheduled elective surgery, planned admission or other procedures requiring general anaesthesia within 7 days of receiving a vaccine.
- Febrile illness (axillary temperature ≥38.0°C) within the previous 24 hours or on the day of vaccination.

For a blood sampling visit only (visit 4 and 6)

- Have received parenteral or oral antibiotics within the last 7 days.

8. TRIAL PROCEDURES

8.1. Recruitment

Recruitment will take place in geographical areas where appropriate approvals have been granted. Parents/legal guardians of potential participants will be informed of the study through similar methods employed for other paediatric studies including website based advertising, social media, contacting families registered with a study site research database and poster advertisements. The participant information will be available on websites if available and recruitment material can direct potential participants to this.

We may also identify potential participants by mailing out invitation letters (with reply slip and pre-paid envelope) and the study information booklets to the parents/legal guardians of age appropriate children via the Open Exeter system of National Health Application and Infrastructure Services, the Child Health Information Service, equivalent NHS database or through the Clinical Research Network.

Those parents/legal guardians that indicate that they do not want to take part in the study and/or receive further communication about the study will not be included in any subsequent contact lists.

8.1. Screening and Eligibility Assessment

Once an expression of interest to take part in this study has been received, study staff will contact parents/legal guardians of potential participants either by phone or email to answer any questions and/or discuss the study further, conduct an eligibility check and book the 1st visit.

During the first study visit, the participant's eligibility will be assessed by a study doctor after a medical history has been taken and examination performed. Parents/legal guardians must have given written informed consent prior to an eligibility check being performed. If available, the participant's mother will be asked to give consent to access her immunisation history. This is due to the UK Department of Health

pertussis immunisation programme that offers all pregnant women in the UK a vaccine against pertussis during pregnancy and this possible effect on infant's immune response to the pertussis vaccine (12). Throughout the study, parents/legal guardians would be discouraged from administering analgesic agents with antipyretic effects in the 12 hours prior to vaccination with 6 in 1(IH) or 6 in 1(V). If this is unavoidable, this should be documented and vaccination and study participation should continue as planned.

8.2. Informed Consent

The parent/legal guardian of the participant will personally sign and date the latest approved version of the Informed Consent form. Where possible, the participant's mother will be asked to sign the consent form to ensure we have permission to obtain her pertussis immunisation history during pregnancy.

A written version and verbal explanation of the Study Information leaflet and Informed Consent will be presented to the parent/legal guardian of the participant detailing:

- the exact nature of the study
- what it will involve for the participant
- the implications and constraints of the protocol
- the known side effects and any risks involved in taking part
- sample handling – participants will be informed that anonymised samples taken during the course of study may be shared with study collaborators, including collaborators outside of the European Union, for the purposes of this study. Any leftover samples will be transferred to a local biobank for storage once the sample is no longer required for the study endpoints if consent to do so has been obtained under local procedures. In Oxford this will be the Oxford Vaccine Centre Biobank. If parents/guardians do not consent to Biobank then all samples will be destroyed at the end of the study.
- We will request permission to contact the child's GP and/or other treating doctors for medical and vaccine history. We will also request permission to inform the child's GP/health visitor that the child is taking part in the study and that we will be administering their routine vaccinations up to and including their 12 months vaccines.

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

The parent/legal guardian of the participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of parent/legal guardian of the participant dated signature, and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator and listed on the delegation log. A copy of the signed informed consent will be given to the parent/legal guardian of the participant. The original signed form will be retained at the trial site.

8.3. Randomisation, blinding and code-breaking

8.3.1 Randomisation

This is a parallel group study with two groups. Participants will be randomised to either Group 1 (6 in 1(IH)) or Group 2 (6 in 1(V)) on a 1:1 basis. Computer generated randomisation lists will be prepared by the study statistician using stratified block randomisation. The randomisation lists will be prepared by the statistician at the Oxford Vaccine Group and will be stratified by study sites, each site will have a unique randomisation list. The randomisation list will be loaded to a central randomisation system and each site will have unique log in details to access their corresponding randomisation list. A detailed description of the randomisation process will be written into the clinical study plan.

8.3.2 Blinding and code breaking

This is an open label trial so there will be no blinding of study staff or participant's parents/legal guardians. Code breaking will thus be unnecessary for this study. Laboratory staff will have no knowledge of the group assignment of the individual participants.

8.4. Study visits

Six study visits will be conducted by trial staff either at the participant's home, or at convenient and suitable venues (with appropriate permission in place). The location of the study visits will be site specific based on local site capacity and visit model for delivery of the trial. A telephone/email follow up may occur at any time prior to the next scheduled study visit should there be a need to clarify data collected in the electronic diary, in particular the reactogenicity data collected after a participant has received a dose of 6 in 1(IH) or 6 in 1(V).

Participants will be eligible if they do not fulfil any of the temporary exclusion criteria for the specific visit listed above. Parents or legal guardians will be asked about adverse events. Table 1 above gives a summary of the study visits.

Visit 1: First infant vaccinations at 8 – 13+0 weeks of age

- Provide explanation of the study to parents/legal guardians.
- Obtain written informed consent from the parents/legal guardians of the participant. As above, where possible consent will be obtained from the participant's mother in order to ascertain her pertussis immunisation history during pregnancy.
- Medical staff will perform a thorough check of inclusion and exclusion criteria using parents/legal guardians recall of relevant medical history and physical examination and record findings, including:
    - Medical history of relevance to the inclusion/exclusion criteria
    - Details and indications of any prescription medications and vaccines
- If all inclusion and exclusion criteria are met the participant will be considered enrolled into the study.
- Record date of birth and gender, for subsequent data analysis.

- History of immunisations received during pregnancy by the participant's mother by parental report and/or GP medical records (if mother consents).
- Measure and record the participant's axillary temperature.
- The parent/guardian will be informed of the randomisation group.
- Administer the following vaccines as per the Green Book guidelines for administration of vaccinations and relevant study site SOPs
    - DTaP-IPV-Hib-HepB (6 in 1(IH) for Group 1, 6 in 1(V) for Group 2) via intramuscular injection into the right upper anterolateral thigh.
    - 4CMenB (Bexsero) via intramuscular injection into the left anterolateral thigh
    - Oral Rotavirus vaccine (Rotarix)
- Observe the participant for 15 minutes after vaccination for any significant acute reactions, with adrenaline readily available in case of anaphylactic reaction. Any adverse events (AEs) that occurred during the observation period should be recorded.
- Issue eDiary/diary card. Give login details to parent/legal guardian for the eDiary. Demonstrate eDiary/diary card to parents/legal guardians for recording AEs and antipyretic use and check understanding.
- Issue a digital thermometer and ruler. Explain how to measure and record temperature, local and systemic reactions, adverse events (for 5 days post vaccination) and concomitant medications administered. Local and systemic reactions to vaccination should be recorded for 5 days post vaccination.
- Parents/legal guardians would be discouraged from administering antipyretics in the 12 hours prior to vaccination. If this is unavoidable, this should be documented and vaccination and study participation should continue as planned.
    - Advise parents to give paracetamol at time of immunisation with 4CMenB as per PHE book guidelines, with 2 further doses over subsequent 24 hours. This written information will be provided.
- Instruct parents/legal guardians to contact the study team as soon as possible should the participant manifest any signs/symptoms they perceive as serious, or if the child is admitted overnight to hospital.
- Schedule next visit.
- Study staff to complete red book (parent held child record) if available, source and electronic CRF and enter onto study database.
- Notify the participant's General Practitioner that they are participating in the study and that the child's routine infant immunisations will be administered by the Oxford Vaccine Group or local study site.
- Notify the Child Health Information Services, or equivalent NHS database that the participant's routine vaccines (including a DTaP-IPV-Hib-HepB vaccine - either 6 in 1(IH) or 6 in 1(V)) have been administered.

Visit 2 – Routine and study immunisation 4-6 weeks post visit 1

- Check inclusion/exclusion criteria are still valid.
    - Check temporary exclusion for a vaccination visit.

- Review eDiary/diary card for AEs (5 days post vaccination only)
- Record and report any SAEs that have occurred since the last visit.
- Measure and record the participant's axillary temperature.
- Administer the following vaccines as per the Green Book guidelines for administration of vaccinations and relevant study site SOPs
    - DTaP-IPV-Hib-HepB (6 in 1(IH) for Group 1, 6 in 1(V) for Group 2) via intramuscular injection into right anterolateral thigh
    - *PCV13 via intramuscular injection into the left anterolateral thigh
    - Oral Rotavirus vaccine (Rotarix)
- Observe the participant for 15 minutes after vaccination for any significant acute reactions, with adrenaline readily available in case of anaphylactic reaction. Any AEs occurring during the observation period should be recorded.
- Parents/legal guardians would be discouraged from administering antipyretics in the 12 hours prior to vaccination. If this is unavoidable, this should be documented and vaccination and study participation should continue as planned.
- Remind parents/legal guardians to
    - Complete the eDiary/diary card for 5 days post vaccination.
    - Contact the study team as soon as possible should the participant manifest any signs/symptoms they perceive as serious, or if the child is admitted overnight to hospital. Ask them to record this within the eDiary/diary card.
- Schedule next visit.
- Study staff to complete red book (parent held child record) if available, source and electronic CRF and enter onto study database.
- Notify the Child Health Information Services, or equivalent NHS database that the participant's routine vaccines (including a DTaP-IPV-Hib-HepB vaccine - either 6 in 1(IH) or 6 in 1(V)) have been administered.

Visit 3 – Routine and study immunisations 4-6 weeks post visit 2

- Check inclusion/exclusion criteria are still valid.
    - Check temporary exclusion for a vaccination visit.
- Review eDiary/diary card for AEs (5 days post vaccination only)
- Record and report any SAEs that have occurred since the last visit
    - Measure and record the participant's axillary temperature.
- Administer the following vaccines as per the Green Book guidelines for administration of vaccinations and relevant study site SOPs
    - DTaP-IPV-Hib-HepB (6 in 1(IH) for Group 1, 6 in 1(V) for Group 2) via intramuscular injection into right upper anterolateral thigh
    - 4CMenB (Bexsero) via intramuscular injection into the left anterolateral thigh
- Observe the participant for 15 minutes after vaccination for any significant acute reactions, with adrenaline readily available in case of anaphylactic reaction. Any AEs occurring during the observation period should be recorded.

- Parents/legal guardians would be discouraged from administering antipyretics in the 12 hours prior to vaccination. If this is unavoidable, this should be documented and vaccination and study participation should continue as planned.
    - Advise parents to give paracetamol at time of immunisation with 4CMenB as per Green book guidelines, with 2 further doses over subsequent 24 hours
- Remind parents/legal guardians to
    - Complete the eDiary/diary card for 5 days post vaccination.
    - Contact the study team as soon as possible should the participant manifest any signs/symptoms they perceive as serious, or if the child is admitted overnight to hospital. Ask them to record this within the eDiary/diary card.
- Schedule next visit.
- Study staff to complete red book (parent held child record) if available, source and electronic CRF and enter onto study database.
- Leave anaesthetic cream, dressing and instructions for next visit for the blood test required by the participant
- Notify the Child Health Information Services, or equivalent NHS database that the participant's routine vaccines (including a DTaP-IPV-Hib-HepB vaccine - either 6 in 1(IH) or 6 in 1(V)) have been administered.

Visit 4 – Blood test 4-6 weeks post visit 3

- Check inclusion/exclusion criteria are still valid
    - Check temporary exclusion for a blood sampling visit.
- Check anaesthetic cream and dressing has been applied, if this has not been done then apply some.
- Review eDiary/diary card for AEs (5 days post vaccination only)
- Record and report any SAEs that have occurred since the last visit
    - Collect 5 ml of venous blood for blood test.
- Schedule next visit.
- Remind parents/legal guardians if the child is admitted to hospital overnight and record this within the eDiary/diary card.
- Study staff to complete source and electronic CRF and enter onto study database.

Visit 5 – Routine immunisations at 12 months of age (+ 28 days)

- Check inclusion/exclusion criteria are still valid.
    - Check temporary exclusion for a vaccination visit.
- Review eDiary/diary card for AEs (5 days post vaccination only)
- Record and report any SAEs that have occurred since the last visit
- Measure and record the participant's axillary temperature.
- Administer the following vaccines as per the Green Book guidelines for administration of vaccinations and relevant study site SOPs
    - MMR (MMRVaxPro or Priorix) via intramuscular injection into the right upper anterolateral thigh separated by at least 2.5cm from the PCV injection site

  - *PCV13 via intramuscular injection into the right lower anterolateral thigh separated by at least 2.5cm from the MMR injection site
  - 4CMenB (Bexsero) via intramuscular injection into the left upper anterolateral thigh
  - MenC/Hib (Menitorix) via intramuscular injection into the left upper arm
- Observe the participant for 15 minutes after vaccination for any significant acute reactions, with adrenaline readily available in case of anaphylactic reaction. Any AEs occurring during the observation period should be recorded.
- Parents/legal guardians would be discouraged from administering antipyretics in the 12 hours prior to vaccination. If this is unavoidable, this should be documented and vaccination and study participation should continue as planned.
- Remind parents/legal guardians to
  - Complete the eDiary/diary card for 5 days post vaccination.
  - Contact the study team as soon as possible should the participant manifest any signs/symptoms they perceive as serious, or if the child is admitted overnight to hospital. Ask them to record this within the eDiary/diary card.
- Schedule next visit.
- Study staff to complete red book (parent held child record) if available, source and electronic CRF and enter onto study database.
- Leave anaesthetic cream, dressing and instructions for next visit for the blood test required by the participant
- Notify the Child Health Information Services, or equivalent NHS database that the participant's routine vaccines have been administered.

Visit 6 – Blood test 4-6 weeks post visit 5

- Check inclusion/exclusion criteria are still valid
  - Check temporary exclusion for a blood sampling visit.
- Check anaesthetic cream and dressing has been applied, if this has not been done then apply some.
- Review eDiary/diary card for AEs (5 days post vaccination only)
- Record and report any SAEs that have occurred since the last visit
- Collect 5 ml of venous blood for blood test
- Study staff to complete source and electronic CRF and enter onto study database.

*PCV 13 will be administered at 3 and 12months (not 2,4 and 12months) to reflect the change to the routine schedule in the UK for infants born on or after 1 January 2020.

In addition, at the Oxford site parents will be asked to consent for any samples taken from their child and not used up in the initial testing to be archived in the Oxford Vaccine Centre biobank (REC ref: 16/SC/0141). There is a separate information and consent form for this and parents will be free to decline this but remain in the main study. This can happen at any study visit.

8.5. Recording symptoms: Diary card/eDiary

The parents/legal guardians of the participant will be asked to maintain an electronic diary/paper diary card detailing all (solicited and unsolicited) reactions in the 5 days following vaccination after each vaccination visit (visit 1, 2, 3 and 5 for all groups). If a symptom persists after 5 days, an end-date should be entered if available, or otherwise recorded as ongoing.

The eDiary will be on a secure website hosted by OVG. The diary will also be available in paper form should internet access be temporarily unavailable. There will be provision to record the following reactions after vaccine visit.

8.5.1. Local reactions

The local reactions that will be recorded include erythema, induration and swelling (Table 3). Tenderness (pain) is listed in table 5. Parents/legal guardians will be issued with a ruler to measure erythema, induration or swelling and tenderness severity will be graded as shown in table 5. Erythema, induration and swelling will be categorised according to the table below:

Table 3: Local reactions

Symptom	Grade	Definition
Injection site reaction (erythema, induration and swelling)	0	No reaction
	1	1 to ≤10mm
	2	11 to ≤25mm
	3	26 to ≤50mm
	4 (severe)	51 to ≤ 100mm
	5 (severe)	>100mm

8.5.2. Temperature

Parents/legal guardians will be asked to record the participants axillary temperature at around six hours post vaccine or before the night time sleep, whichever comes first, and daily for the 5 days following immunisation. The axillary temperature will also be measured if at any time, the parent/legal guardian feels that the participant may have developed a fever. Temperature taken by the axillary route will be graded as follows:

Table 4: Temperature grading

Temperature Grade	Temperature definition (degrees Celsius)
0	< 37.6
1	37.6 – 38.0
2	38.1 – 39.0
3 (severe)	> 39.0

8.5.3. Solicited systemic reactions

The eDiary/diary card will record the presence or absence of a number of systemic symptoms that have previously been reported following vaccination: change in feeding, lethargy, malaise, vomiting, diarrhoea and excessive crying. Parents/legal guardians will grade severity according to the descriptions in Table 5.

Table 5: Grading of local and systemic reactions

	Grading of severity		
Solicited Reactions	**1. Mild**	**2. Moderate**	**3. Severe**
Tenderness (pain) at the injection site	Minor reaction to touch	Cries/protests on touch	Cries when limb is moved/spontaneously painful
Change in feeding/eating habit	Feeding/eating less than usual/ no effect on normal activity	Feeding/eating less than usual with an effect on normal activity	Not feeding/eating at all
Drowsiness	Drowsiness easily tolerated	Drowsiness that interferes with normal activity	Drowsiness that prevents normal activity
Vomiting	1-2 episodes without interfering with routine	Several episodes & cannot keep any food down	Frequent episodes & not feeding/eating at all
Diarrhoea	Stools are more loose than normal	Frequent runny stools without much solid material	Multiple liquid stools without much solid material

Irritability/fussiness	Crying more than usual / no effect on normal activity	Crying more than usual / interferes with normal activity	Crying that cannot be comforted / prevents normal activity

8.5.4. Unsolicited adverse events

There will be space to record any other symptoms that occur in the 5 days post vaccination.

The eDiary card will be reviewed in real time after visit 1, 2, 3 and 5 for both study groups. Telephone/email contact will occur at any time if there is data that needs to be clarified. Parents/legal guardians will be provided with a 24 hour phone number to access a member of the study team should they require urgent advice following vaccination.

If a parent is unable to enter data electronically the site staff will collect the paper version and enter data into the relevant system. The paper records will remain with the site and be stored in the ISF at the end of the study.

8.6. Blood sample

Blood sampling will be carried out in line with local SOPs at visit 4 and 6. A local anaesthetic cream will be offered prior to each venepuncture. A maximum of 5ml of blood will be obtained during blood visits for laboratory analysis. If the initial attempt at venepuncture draws less than 5ml, verbal consent will be sought for a further attempt at that visit. Finger or heel prick may be attempted (with parental approval) if 2 attempts at venous sampling has been unsuccessful. An additional visit may be rescheduled for another day within the visit timelines if no blood is obtained at all. Blood samples that are obtained will be centrifuged, separated and frozen within 24 hours. They will then be stored at the local study site laboratories prior to shipment. Samples will be shipped to laboratories for processing as follows. Processing of anti-PRP (Hib) IgG concentrations and IgG concentrations against diphtheria-toxoid, tetanus-toxoid and pertussis antigens and polio neutralizing antibodies and serum bactericidal activity against meningococcal strains will be processed at the Public Health England (PHE) laboratories. IgG concentrations against hepatitis B will be processed by Oxford University Hospital NHS Foundation Trust laboratory. IgG concentrations against vaccine-serotype pneumococcal capsule antigens will be processed at the University College London laboratory.

8.7. Discontinuation/Withdrawal of participants from trial treatment

The parents/legal guardians of participants have the right to withdraw the participants from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or trial requirements

- An adverse event which requires discontinuation of the trial vaccines or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of vaccination or results in inability to continue to comply with trial procedures
- Withdrawal of Consent
- Loss to follow up

Data from participants will continue to be analysed for the study unless the parents/legal guardians request this to be withdrawn. If participants withdraw prior to administration of vaccines in visit 1 then they will be replaced.

The reason for withdrawal will be recorded in the CRF.

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.

8.8. Definition of End of Trial

The end of study will be when laboratory analysis of the primary and secondary endpoints has been completed for all biological samples. All visits will have been completed by this point.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1 IMP Description

6 in 1(IH) (Infanrix hexa)

6 in 1(IH) is a multivalent vaccine that protects against DTaP/IPV/Hib/HepB (diphtheria, tetanus, pertussis, poliomyelitis, *Haemophilus influenza* type B and Hepatitis B virus). It is produced as a powder and suspension for injection which must be combined by the provider before administration. The total volume of the vaccine when reconstituted is 0.5ml and should be given intramuscularly as 2-3 primary doses at least 1 month apart with a booster usually given 6 months later. The packaging and labelling will be as per the manufacturer as is standard practice. (1)

Table 6: Components of 6 in 1(IH) (1)

Component	Dose	Additional information
Diphtheria toxoid	Not less than 20 international units (IU)	Absorbed onto aluminium hydroxide
Tetanus toxoid	Not less than 40 international units (IU)	Absorbed onto aluminium hydroxide
Bordetella pertussis antigens		
- Pertussis toxoid (PT)	25 micrograms	Absorbed onto aluminium hydroxide

- Filamentous Haemagglutinin (FHA)	25 micrograms	Absorbed onto aluminium hydroxide
- Pertactin (PRN)	8 micrograms	Absorbed onto aluminium hydroxide
Hepatitis B surface antigen	10 micrograms	- Produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology - absorbed on aluminium phosphate ($AIPO_4$)
Poliovirus (inactivated) IPV		
- Type 1 (Mahoney strain)	40 D-antigen unit	Propagated in VERO cells
- Type 2 (MEF-1 strain)	8 D-antigen unit	Propagated in VERO cells
- Type 3 (Saukett strain)	32 D-antigen unit	Propagated in VERO cells
Haemophilus influenza type b polysaccharide	10 micrograms	Absorbed on aluminium phosphate ($AIPO_4$)

6 in 1(V) (Vaxelis)

Developed by Sanofi Pasteur, 6 in 1(V) is the other hexavalent vaccine that includes Hepatitis B that is licensed in Europe. It is produced in a fully liquid form in a ready to use injection and protects against the same organisms as 6 in 1(IH) however the structure of some components differs as outlined below. The total volume of each dose is 0.5ml. The packaging and labelling will be as per the manufacturer as is standard practice (2).

Table 7: Components of 6 in 1(V) (2)

Component	**Dose**	**Additional information**
Diphtheria toxoid	Not less than 20 international units (IU)	Absorbed onto aluminium hydroxide
Tetanus toxoid	Not less than 40 international units (IU)	
Bordetella pertussis antigens		
- Pertussis toxoid (PT)	20 micrograms	Absorbed onto aluminium hydroxide
- Filamentous Haemagglutinin (FHA)	20 micrograms	
- Pertactin (PRN)	3 micrograms	
- Fimbriae Types 2 and 3 (FIM)	5 micrograms	
Hepatitis B surface antigen	10 micrograms	- Produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology - Absorbed onto aluminium hydroxyphosphate sulfate

Poliovirus (inactivated) IPV		
- Type 1 (Mahoney strain)	40 D-antigen unit	Propagated in VERO cells
- Type 2 (MEF-1 strain)	8 D-antigen unit	Propagated in VERO cells
- Type 3 (Saukett strain)	32 D-antigen unit	Propagated in VERO cells
Haemophilus influenza type b polysaccharide - conjugated to meningococcal protein	3 micrograms 50 micrograms	Absorbed onto aluminium hydroxyphosphate sulfate

Meningococcal Group B vaccine (Bexsero)

A vaccine developed by GlaxoSmithKline UK. A suspension for injection containing Meningococcal group B vaccine (rDNA, component, absorbed). Each 0.5ml dose contains: recombinant *Neisseria meningitidis* group B Neisseria heparin binding antigen/NHBA fusion protein 50 micrograms, recombinant *Neisseria meningitidis* group B Neisserial adhesion A/NadA protein 50 micrograms, recombinant *Neisseria meningitidis* group B factor H binding protein/fHbp fusion protein 50 micrograms, outer membrane vesicles (OMV) from *Neisseria meningitidis group B* strain NZ98/254 25 micrograms. Produced in E. Coli cells by recombinant DNA technology, absorbed on aluminium hydroxide. The packaging and labelling will be as per the manufacturer as is standard practice.

Haemophilus type b and Meningococcal group C conjugate vaccine (Menitorix)

A vaccine developed by GlaxoSmithKline UK. A powder and solvent solution for injection containing a *Haemophilus* type b and Meningococcal group C conjugate vaccine. Each 0.5 ml dose after reconstitution contains: Haemophilus type polysaccharide (polyribosylribitol phosphate) 5 micrograms conjugated to tetanus toxoid as a carrier protein 12.5 micrograms, *Neisseria meningitidis* group C (strain C11) polysaccharide 5 micrograms conjugated to tetanus toxoid as carrier protein 5 micrograms.

Measles, mumps and rubella vaccine (live) (M-M-RVAXPRO)

A vaccine developed by Merck Sharp & Dohme Limited. M-M-RVAXPRO powder and solvent for injection containing a measles, mumps, and rubella vaccine (live). After reconstitution each 0.5 ml dose contains: measles virus[1] Enders' Edmonston strain (live, attenuated) not less than $1x10^3$ $CCID_{50}$, mumps virus[1] Jerly Lynn (level B) strain (live, attenuated) not less than $2.5x10^3$ $CCID_{50}$, Rubella virus[2] Wistar RA 27/3 strain (live, attenuated) not less than $1x10^3$ $CCID_{50}$. [1] Produced in chick embryo cells, [2] produced in WI-38 human diploid lung fibroblasts. The vaccine may contain traces of recombinant human albumin (rHA) and trace amount of neomycin. The vaccine contains 14.5 micrograms of sorbitol.

Measles, mumps and rubella vaccine (live) Priorix

A vaccine developed by GlaxoSmithKline UK. A powder and solvent for injection containing measles, mumps and rubella vaccine (live). After reconstitution each 0.5 ml dose contains: live attenuated measles virus[1] (Schwarz strain) not less than $10^{3.0}$ $CCID_{50}$[3], live attenuated mumps virus[1] (RIT 4835 strain, derived from Jeryl Lynn strain) not less than $10^{3.7}$ $CCID_{50}$[3], live attenuated rubella virus[2] (Wistar RA 27/3 strain) not

less than $10^{3.0}$ $CCID_{50}$[3]. [1] Produced in chick embryo cells, [2] produced in human diploid (MRC-5) cells and [3] cell culture infective dose. The vaccine contains a trace amount of neomycin.

Pneumococcal polysaccharide conjugate vaccine (Prevenar 13)

A vaccine developed by Pfizer Limited. Prevenar 13 is a suspension for injection containing a Pneumococcal polysaccharide conjugate vaccine (13-valent, absorbed). Each 0.5 ml dose contains: Pneumococcal polysaccharide serotype 1[1] 2.2 micrograms, Pneumococcal polysaccharide serotype 3[1] 2.2 micrograms, Pneumococcal polysaccharide serotype 4[1] 2.2 micrograms, Pneumococcal polysaccharide serotype 5[1] 2.2 micrograms, Pneumococcal polysaccharide serotype 6A[1]2.2 micrograms , Pneumococcal polysaccharide serotype 6B[1] 4.4 micrograms , Pneumococcal polysaccharide serotype 7F[1] 2.2 micrograms , Pneumococcal polysaccharide serotype 9V[1] 2.2 micrograms, Pneumococcal polysaccharide serotype 14[1] 2.2 micrograms, Pneumococcal polysaccharide serotype 18C[1] 2.2 micrograms, Pneumococcal polysaccharide serotype 19A[1] 2.2 micrograms, Pneumococcal polysaccharide serotype 19F[1] 2.2 micrograms and Pneumococcal polysaccharide serotype 23F[1] 2.2 micrograms. [1] Conjugated to CRM_{197} carrier protein, absorbed on aluminium phosphate. Each 0.5 ml dose contains approximately 32 micrograms CRM_{197} carrier protein and 0.125 milligrams of aluminium.

Rotavirus vaccine live (Rotarix)

A vaccine developed by GlaxoSmithKline UK. An oral suspension containing a live rotavirus vaccine. Each 1.5 ml dose contains: human rotavirus RIX4414 strain (live, attenuated)* not less than $10^{6.0}$ $CCID_{50}$. * Produced on Vero cells. The vaccine contains sucrose 1,073 milligrams.

9.2 Storage of IMP

Supply of 6 in 1(IH) and the vaccines in the routine schedule will be through the Department of Health. 6 in 1(V) will be supplied by MCM. Vaccines will be stored in 2 – 8 degree Celsius fridges at each study site or in hospital pharmacies, as per local arrangements. All fridges will be temperature monitored.

Vaccines will be transported to participants homes or to a suitable and convenient location in 'cool-boxes' that are able to maintain temperatures between 2 – 8 degrees Celsius.

9.3 Compliance with Trial Treatment

The parents/legal guardians will need to ensure ongoing availability and access for study visits to occur in order to comply with the trial. All vaccines in the trial will be administered by trained study staff.

9.4 Accountability of the Trial Treatment

6 in 1(IH) and the other standard schedule vaccinations will be ordered through NHS supplies. 6 in 1(V) will be ordered directly from MCM by the individual sites. Accountability will be documented according to local policy and final vaccine accountability will be recorded.

9.5 Concomitant Medication

Medication associated with an AE (5 days following vaccine administration) will be recorded in the ediary.

9.6 Post-trial Treatment

There will be no provision of the IMP after the trial has finished.

10 SAFETY REPORTING

10.1 Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial 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 trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. Planned hospitalisations for management of pre-existing conditions need not be reported as an SAE unless this condition has deteriorated during the course of the study. 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

10.2 Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

10.3 Procedures for Recording Adverse Events

All AEs that occur within 5 days of a vaccination visit and all SAEs that occur during the study that are observed by the Investigator or reported by the participant's parent/guardian, will be recorded on the CRF, whether or not attributed to trial vaccines.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

SAEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. The parents/legal guardians of participants may also voluntarily withdraw from treatment due to what they perceive as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

10.4 Reporting Procedures for Serious Adverse Events

All SAEs (other than those defined in the protocol as not requiring reporting) must be reported on the Oxford Vaccine Group SAE reporting form and emailed to the Chief Investigator within 24 hours of the site study team becoming aware of the event. The CI or delegate within the OVG will perform an initial check of the report, request any additional information. OVG will forward the SAE form to the Sponsor (CTRG) via the safety reporting mailbox for review by the Medical Monitor and Trial Safety Group. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and emailed to CI or delegate within the OVG who will review and forward updated information to the Sponsor (CTRG). SAEs experienced by participants receiving 6 in 1-V will also be reported to MCM on the same form by the CI or delegate.

10.5 Expectedness

Expectedness will be determined according to the approved RSI within the Summary of Product Characteristics. The local PI will assess relatedness, but the CI or delegate will assess expectedness (as delegated by the Sponsor to the CI).

10.6 SUSAR Reporting

All SUSARs will be reported by the CI to the relevant Competent Authority and to the REC and other parties, including MCM. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

10.7 Safety Monitoring Committee

As these are licensed vaccines a study specific Safety Committee will not be convened.

10.8 Development Safety Update Reports

The Oxford Vaccine Group will submit DSURs once a year throughout the clinical trial, or on request to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust Sponsor and MCM.

11 STATISTICS

11.1 Sample size calculation

The original sample calculation was based on the following assumptions:

1. The non-inferiority margin is 0.5 fold-difference between the GMC in the 6 in 1(V) arm and that in the 6 in 1(IH) arm (reference) or -0.3 absolute difference of GMC on log scale (base 10). 2. The standard deviation of GMC on log scale (base 10) is 0.72 (12)
3. The true difference of GMC on log scale (base 10) is 0.

Based on the above assumptions, the study would have needed to recruit 104 infants for each arm to achieve 85% of power at two-sided 5% significance level. The attrition rate was expected to be approximately 10%. To incorporate further allowances for protocol violations and unexpected dropouts, the target sample size was 240 infants (120 per arm).

The protective threshold for Hib is 0.15 µg/ml. (13) Assuming the proportion of infant with anti-PRP IgG concentrations at 5 months of age≥ 0.15 µg/ml is 91%, this trial would have had >70% of power with two-sided 5% significance level to claim the 6 in 1(V) is non-inferior to 6 in 1(IH) at a margin of 10%. (12)

After reviewing the current disruption on clinical activities by COVID-19 and the urgency to obtain the data for policy making in the UK, the study team decided to evaluate the study power based on the recruitment up to the time this was paused for the COVID-19 pandemic, and decided to increase the type I error from two-sided 5% (one-sided 2.5%) to one-sided 5%, which is a common type I error rate in non-inferiority trials. At this stage the study had recruited 194 participants. From these there was approximately 172 participants with blood samples likely to be available for primary endpoints in the ITT analysis. Based on the original assumptions and the 5% type I error, the current study power is 85%. Since the current study recruitment has achieved the planned power based on the adjusted type I error, the study CI, sponsor and funder group decided not to resume recruiting and continue with a sample size of 194 participants.

11.2 Description of Statistical Methods

The primary outcome is anti-PRP Hib IgG concentrations at 5 months of age as measured by ELISA. The geometric mean concentrations (GMC) of anti-PRP IgG will be compared between 6 in 1(IH) and 6 in 1(V) under the hypothesis:

$$H_0: GMC_{6\text{ in }1(V)} / GMC_{6\text{ in }1\text{-}(IH)} \leq 0.5 \text{ or } log_{10} GMC_{6\text{ in }1(V)} - log_{10} GMC_{6\text{ in }1(IH)} \leq -0.3;$$

$$H_0: GMC_{6\text{ in }1(V)} / GMC_{6\text{ in }1(IH)} > 0.5 \text{ or } log_{10} GMC_{6\text{ in }1(V)} - log_{10} GMC_{6\text{ in }1(IH)} > -0.3.$$

The GMC will be transferred using logarithmic transformations (base 10) to render a normal distribution.

We will test the above hypothesis using the multiple regression on log_{10}GMC adjusting for the design effect and the pre-specified prognostic factors. The adjusted mean difference of log_{10}GMC will be presented with the 95% confidence interval (CI). The difference will be calculated as the mean of log_{10}GMC in 6 in 1(V) arm compared to that in the 6 in 1(IH) arm. We will claim 6 in 1(V) is non-inferior to 6 in 1(IH) if the lower CI lies above -0.3.

The proportion of infant with anti-PRP Hib IgG concentrations at 5 months of age≥ 0.15 µg/ml will be compared between 6 in 1(IH) and 6 in 1(V) arms and the adjusted difference of the proportion will be presented with the 95% CI.

The primary analysis will be conducted on the intent-to-treat basis. The per-protocol analysis will be considered as a sensitivity analysis if the crossover rate is high in this trial.

The analysis on primary outcome will be conducted after the 5-month anti-PRP Hib IgG concentrations are available for all participants, while the trial will continue to follow up all participants till 13 months of age. The final analysis for the other outcomes will be carried out once the 5-month and 13-month data are available for all participants.

A fully detailed statistical analysis plan will be prepared and will be signed off by the Chief Investigator prior to conducting any data analyses.

11.3 Missing data

The level and pattern of the missing data in the baseline variables and outcomes will be reported. The potential causes of any missing data will be investigated and documented as far as possible. Any missing data will be dealt with using methods appropriate to the conjectured missing mechanism and level of missing.

12 DATA MANAGEMENT

12.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF 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, microfiches, radiographs, 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. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

12.2 Access to Data

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. Access to medical records by those outside the direct healthcare team, will only occur if consent has been received. This would be for the purpose of clarifying medical history in relation to the inclusion/exclusion criteria and safety reporting.

12.3 Data Recording and Record Keeping

CRF data will be recorded directly into an EDC system (e.g. OpenClinica/REDCap) or onto a paper source document for later entry into EDC if direct entry is not available. Any additional information that needs recording but is not relevant for the CRF (such as sites for venepuncture, parental availability etc) will be recorded on a separate paper source document. All documents will be stored safely in confidential conditions.

Parents/legal guardians will consent for email addresses to be entered into an electronic diary system. This enables the diary to be sent to parents to complete online. The EDC systems (electronic diary and CRF data) uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. The database includes a complete suite of features which are compliant with EU and UK regulations and NHS security policies, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server will both be housed on secure servers operated by the University of Oxford IT Services. The servers are in a physically secure location in Oxford and are backed up in Oxford, with the backups stored in accordance with the IT department schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The IT servers provide a stable, secure, well-maintained, and highcapacity data storage environment, Drupal and MySQL are widely-used, powerful, reliable, well-supported systems. Access to the study's database and the diary will be restricted to the members of the study team by username and password.

All entries made to the research notes should be printed legibly. If any entry error has been made, to correct such an error, a single straight line should be drawn through the incorrect entry and the correct data entered above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, the clarification should be printed above the item, and this should also be initialled and dated. Information entered into the research notes must be subsequently transferred onto the database by the site collecting the data. The participants will be identified by a unique study specific number in any database. The name and any other identifying detail will NOT be included in any study data file.

The investigator at each investigational site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (International Conference on Harmonisation (ICH) E6, Guideline for Good Clinical Practice) including the Investigator Site File. Copies of all study documents will be retained after the completion or discontinuation of the study for 3 years after the youngest participant turns 18 years. In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities). The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation of this transfer of responsibility to their successor must be documented in writing.

The participants will be identified by a unique trial specific number and/or code in any database.

13 QUALITY ASSURANCE PROCEDURES

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

This trial has been assessed as a low risk CTIMP and as such, monitoring of study conduct and protocol compliance will be delegated by the sponsor to the trials unit. Regular monitoring will be performed by the Oxford Vaccine Centre Quality Assurance team, with details outlined in a study monitoring plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following the 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.

14 PROTOCOL DEVIATIONS

A trial related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process or IMP administration) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file.

15 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

16 ETHICAL AND REGULATORY CONSIDERATIONS

16.1 Declaration of Helsinki

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

16.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), 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.

16.4 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation, Sponsor and MCM.

In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

16.5 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all trial documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial will comply with the General Data Protection Regulation (GDPR), including the requirement that data to be anonymised as soon as it is practical to do so.

16.6 Expenses and Benefits

As study visits will be occurring in the participant's homes, reimbursement will not be necessary.

16.7 Other Ethical Considerations

There is a potential for co-administration of 6 in 1-(V) and MenB vaccines to influence the immune responses to the Hib component of 6 in 1-(V), either enhancing or inhibiting the immunogenicity of this component. If any participants (in either group) have a sub-optimal response to the Hib component of the immunisation schedule (i.e. anti-PRP IgG < 1.0 mg/ml at 13 months of age), their GP will be contacted and advised that the participant requires an additional dose of the Hib-MenC combination vaccine. The HibMenC vaccine is used in the UK to boost protection against Hib disease and protects against meningococcal disease caused by type C Neisseria meningitidis bacteria. In the UK the Hib-MenC vaccine is given at 12-13 months (the brand name of the vaccine used in the UK schedule is Menitorix).

Due to the need to obtain maternal immunisation history, if available, the participant's mother will be asked to give consent to access her immunisation history.

17 FINANCE AND INSURANCE

17.1 Funding

This study will be funded by MCM.

17.2 Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

18 PUBLICATION POLICY

The Investigators 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. Authors will acknowledge that the study funded by MCM. Authorship will be determined in accordance with the ICMJE (International Committee of Medical Journal Editors) guidelines and other contributors will be acknowledged.

Further details of funders review prior to publication will be outlined in the Clinical Trials agreement.

19 REFERENCES

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b. **Kayhty, H, et al.** 6, 1983, The Journal of Infectious Diseases, Vol. 147, p. 1100.

20 APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	1.1	21-FEB-19	K.Jefferies	As per REC recommendations. Removal of paracetamol dose from V5 and unblinding from SAE section
2	1.2	21-MAR-19	K.Jefferies	Correction of grammatical errors and clarification of AE/SAE reporting procedures. Clarification of injection site administration
3	2.0	23-APR-19	K.Jefferies	Schedule change to PCV13
4	2.1	22-JUL-19	K.Jefferies	Deletion of sentence referencing PCV13 in Visit 1 Correction of grammatical errors
5	3.0	07-JAN-20	S Rhead	Updated sentence regarding PCV13 2020 immunisation schedule Re-wording of sentence regarding blood sampling attempts

6	4.0	17-AUG-20	X. Liu N.Owino M.Snape	Addition of adjusted sample size Updated sample size calculation section in relation to adjusted sample size

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.