# Babies born Early Antibody Response to Men B vaccination: BEAR Men B

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Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical/regulatory review of the study, without written authorisation from St George’s Joint Research and Enterprise Office (JREO) or its affiliates.

**Signature Page and Statement**

The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except in the case of medical emergency or where departures from the protocol are agreed in writing by the Sponsor.

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the St George’s NHS Trust Information Governance Policy (or other local equivalent), UK Policy Framework for Health and Social Care Research v3.2 October 2017, the Sponsor’s Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

This protocol has been written in accordance to the Sponsor’s procedure identified as: JREOSOP0039 ‘Protocol Design’ and is intended for use at UK sites only.

|  |  |  |
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**Acknowledgements and Protocol contributories**

This study was devised by Anna Calvert and Paul Heath and was developed by Anna Calvert, Paul Heath, Shamez Ladhani and Helen Findlow, and also incorporates comments and input from the prospective collaborating PIs. Paul Heath is the grant holder. Nick Andrews provided statistical expertise in clinical trial design and will be conducting primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final version.

We are grateful for the funding from Meningitis Now and GlaxoSmithKline. These bodies have had no input into the design of this study and will have no role in data collection, management, analysis, or interpretation of the findings. The preparation of the report will be done by the study authors and will be entirely independent of the funding organisations. The funding organisations will have no influence over the content of the final report submitted for publication, or the decision to submit.Contents

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# List of abbreviations

AE Adverse Event

AR Adverse Reaction

CA Competent Authority

CI Chief Investigator

CRF Case Report Form

CTA Clinical Trial Authorisation

CTIMP Clinical Trial of Investigational Medicinal Product

DMC Data Monitoring Committee

DSUR Development Safety Update Report

EMA European Medicines Agency

EU European Union

EUCTD European Clinical Trials Directive

EudraCT European Clinical Trials Database

fHbp factor H binding protein

GCP Good Clinical Practice

GMT Geometric Mean Titres

HRA Health Research Authority

hSBA human Serum Bactericidal Antibody

ICF Informed Consent Form

IMP Investigational Medicinal Product

ISF Investigator Site File

ISRCTN International Standard Randomised Controlled Trial Number

ITT Intention to treat

JREO Joint Research and Enterprise Office

MHRA Medicines and Healthcare products Regulatory Agency

MoU Memorandum of Understanding

NadA Neisserial adhesinA

NIMP Non- Investigational Medicinal Product

PHE Public Health England

PI Principal Investigator

PIS Participant Information Sheet

PorA Porin A

RCT Randomised Control Trial

REC Research Ethics Committee

RSI Reference Safety Information

SAR Serious Adverse Reaction

SAE Serious Adverse Event

SDV Source Document Verification

SOP Standard Operating Procedure

SmPC Summary of Product Characteristics

SSAR Suspected Serious Adverse Reaction

SUSAR Suspected Unexpected Serious Adverse Reaction

TMF Trial Master File

TMG Trial Management Group

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# Study synopsis

|  |  |
| --- | --- |
| **Brief Title** |  **BEAR** MenB |
| **Official title:**  | **B**abies born **E**arly **A**ntibody **R**esponse to **Men B** vaccination: **BEAR MenB** |
| **Brief Summary** | A phase IV multicentre study to evaluate the primary and booster immune responses in UK preterm infants receiving routine immunisations and incorporating a randomisation study of a three dose versus a two dose schedule of Bexsero® for primary immunisation. |
| **Sponsor reference number:** | 16.0247 |
| **Public database Trial identifier number** | ClinicalTrials. Gov NCT03125616 |
| **Study type & Phase** | Phase IV randomisation study of two Men B vaccine schedules in preterm infants |
| **Study Design** | Preterm infants will be randomised to one of two 4CMenB schedules. Blood samples will be taken to assess vaccine responses at 5, 12 and 13 months of age and a diary card will be used to assess reactogenicity of the vaccines.  |
| **Chief Investigator:** | Professor Paul HeathProfessor Paediatric Infectious DiseasesSt George’s, University of London |
| **Study Population** | Preterm infants born at <35 weeks gestation (i.e. up to 34 weeks and 6 days), 50% <30 weeks gestation (i.e. up to 29 weeks and 6 days) |
| **Condition** | Prematurity |
| **Study Group/cohort (s)** | Infants will be randomised to one of two 4CMenB schedules. One group will receive two 4CMenB vaccinations, i.e. at 8 and 16 weeks of age as per current UK schedule, while the other group will receive three 4CMenB vaccinations, i.e. at 8, 12 and 16 weeks of age. Both groups will receive a 4CMenB booster at 12 months of age.  |
| **Eligibility criteria:** | ***Inclusion criteria:**** Premature infant born at <35 weeks gestation
* No contraindications to vaccination according to the ‘Green Book’
* Willing and able to comply with study procedures
* Written informed consent
 |
| ***Exclusion criteria:**** Contraindication to vaccination according to the Green Book
* Life-limiting congenital abnormality or condition
* Prior diagnosis of an immunodeficiency syndrome
* Considered unlikely to complete expected follow up until the end of the study
* Child in care
 |
| **Target number of participants:** | 132 |
| **Criteria for evaluation:** | ***Primary outcome measure(s):*** 1. hSBA GMTs 1 month after completion of primary immunisations for relevant Bexsero® antigens: fHbp, NadA and PorA
2. hSBA proportions ≥1:4, at 1 month after completion of primary immunisations for relevant Bexsero® antigens: fHbp, NadA and PorA.
 |
| ***Secondary outcome measure(s):*** (i) The percentage of infants presenting with fever, local reactions and non-febrile systemic reactions within the 7 days following each Bexsero® vaccine dose; (ii)The percentage of inpatients who have a change/deterioration in cardiorespiratory status within the 72 hours following each Bexsero® vaccine dose; (iii)The percentage of infants investigated for sepsis and commenced on antibiotics within 7 days of Bexsero® vaccination;(iv) hSBA GMTs at 12 months of chronological age (pre booster) for relevant Bexsero® antigens: fHbp, NadA and PorA;  (v) hSBA proportions ≥1:4, at 12 months of chronological age (pre booster) for relevant Bexsero® antigens: fHbp, NadA and PorA; (vi) hSBA GMTs at 13 months of chronological age (4-6 weeks post booster) for relevant Bexsero® antigens: fHbp, NadA and PorA;  (vii) hSBA proportions ≥1:4, at 13 months of age (post booster) for relevant Bexsero® antigens: fHbp, NadA and PorA. |
| **Sources of funding:** | Meningitis Now GSK  |
| **Anticipated start date:** | June 2017 |
| **Anticipated primary completion date:** | March 2020 |
| **Sponsor** | St George’s, University of London |
| **Contact names** | Sponsor Contact:Debbie RolfeTel: 020 8725 5013Fax:020 8725 0794Email:drolfe@sgul.ac.ukChief Investigator: Professor Paul HeathProfessor Paediatric Infectious DiseasesSt George’s, University of London |

# Primary Objectives

To compare the immunological responses of infants born preterm to Bexsero® after two primary doses given at 2 and 4 months chronological age with three doses given at 2, 3 and 4 months chronological age.

# Secondary Objectives

-To describe the safety of routine vaccines (including Bexsero®) in premature infants;

-To compare the persistence of immunological responses to Bexsero® at 12 months chronological age after two doses at 2 and 4 months of age with three doses at 2, 3 and 4 months of age;

-To compare the immunological responses following the 12-month Bexsero® booster in babies who received two doses at 2 and 4 months of age with those who received three doses at 2, 3 and 4 months of age.

# Background

# Study disease

*Neisseria meningitidis* (meningococcus) is a bacterium which causes meningitis and septicaemia. There are 13 serogroups of meningococcus, 6 (A, B, C, W, X and Y) cause most disease of which Men B is the most common cause of meningococcal disease in the UK. Babies are the most frequently affected group, with the main burden of disease falling in the second 6 months of life. In 2015 the UK became the first country in the world to introduce Men B vaccination into its routine schedule, with a two-dose priming regime with a booster at 12 months. A recent paper has shown this schedule to be highly effective in preventing Men B disease in infants (Parikh et al, 2016).

Premature delivery affects a significant minority of infants: around 7% in the UK and around 10% globally. These infants are more at risk from vaccine-preventable diseases and it is therefore very important that they are adequately vaccinated. Premature infants are vaccinated according to their chronological age (see table 1 for current vaccination schedule), but this may provide them with less protection than their term counterparts. There is existing evidence that preterm infants have a lower response to a range of routine vaccines including Hib (Heath et al, 2003), pneumococcal conjugates (Ruggeberg et al, 2005), Hepatitis B (Losonsky et al, 1999), and DTP (Robinson et al, 2004), and that the response to pneumococcal vaccination in premature infants is dependent on the primary schedule they receive (Kent et al, 2016). There are currently no data available on the response of preterm infants to the Bexsero® vaccine.

The vaccine schedule changed in August 2017 from a 5-in-1 to a 6-in-1 vaccine being given at each of the primary vaccinations. All babies born on or after the 1st August 2017 will receive the 6-in-1 vaccine.

|  |  |  |
| --- | --- | --- |
| Vaccine | Product names | Age (months) |
| 2 | 3 | 4 | 12 |
| DTaP/IPV/Hib/Hep B | Infanrix Hexa® | ✓ | ✓ | ✓ |  |
| Rotavirus | Rotarix® | ✓ | ✓ |  |  |
| MenB | Bexsero® | ✓ |  | ✓ | ✓ |
| PCV13 | Prevenar13® | ✓ |  | ✓ | ✓ |
| MCC-TT/Hib-TT | Menitorix® |  |  |  | ✓ |
| MMR | Priorix® |  |  |  | ✓ |

Table 1: UK infant vaccination schedule (from August 2017)

Investigational Medicinal Product (IMP)

* Bexsero® (Manufactured by Glaxo Smith Kline in Italy). (MenB): a four component vaccine that protects against *Neisseria meningitidis* serogroup B

## Non-investigational Medicinal Products (NIMPs)

* Infanrix IPV/Hib® (DTaP/IPV/Hib): a 5-in-1 combination vaccine that protects against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* serotype b (Hib)
* Pediacel®(DTaP/IPV/Hib): a 5-in-1 combination vaccine that protects against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* serotype b (Hib)
* Infanrix hexa®(DTaP/IPV/Hib/Hep B): a 6-in-1 combination vaccine that protects against diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* serotype b (Hib) and hepatitis B.
* Prevenar 13® (PCV 13): a 13-valent pneumococcal conjugate vaccine that protects against 13 different pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F)
* Rotarix®:an oral vaccine containing live attenuated rotavirus that protects against rotavirus
* Menitorix® (MCC-TT/Hib-TT): a combined *Haemophilus influenzae* serotype b (Hib) and meningococcal serogroup C conjugate vaccine where the capsular polysaccharides of both organisms are covalently linked to tetanus toxoid carriers
* Priorix® (MMR): a live attenuated vaccine that protects against measles, mumps and rubella

All the above vaccines are licensed for routine childhood immunisation in the UK. The Summary of medical Product Characteristics (SmPC) for each of the vaccines will be included in the Investigator Site File (ISF) and the Trial Master File (TMF).

## Study Rationale and risk/benefit analysis

This study is being undertaken to compare the immune responses of preterm infants who are vaccinated according to two different schedules. There is evidence that preterm infants respond less well to vaccinations than their term counterparts for some vaccines and this has not previously been studied for Bexsero®. The clinical trial will only use vaccines that have been licensed for routine childhood immunisation in the UK. One group will receive vaccinations according to the UK schedule and the other will receive vaccinations according to the original licence. Because the infants enrolled in the study would have received the same vaccines as part of their routine immunisation, this study is unlikely to be associated with any added risk of adverse events. Blood sampling will be performed by appropriately trained members of the research team and the volume of blood obtained at each visit will not exceed 1% of the infant’s circulating blood volume, based on an estimated total circulating blood volume value for preterm infants of 90 mL/kg.

**Assessment & management of potential risk**

There is always a small risk of an adverse reaction following vaccination and this will be explained to parents, but the per dose risk will not be greater for infants in this study compared to those who receive routine care. The Bexsero® vaccine is particularly associated with fever following vaccination and parents will receive advice about this.

Vaccines will be given by experienced medical or nursing staff who are trained in how to manage an allergic reaction following vaccination and who will have with them emergency equipment according to their local SOPs.

The parents/legal guardians of the study infants will be asked to record in a diary card any symptoms or illness occurring up to 7 days after the Bexsero® vaccine is administered. This will include local reactions, general reactions and episodes of fever. Parents/legal guardians will also be provided with a 24-hour telephone number to contact in case of any queries or concerns and will be asked to contact the study team in the event of serious illness or illness requiring hospitalisation which will allow early identification of serious adverse events. In addition all illnesses will be enquired about at each study visit so that all adverse events, which are not solicited in the diary card, can be recorded. Solicited adverse events recorded in the diary card (e.g fever in the 7 days post vaccination, redness at the vaccine site etc.) do not need to be recorded in the adverse events log. Information about all SAEs occurring at any time within the study period (i.e. after consent has been taken) will be collected.

According to the MRC/DH/MHRA Joint Project on Risk-adapted Approaches to the Management of Clinical Trials of IMPs (October 2011), this trial is categorised as Type A (Risk no higher than that of standard medical care). Bexsero will be dispensed in accordance with a prescription given by an authorised healthcare professional and will be labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994 (b) that apply in relation to dispensed relevant medicinal products. A Sponsor approved prescription template will be provided to participating sites to prompt appropriate documentation in the Pharmacy Site file.

# Trial design

## Overall design

This will be an open label, phase IV study. After appropriate consent, 132 premature infants born at <35 weeks gestation (i.e. up to 34 weeks and 6 days), 50% <30 weeks gestation (i.e. up to 29 weeks and 6 days) will be randomised to 1 of 2 4CMen B schedules (Table 1).  Babies will remain in the study for around 12 months, from recruitment to 13 months of age. All visits can be performed at the participant’s home or in clinic, depending on the preference of the parents and study team.

Blood samples will be obtained at 5 months of age (post primary sample), 12 months (persistence sample) and 13 months (post booster sample). Reactogenicity and safety will be assessed by caregiver completion of a 7-day diary after each vaccine dose.  Inpatients will be monitored for cardiorespiratory events for 72 hours after vaccination by healthcare staff and this information will be collected on the CRF. This will include details of oxygen saturations, heart rate, respiratory rate and details of any episodes of desaturation, bradycardia or apnoea. If an infant is medically fit for discharge prior to the end of this 72 hours of observation the decision to discharge must be discussed with the PI, but will not be considered a protocol deviation. This decision must be documented on the appropriate CRF. Particular emphasis will be placed on rates, timing and intensity of fever and other adverse reactions in the first 24 hours after vaccination, because this remains a cause of great concern amongst neonatologists. Parents will be advised to give three doses of paracetamol after receiving Bexsero®, according to UK guidance unless the infant is an in-patient in which case local policy will be followed. If participants are outpatients at the time of Bexsero administration their parents will be provided with information about paracetamol administration following Men B vaccination and if the infant was born at less than 32 weeks an appropriate dose of paracetamol will be calculated by the study team and communicated to the parents. Administration of paracetamol will be systematically recorded on the diary card including number of doses given and whether given prophylactically or in response to a fever.

Table 2. Timing of vaccinations and blood sampling

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Visit Number**  | **1**  | **2**  | **3**  | **4**  | **5** | **6**  |
| **Age** | 2 months49-84 days | 3 months28-42 days after V1 | 4 months28-42 days after V2 | 5 months28-42 days after V3 | 12 months364- 393 days  | 13 months28-42 days after V5 |
| **Group 1** | **Bexsero®**RV | RV | **Bexsero®**RV | \* | **Bexsero®**RV\* | \* |
| **Group 2** | **Bexsero®**RV | **Bexsero®**RV | **Bexsero®**RV | \* | **Bexsero®**RV\* | \* |

RV=Routine vaccines \*= Blood sampling

Ages of scheduled vaccination refer to chronological ages.

## Schematic of trial design

## *Study procedures*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study procedures | Screening | 2 monthsV1 | 3 monthsV2 | 4 monthsV3 | 5 monthsV4 | 12 monthsV5 | 13 monthsV6 |
| Discuss study with parent/guardian | ✓ |  |  |  |  |  |  |
| Check eligibility criteria | ✓ |  |  |  |  |  |  |
| Arrange first appointment | ✓ |  |  |  |  |  |  |
| Reconfirm eligibility |  | ✓ |  |  |  |  |  |
| Informed Consent | ✓ (Can be done at this visit) | ✓ |  |  |  |  |  |
| Randomisation |  | ✓ |  |  |  |  |  |
| Medical history |  | ✓ |  |  |  |  |  |
| Record details of physical examination |  | ✓ |  |  |  |  |  |
| Check for concomitant medications |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Vaccine administration |  | ✓ | ✓ | ✓ |  | ✓ |  |
| Post vaccination monitoring |  | ✓ | ✓ | ✓ |  | ✓ |  |
| Ask about AEs/SAEs |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |
| Blood sampling  |  |  |  |  | ✓ | ✓ | ✓ |
| Distribution of diary card |  | ✓ | ✓ | ✓ |  | ✓ |  |
| Checking diary card with parents |  |  | ✓ | ✓ | ✓ |  | ✓ |

# IMP Dosage regimen and rationale

**Bexsero®** (manufactured by Glaxo Smith Kline) is a four component vaccine that protects against *Neisseria meningitidis* serogroup B. It is indicated for use from 2 months of age and will be given according to the UK schedule at 2, 4 and 12 months or at 2, 3, 4 and 12 months for those babies randomised to receive a 3+1 regime.

## Source of IMP and NIMPs

All vaccines will be obtained by local sites from national stock using the ImmForm system. Vaccines will be received by hospital clinical trials pharmacist or research teams as decided by individual sites and will be placed into quarantine until documentation of the cold chain had been reviewed to confirm that they may be released for use.

Vaccines used in this study will be labelled in accordance with the Medicines (Marketing Authorisations etc.) Regulations 1994 as amended and supplied by a pharmacy department without any need of special labelling.

8.2 Accountability procedures for the IMP **and NIMPs**

The research or hospital pharmacy department will be responsible for maintaining and updating the IMP/NIMP Accountability Log, filed in the pharmacy site file. IMP and NIMP(s) destruction will be conducted, once agreed by the Sponsor, in accordance to local pharmacy practice and will be documented on the Destruction Log filed in the pharmacy site file. All used/unused IMP/NIMP(s) must be returned to the trial pharmacist. Alternative arrangements relating to the accountability procedures for the IMP and NIMPs are to be agreed in writing with the Sponsor in advance of their implementation.

## Post-trial IMP arrangements

Bexsero® is already part of the infant vaccine schedule in the UK and so no additional arrangements are required.

## Name and description of each non-IMP (NIMP)

The following vaccines will be used as part of the study. All vaccines will be identified clearly with a participant number when they have been issued.

***In babies born before 1st August* 2017 Infanrix IPV+Hib®**(manufactured by GSK) contains diphtheria toxoid, tetanus toxoid, three pertussis antigens (pertussis toxin, filamentous haemagglutinin and pertactin), three inactivated poliovirus strains and *Haemophilus influenzae* type b polysaccharide. This vaccine is indicated for use in infants from the age of 2 months and will be given according to the UK schedule of vaccination at 2, 3 and 4 months. Infanrix IPV+Hib® has been available to use in the UK since June 2014 at which time it had been introduced alongside Pediacel®, the vaccinewhich had originally been chosen to replace the whole cell pertussis vaccine. The routine vaccine programme changed from a 5-in-1 to a 6-in-1 vaccine on 1st August 2017 so the 5-in-1 vaccine will be given only to babies born before this date.

***In babies born before 1st August* 2017 Pediacel®** (manufactured by Sanofi Pasteur) contains diphtheria toxoid, tetanus toxoid, five pertussis antigens (pertussis toxin, filamentous haemagglutinin, pertactin, fimbriae 2 and 3), three inactivated poliovirus strains, and *Haemophilus influenzae* type b polysaccharide. This vaccine is indicated from the age of 6 weeks and will be given according to the UK schedule of vaccination at 2, 3 and 4 months. Pediacel will be used interchangeably with Infanrix IPV/Hib according to availability in national stock. The routine vaccine programme changed from a 5-in-1 to a 6-in-1 vaccine on 1st August 2017 so the 5-in-1 vaccine will be given only to babies born before this date.

***In babies born on or after 1st August* 2017 Infanrix-hexa®** (manufactured by GSK) contains diphtheria toxoid, tetanus toxoid, three pertussis antigens (pertussis toxin, filamentous haemagglutinin and pertactin), three inactivated poliovirus strains, *Haemophilus influenzae* type b polysaccharide and hepatitis B virus surface antigen recombinant. This vaccine is indicated for use in infants from the age of 2 months and will be given according to the UK schedule of vaccination at 2, 3 and 4 months to all babies born on or after 1st August 2017.

**Prevenar 13®** (manufactured by Pfizer) contains 13 pneumococcal serotypes and has been used in the UK infant schedule since 2010. The vaccine is indicated for use from 6weeks of age and will be given according the UK schedule at 2, 4 and 12 months.

**Rotarix®** (manufactured by GSK) is an oral vaccine which contains live, attenuated human rotavirus and has been used in the UK schedule since July 2013. It is indicated for use from 6 to 24 weeks of age and will be given according to the UK schedule at 2 and 3 months.

**Menitorix®**(manufactured by GSK) is a combined *Haemophilus influenzae* serotype b (Hib) and meningococcal serogroup C conjugate vaccine. It is indicated for use from 2 months to 2 years of age and will be given at 12 months according to the UK schedule.

**Priorix®**(manufactured by GSK) is a live attenuated vaccine that protects against measles, mumps and rubella. This is indicated for use from 9 months of age and will be given at 12 months according the UK schedule.

## Concomitant treatment

Receipt of immunoglobulin or corticosteroids during the neonatal course will not be an exclusion criterion. Medications of interest will be recorded at each visit on a concomitant medication form. These will include antibiotics, non-study vaccines, immunosuppressant medication and Palivizumab. Both medications currently being taken and a history of medication use since the previous visit will be recorded.

# Participant Selection criteria

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility should be addressed prior to inclusion.

The eligibility criteria have been carefully considered and are chosen to ensure both the safety of the participants and that the trial results can be appropriately used to make future decisions for babies born prematurely as a general group. It is therefore vital that exceptions are not made to the selection criteria. Deviations from the eligibility criteria are considered to be protocol violations and may be reported to the MHRA as a serious breach.

All participants that are screened for inclusion into the study must be entered onto the Sponsor screening log JREOLOG0001 and will be assigned a sequential number. Participants will be considered eligible for enrolment into this trial if they fulfil all of the inclusion criteria and none of the exclusion criteria as defined below.

Eligible participants will be entered onto the Sponsors Subject ID log JREOLOG0002 and assigned a Trial specific Identification number in a pre-agreed format in accordance with Site identifier and next sequential numerical value e.g. SG001

##  Inclusion criteria

* Premature infant born at <35 weeks gestation
* No contraindications to vaccination according to the ‘Green Book’
* Willing and able to comply with study procedures
* Written informed consent

##  Exclusion criteria

* Contraindication to vaccination according to the Green Book
* Life-limiting congenital abnormality or condition
* Prior diagnosis of an immunodeficiency syndrome
* Considered unlikely to complete expected follow up until the end of the study
* Child in care
1. **Subject/Patient Recruitment process**

Patient recruitment at a site will only commence once evidence of the following are in place:

1. REC approval, MHRA Confirmation of Trial notification, Health Research Authority (HRA) approval

2. Signed Delegation of Duties and Sponsorship Agreement returned to the JREO

3. Final approval of the Sponsor (which may include evidence of local Pharmacy Green light) issued by Sponsor representative of the JREO

4. Confirmation of Capacity and Capability issued by the local R&D department,

5. The trial initiation procedure completed and the issue of the ‘Open to recruitment’ letter by the JREO

All sites participating in the trial will also be asked to provide a copy of the following:

1. Signed Clinical Trial Site Agreement (CTSA) or HRA Statement of Activities,

2. Confirmation of Capacity and Capability issued by the local R&D department

All potential participants whose parents wish them to enter the study will be fully screened and consented by the Principal Investigator, or one of the qualified clinicians involved in the study as Clinical Co-investigators. These may be medical or nursing staff.

132 participants will be recruited from suitable participating sites.

A variety of recruitment strategies will be used to recruit eligible participants. If babies are still on the neonatal unit the clinical team will identify potentially eligible babies and will check that families of these infants are happy to meet the research team to discuss the study. Parents will then be approached to discuss the study and be offered the chance of participation. There will be posters and leaflets about the study on the neonatal unit, in neonatal clinic waiting rooms and in the hospital more generally. Some units may choose to advertise the study on institutional websites or newsletters, or on posters in the community (e.g. in GP practices). Parents of recently discharged infants may be contacted by letter, email or phone informing them of the study. In this instance the information packs will be provided by the research team, but the patient details will be accessed by the direct care team and the packs despatched by them. We will have a twitter account to allow parents to follow the progress of the study, although this will not be used explicitly for recruitment.

# Study procedures

## Informed consent

Please note, it is essential that all trial personnel/staff undertaking the informed consent process have signed the Sponsor’s Delegation of Responsibilities Log JREOLOG0004 to ensure that the person has been delegated the responsibility by the study CI/PI. All personnel taking informed consent must be GCP trained. Refer to Sponsor SOP JREOSOP0027

Informed consent from a parent or guardian must be obtained following explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific procedures are performed. The only procedures that may be performed in advance of written informed consent being taken are those that would have been performed on all participants in the same situation as routine clinical practice. Consent will be re-sought for babies whose legal guardian has changed.

Consent can be taken by any member of the medical or nursing staff who is in possession of an up to date GCP qualification and who has been trained on the specifics of this study. Informed consent will be taken after the parents have had sufficient opportunity to read the information and ask questions about the study. There is no time limit on the period between receiving information and consenting to the study providing that the parents feel they have had all their questions answered. Screening for eligibility and informed consent can take place at the initial contact with parents if they feel they have had sufficient time to consider the study, or can take place at the first visit (V1).

The Investigator or designee will explain that the parents are under no obligation to have their infant enter the trial and that they can withdraw their consent at any time during the trial, without having to give a reason.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Parent Information Sheet (PIS) will be given to the parent/guardian of the study participant. The original signed and dated consent form will be retained in the site file, and a copy will be placed in the medical notes along with the corresponding version of the PIS.

If new safety information results in significant changes to the risk–benefit assessment, the consent form will be reviewed and updated if necessary. Parents/guardians of all participants, including of those already enrolled in the study, will be informed of the relevant new information, given a copy of the revised consent form, and asked to re-consent if they choose to continue in the study.

## Randomisation procedure

Two computerised block randomisation lists (one for gestational age <30 weeks and one for 30-34+6 weeks) will be produced by the statistician at Public Health England for each site. These will be placed inside opaque envelopes bearing the corresponding participant number by a team of staff from SGUL who are not otherwise involved in the study. Each centre will be provided with the necessary envelopes. On recruitment to the study, each participant will be allocated, in order of inclusion, the next available participant number from the appropriate list depending on gestation. Following informed consent and prior to the first vaccinations the local study team will open the envelope and reveal the group number. This will define the group to which the baby is assigned and, therefore, the vaccination schedule the baby will receive. **Please note- randomisation must take place at the first visit even if consent has been obtained previously.**

Participants may be replaced if they are withdrawn from the study prior to receiving their first vaccinations. Participants will not be replaced if they are withdrawn from the study after they have received their first vaccinations.

**11.3 Prescribing and Dispensing of IMP**

A study specific prescription chart will be used for this study. This will be provided by the lead site, or individual sites may choose to use their own prescription charts and/or electronic prescribing system. For those participants who are inpatients, the vaccines will also be prescribed on their hospital prescription chart. The person prescribing the vaccines on the study specific prescription chart must have been signed off by the PI on the Staff delegation of duties log JREOLOG0004 for that task, however any member of the clinical team who normally prescribes vaccines may transcribe on the hospital prescription chart without being on the delegation log. A sample signature of all delegated prescribers must be provided for the Pharmacy Site File prior to receipt of the 1st trial prescription.

Vaccines will be obtained by individual sites from national stock using the ImmForm system or any other system used locally. Vaccines may be stored by sites in either a hospital or research pharmacy or in an appropriately monitored fridge in the clinical research site.

**11.4 Overdose of Trial medication**

In the event of an overdose of trial medication advice should be sought immediately from the PI in the institution or from the CI.

## Discontinuation/withdrawal of participants and stopping rules

Because this study only involves licensed vaccines that would be routinely offered to premature infants as part of the national childhood immunisation programme, we do not foresee any reason for stopping the study prematurely. Parents/legal guardians may withdraw their infants from the study at any time without offering an explanation. Exceptionally, the local PI may also withdraw an individual participant if there are significant safety concerns regarding ongoing participation, though it is expected that as far possible there should have been prior discussion with the CI. This study is powered to allow for ~10% drop out of subjects over the course of the study and withdrawn subjects will not be replaced. If an infant is withdrawn from the study permission will be sought to contact the family by phone to ask about any adverse events 1 month after the final study visit in which IMP is administered, and the parent/guardian will also be asked if they will agree to contact the local research team should the infant have an illness requiring medical review.

At all stages it will be made clear to the parents that they remain free to withdraw their baby from the trial at any time without the need to provide any reason or explanation. Parents will be made aware that a decision to withdraw their baby will have no impact on any aspect of their baby’s continuing care. If parents choose to withdraw their baby from trial participation, permission will be sought to complete data collection and use data up to the point of withdrawal from the trial.

## 11.6 Participant transfers

If a participant moves from the area every effort will be made to keep them within the study. If they move such a distance as to make continued follow up at their local trial site centre inappropriate, every effort should be made for them to be followed up at another Sponsor-approved trial centre. Written consent should be taken at the new centre and then a copy of the participant’s CRF to date should be provided to the new centre. Original CRF paperwork will remain at the site responsible for completing that visit / data collection. Responsibility for the participant remains with the original consenting centre until the new consent process is complete at the new centre. Participants who are transferred between sites temporarily over study Visit window(s) will retain a copy of preceding CRF(s) together with original CRF(s) completed at the ‘secondary’ site. Should the participant be transferred back to the primary centre a copy of the CRFs completed at the new ‘secondary’ centre will be provided to complete the primary centre records.

## 11.7 Loss to follow up

Every effort will be made to maintain contact with participants. If unable to make contact after three consecutive phone calls or emails, the participant’s GP will be contacted to check the contact details. Permission to allow this will be included within the consent form. If the details are incorrect then contact should be attempted on up to three further occasions using the correct details. If contact is not subsequently obtained despite three attempts a letter will be sent to the participant’s home asking the parents to make contact with the study team. If there is no contact within 1 month of sending this letter the participant will be classified as lost to follow up.

## 11.8 Definition of the End of Trial

The end of trial for an individual infant is defined as being on completion of their final study visit (V6) schedule at age 13 months. The end of the trial overall will be defined as the time of final database lock following laboratory analysis of serum samples. The approving REC and the MHRA require notification of the end of trial within 90 days of its planned completion or within 15 days if the study is terminated early. The responsibility for submitting the Clinical Study Report will lie with the Chief Investigator and Sponsor. Refer to JREOSOP0015 and inform the JREO to facilitate assistance and compliance with requirements.

# Study Assessments

## Screening assessments

A standardised Case Report Form (CRF) will be completed after obtaining written consent which will check the infant’s eligibility, medical history, concomitant medications and any contraindications to vaccination. A record of physical examination will be made. The intention of this record of physical examination is to document that there are no clinical contraindications to vaccination and this may take a variety of forms: for participants who are still in-patients, recent documentation of physical examination and agreement from the clinical team that vaccination is appropriate is sufficient, for babies who were discharged at around 6-8 weeks, documentation of an examination at the time of discharge or evidence that the clinical team were happy for vaccination to take place (for example in discharge summary) is acceptable. For those discharged before 6 weeks of age in most cases the infant will have had the 6-8 week check performed by the GP and if this is the case a copy of this will suffice along with a check with the parents that they have no new concerns. If there is no evidence of a physical examination having taking place after the first few days of life an investigator trained to perform physical examinations on infants will perform a physical examination.

## Baseline assessments

Baseline assessment will include collection of demographic information about the infant, contact details for the family, and for the GP. The temperature will be assessed using an axillary thermometer prior to administration of the vaccine. Vaccinations will not be given if the temperature is 38.0oC or above.

## Treatment procedure

The study personnel will reconstitute and administer the vaccines according to the SmPC for each vaccine. The dose or route of administration will not be modified for any of the vaccines under any circumstances. Vaccines will be administered in hospital if the participant is still an in-patient. If vaccines are given in hospital these may be administered by a member of the clinical team who may not be on the delegation log but whom the PI is willing to take responsibility for. If this is the case the vaccines must be given according to the study specific instructions regarding anatomical locations for vaccination. A member of the research team should be present at the time of vaccination to assist in protocol compliance and to ensure that all other study tasks are performed. Following discharge, all vaccine doses administered to participants will be either in hospital or at home depending on family preference and local strategy. Before each dose is given, the infant’s temperature will be checked. Vaccination will be deferred if the axillary temperature is ≥38.0oC, or if there is acute illness on the day of vaccination. Those infants who are still in hospital at the time of vaccination will have observations recorded in their CRF for a period of 24 hours prior to immunisation and for 72 hours after immunisation.

The vaccines will be administered by intramuscular injection into the antero-lateral thighs. These should be given according to the practice outline in The Green Book. If needles are provided with the vaccine these should be used, if needles are not provided, the person giving the vaccine should make a decision based on the size of the infant. It is recommended that a 25mm 23G (blue) or 25mm 25G (orange) needle should be used in most infants with the smaller 16mm 25G (orange) needle being more suitable for smaller preterm infants. For the 2, 3 and 4 month vaccinations, Bexsero® will be given in the left thigh, Infanrix IPV/Hib®/Pediacel®/Infanrix hexa® will be given in the upper right thigh and Prevenar 13® will be given in the lower right thigh and Rotarix® will be given orally. For the 12-month vaccination, Bexsero® will be given in the left thigh, Priorix® in the lower right thigh, Prevenar13® in the upper right thigh and Menitorix® in the right arm. The skin at the injection site should be stretched flat between the thumb and forefinger with the needle inserted at a 90o angle to the skin. Where more than one injection is to be given in the same limb, they will be administered at least 2.5 cm apart. Standard immunisation practices and appropriate precautions for any anaphylactic reaction will be followed. Subjects will be monitored in person for 20 minutes post-vaccination.

Immunisations given to infants participating in this study will still count for primary care target and remuneration purposes as though they had been given by the practice of the infant’s General Practitioner (GP). GPs will be informed in writing of the participation of any of their participants in the study. A copy of the letter sent to the GP will be kept with the participant’s identifiable study file. The research team will notify the GP of the vaccine details after every vaccination visit.

A diary card will be provided to parents at each vaccination visit to monitor for local and generalised reactions to Bexsero® and the other routine vaccinations. The information required will be clearly explained to the parents and the diary will be checked by research staff at the subsequent visits so that any necessary additional information can be sought.

Paracetamol administration following vaccination

Parents will be advised to give three doses of paracetamol following administration of Bexsero® at 4-6 hourly intervals according to UK guidance unless the infant is an in-patient in which case local policy will be followed. Parents may be provided with an information sheet about paracetamol following Bexsero®. If the infant was born at less than 32 weeks gestation an appropriate dose of paracetamol should be calculated and this should be clearly communicated to the parents along with a recommendation for 6-8 hourly administration. The paracetamol administration record in the pharmacy pack may be used for this purpose (Appendix 3). Administration of paracetamol will be systematically recorded on the diary card including number of doses given and whether given prophylactically or in response to a fever.

## 12.4 Subsequent assessments

Prior to administering subsequent doses of vaccines, the diary cards for each infant will be reviewed and the parents will be asked about any episodes of illness since the previous visit. Any adverse events will be recorded on the CRF and managed according to the protocol. Any concomitant medication of interest which is being taken or has been received since the last visit will also be recorded in the CRF. Peripheral temperature will then be measured and the vaccine will be administered after ensuring that the infant is fit for vaccination. Following administration of each set of vaccinations, infants will be observed in person for at least 20 minutes for any unexpected acute adverse events. Infants who are on a neonatal unit at the time of immunisation will have 24-hours pre-vaccination and 72-hours post-vaccination observations recorded in the CRF. AEs and SAEs will be solicited at each study visit and parents will be asked to contact the study team if the infant is seriously unwell or hospitalised between visits.

## Summary flow chart of study assessments

*Refer to Appendix 2*

## Methods

###  Samples

### Obtaining, labelling, storing at local site

1. Blood sampling will be postponed for at least 48 hours after the end of any course of antibiotics. If this is not possible, this will be recorded as a protocol deviation and a record should be taken of the antibiotic regime being received at the time of blood sampling.
2. Blood sampling will be obtained by venepuncture where possible. Finger prick or heel prick may be attempted only as a last resort if venepuncture is not possible. Topical application of anaesthetic cream (EMLA or Ametop) and/or a milk feed or oral sucrose may be offered to all subjects aged 1 month corrected gestational age or above at the time of intended venepuncture site to minimise discomfort.
3. Up to 3 mL of blood will be collected into a 5 mL serum separating tube.
4. The research staff will clearly mark the tube with the participant’s study number, visit number, and date of sampling. Dedicated study labelling stickers will facilitate this process

#### Transporting samples to SGUL

1. Samples will be packaged in hard plastic containers within a cardboard box which will then be placed in Royal Mail packaging for guaranteed next day delivery. This will accord with regulations for posting of biological specimens through public post. The preference will be for samples to be sent on the same day they are obtained, however if this is not possible they should be stored in the fridge. Samples must be posted with consideration to ensure that they will arrive the next day on or between a Monday and a Friday (i.e. no samples to be sent on a Friday or Saturday).
2. The samples will be transported at ambient temperature and will not need monitoring
3. Before sending the sample local staff will email the coordinating team at SGUL to inform them that a sample is being despatched and the tracking number of the sample so that any missing samples can be traced.
4. When samples arrive at SGUL, a standard email of receipt will be returned to the local site sending the sample

#### Processing samples at SGUL

* 1. Samples will be centrifuged within 4 hours of being received by SGUL study staff and the serum will be pipetted into cryovials. The first 0.5 mL of serum will be placed in a cryovial for transfer to PHE laboratory, Manchester, and the remainder will be retained at SGUL in case a sample is lost, or, subject to parental consent, to be used in future ethically-approved research. Parents will be asked specifically to consent for the retention of samples for such purposes. All cryovials will be immediately placed in the -80oC freezer.
	2. A log will be kept of samples being stored in this freezer

#### Transporting samples to PHE Manchester

* 1. Samples will be sent in batches on dry ice by courier to the Public Health England laboratory in Manchester at various time points throughout the study.

### Laboratory procedures

All laboratory testing for this study will be undertaken at the Public Health England laboratory in Manchester. Serum will be tested for functional antibody to the vaccine-containing antigens fHbp, NadA and PorA by Serum Bactericidal Assay (SBA) utilising human complement.

# Pharmacovigilance

##  Definitions

**Adverse Event (AE)—**any untoward medical occurrence in a patient or clinical trial subject who is administered an IMP and which does not necessarily have a causal relationship with this treatment which may include an exacerbation of a pre-existing illness; increase in frequency or severity of pre-existing episodic condition; a condition (regardless of whether present prior to the start of the trial) that is detected after trial drug administration. (This does not include pre-existing conditions recorded as such at baseline).

**Adverse Reaction (AR)—**any untoward and unintended responses to an IMP related to any dose administered.

**Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)**—any Adverse Event or Reaction that at any dose:

* Results in death; or
* Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
* Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)
* Results in persistent or significant disability or incapacity (substantial disruption of one’s ability to conduct normal life functions)
* Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the IMP regardless of time of diagnosis).
* Or is another important medical condition

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

**Suspected Unexpected Serious Adverse Reaction (SUSAR)—**an Adverse Reaction which is classed in nature as both serious and unexpected.

An ‘Unexpected Adverse Reaction’ is when both the nature and severity of the event is not consistent with the reference safety information available for the IMP in question.

## Investigator responsibilities relating to safety reporting

All unsolicited adverse events which occur within 28 days of vaccination will be recorded on the CRF, as will all medically attended adverse events occurring at any time during the study i.e. until an individual infant has reached the end of the study. Unsolicited adverse events should also be recorded on the AE Log JREOLOG0007.

SAEs and SARs will be recorded throughout the study and must be notified to the Sponsor within 24 hours of the investigator becoming aware of the event. Refer to JREOSOP0006 and ensure the completed SAE report form JREODOC0012 is sent to the sponsor via fax on 020 8725 0794 or E-mailed to adverseevents@sgul.ac.uk .

In order to prevent a breach of patient confidentiality, SAE reports and any accompanying information should contain only anonymised or pseudo-anonymised patient data.

It is recognised that all information may not be available while the SAE report form is being completed, however the initial report must contain the following as a minimum:

* Identifiable event
* Identifiable patient
* Identifiable IMP (i.e. by providing batch number)
* Identifiable Reporter

If the information available is less than the specified minimum or if the SAE Form is not available for completion and reporting to meet the 24-hours deadline an initial report can be made verbally but must be followed within 48 hours by a detailed, written report.

All unforeseeable SAEs including SUSARs must be followed up by the PI/CI until satisfactory resolution and this should be recorded as a Follow Up report on the SAE form, and on the AE log. At each stage of follow up the PI/CI should sign and date the form.

The Sponsor will notify all SUSARs to the MHRA electronically and the REC utilising the eSUSAR system and within the required expedited reporting timescales:

* The Sponsor will inform the MHRA and the REC of fatal or life threatening SUSARs as soon as possible, but no later than 7 calendar days after the receipt of the SAE report form. Any additional information will be reported within 8 days of sending the initial report.
* The Sponsor must report all other SUSARs and safety issues to the MHRA and REC, as soon as possible but no later than 15 calendar days after the Sponsor has first knowledge of the minimum criteria for expedited reporting.

Causality Assessment—must be made by a medically qualified doctor as these decisions require medical and scientific judgment as well as knowledge of the participant concerned. The investigator must assess the causality of all SAEs or SARs in relation to the IMP using the following descriptions:

Definitely—there is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Probably—there is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

Possibly—there is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (i.e. the patient’s clinical condition, other concomitant events).

Unlikely—there is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant’s clinical condition, or other concomitant treatments).

Unrelated—there is no evidence of any causal relationship.

Not Assessable – note - if this description is used the sponsor will assume the event is related to the IMP until follow up information is received from the investigator to confirm a definitive causality assessment

Any SUSAR assessed as related to the IMP will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.

Expectedness should be based solely on the available RSI for the IMP and will be described using following categories:

Expected—an AE that is classed in nature as serious and which is consistent with the information about the IMP listed in the RSI or clearly defined in this protocol.

Unexpected—an AE that is classed in nature as serious and which is not consistent with the information about the IMP listed in the RSI

The completed AE Log JREOLOG0007 should be regularly reviewed and signed by the PI to detect any change in frequency or severity of reported events. The log will be sent to Sponsor upon request and/or every 2 months.

The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible. Follow up reports must continually be completed within acceptable time-frames and sent to the sponsor as detailed above until the reportable event is considered resolved.

All SAEs and SARs which occur at other sites will be notified to the Sponsor and to the CI within 24 hours. If there is safety information which needs to be disseminated relating to the study, the lead investigator at SGUL or a delegate will communicate with the PIs at the other sites. All SAEs will be communicated to GSK within 24 hours of Sponsor’s first awareness of the event by the team at SGUL. Follow up information on safety reports will be provided within 24 hours of any request. Any emerging safety issues related to Bexsero and in connection with the study will be communicated to GSK within 48 hours of the Sponsor becoming aware of them.

## Notification of deaths

 All deaths will be reported to the Sponsor immediately uponfirst knowledge irrespective of whether the death is related to disease progression, the IMP, or an unrelated event.

## Annual Progress Reports (APRs)

The Chief Investigator will prepare the APR in accordance with JREOSOP0043. Following review by the sponsor the report will be sent to the REC. The APR is due for submission annually within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, until the trial is declared ended.

## Reporting Urgent Safety Measures

The Sponsor and Investigator may take appropriate urgent safety measures in order to protect the participants against any immediate hazard to their health or safety. If such measures are taken the Sponsor shall immediately or no later than 3 days from the date the measures are taken give written notice to the MHRA and REC of the measures taken and the circumstances given rise to such measures. The CI must notify the Sponsor immediately to facilitate compliance with the regulations. The Sponsor will assist the CI in cascading relevant information to participating sites and relevant staff.

Refer to Sponsor SOP Management of Amendments JREOSOP0011 for guidance.

## Notification of Serious Breaches of GCP and/or the protocol

Any Protocol Deviations, Violations will be documented using JREODOC0061, and entered onto the Sponsor’s log JREOLOG0005. Potential Serious Breaches and Urgent Safety Measures will be recorded both on the Sponsor’s Log JREOLOG0005 and processed according to JREOSOP0012 and where necessary JREOSOP0032

A “serious breach” is a breach which is likely to effect to a significant degree:

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

(b) The scientific value of the trial.

The CI will notify the Sponsor immediately of any case where there exists a possible occurrence of a serious breach

# Data management and quality assurance

## Confidentiality

All data will be handled in accordance with the Data Protection Act 1998.

Contact details will be collected onto a data capture format the local site. This will contain patient identifiable information which will allow the local team to remain in touch with participants during the study. These will not be sent from other sites to SGUL. All CRFs sent to SGUL will be identified by the participant’s trial identification number only.

## Data collection tool

Case Report Forms will be designed by the CI and the final version will be approved by the Sponsor. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator’s responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Staff Delegation of Responsibilities Log JREOLOG0004 will identify all trial personnel responsible for data collection, entry, handling and managing the database.

Data will be recorded directly onto specially designed CRFs for the study. CRFs will be photocopied by individual sites and the photocopies sent to SGUL for entering into the study database. Originals will be kept by the individual sites.

## Data handling and analysis

A secure password-protected database will be designed and set up using REDCAP at SGUL. Copies of CRFs will be transferred from sites to SGUL by post or by email (BEARMenB@sgul.ac.uk) and identifiable patient information will not be transferred. Data from diary cards and CRFs will be entered into the database and checked by different members of the study team. Any queries will be resolved and corrected in the database by referring to the original documentation. Self-evident corrections will be amended by the team at SGUL without needing to contact the sites. If the original documentation is unclear clarification will be sought from sites. All paperwork relating to the study will be stored in secure locked cupboards/rooms in the sites participating in the study. At individual sites the CRFs will be contained within a plastic wallet in the patient files. No identifiable data will be transferred to SGUL. Access to the trials database will be restricted to the study team at SGUL and PIs from other sites if requested. Data analysis will be performed by the Clinical Trials Statistician at PHE Colindale. The Chief Investigator will have full access to the CRFs / diaries and trial database if required and PIs from other sites may access this information following a request to the CI. Any digital data transferred from the sites to SGUL will be documented at source and be fully anonymised and encrypted prior to transfer in strict accordance with the 1998 Data Protection Act as well as SGUL Information Governance Policies.

# Archiving arrangements

The trial essential documents along with the trial database will be archived in accordance with the sponsor SOP JREOSOP0016. The agreed archiving period for this trial will be defined within the Delegation of Duties Sponsorship Agreement JREODOC0013

Each PI at any participating site will make arrangements for archiving of the trial essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement

# Statistical design

## Statistical input in trial design

A formal statistical plan will be produced by the Trial Statistician prior to commencement of the study. Data will be analysed using a modified intention to treat analysis whereby all infants vaccinated and with at least one post vaccination blood sample taken will be included in the analysis. Per protocol analysis (whereby all vaccinated infants with at least one post vaccination blood sample taken and with no major protocol deviations) may also be performed if major protocol deviations are recorded. Infants with missing results (e.g. unable to obtain or insufficient blood sample) at the different time-points (e.g. post-primary immunisation, pre-booster and post-booster) will not be included in the analysis for that particular time-point). The primary objective of the study is to compare the hSBA GMT for Bexsero® antigens fHbp, NadA and PorA 1 month after completing the primary vaccinations according to two different schedules.

## Endpoints

### **16.2.1 Primary endpoints**

1. hSBA GMT one month after completing primary immunisations for relevant Bexsero® antigens: fHbp, NadA and PorA
2. hSBA proportions ≥ 1:4, one month after completing primary immunisations for relevant Bexsero® antigens: fHbp, NadA and PorA.

###

### **Secondary endpoints**

* + - 1. The percentage of infants experiencing fever, local reactions and non-febrile systemic reactions within the 7 days following each vaccine dose;
			2. The percentage of inpatients experiencing change / deterioration in cardiorespiratory status within the 72 hours following each vaccine dose;
1. The percentage of infants investigated for sepsis and commenced on antibiotics within 7 days of vaccination;
2. The percentage of infants who experience fever and/or are investigated for sepsis and commenced on antibiotics within 28 days of vaccination;
3. The percentage of infants who experience a serious adverse event at any point within the study;
4. hSBA GMTs at 12 months of age (pre booster) for relevant Bexsero® antigens: fHbp, NadA and PorA;
5. hSBA proportions ≥1:4, at 12 months of age (pre booster) for relevant Bexsero® antigens: fHbp, NadA and PorA;
6. hSBA GMTs at 13 months of age (post booster) for relevant Bexsero® antigens: fHbp, NadA and PorA;
7. hSBA proportions ≥1:4, at 13 months of age (post booster) for relevant Bexsero® antigens: fHbp, NadA and PorA.

## Sample size and recruitment

### **16.3.1 Sample size calculation**

Sample size calculations are complicated because of the multiple components in Bexsero®. We will assess the immune responses to 3 antigens. We propose that a comparison of 2 schedules with respect to doses of Bexsero® will require 60 infants in each arm. Based on data from a recent study (Gossger et al. 2012) the standard deviation of the GMT responses to the 3 antigens is expected to be around 1.0 loge units. Therefore, a sample size of 60 per group will allow a 1.7 fold difference between groups to be detectable at 80% power with 5% significance. Based on our experience from the PUNS (Prems Under a New Schedule) study, we expect a drop-out rate of around 10% so aim to recruit a total of 132 infants.

### **16.3.2 Planned recruitment rate**

It is hoped recruitment to the study will be completed in a 6-12 month time frame. However, as with all paediatric studies, the recruitment rate depends on parental attitude and is largely unpredictable.

## Summary of baseline data and flow of patients

At the end of the study, a flowchart will be used to summarise the number of infants approached, consented, recruited, assigned to the different study arms, receiving the intended vaccines, completing the study protocol and analysed for the primary outcome, as recommended by the CONSORT statement (http://www.consort-statement.org/). Baseline data comparing the two trial arms will be summarised in a table format and will compare median gestation age at birth, age at first vaccination, gender, recruiting study site, birth weight, underlying medical conditions, ventilation status, oxygen requirement, and receipt of immunoglobulins, blood transfusions, steroids, and other relevant concomitant medications or vaccines.

### 16.4.1 Primary endpoint analysis

For each schedule geometric mean titres (GMTs) of the hSBA titres to the three antigens (fHbp, NadA and PorA) will be calculated with 95% confidence intervals 1 month post primary vaccination. Schedules will be compared using unpaired t-tests on log-transformed titres or the Kruskal Wallis test if log-titres are not normally distributed. Proportions with titres ≥1:4 will also be calculated with exact binomial 95% confidence intervals and compared between groups by Fisher’s exact test. Significance will be at a 5% level with no adjustment for multiple comparisons since whilst there are three antigens there are only two groups being compared.

Analysis will be by modified intention to treat (mITT), meaning individuals are analysed according to the group they are randomised to, but only those with at least one blood taken and antibody result will be included, with missing data (e.g. from withdrawals, non-compliers) assumed missing at random. The mITT analysis will include blood samples taken outside the recommended timing. A per-protocol analysis will also be performed if there are major protocol deviations. Spurious data will be checked to source records and investigated, but included if no cause is identified.

The main subgroup analysis will be stratification by level of prematurity (<30weeks/ 30+0-34+6 weeks). A multivariable normal errors regression on logged titres will be used to investigate the influence of prematurity, receipt of blood products or steroids, gestational age, gender, and birthweight.

### 16.4.2 Secondary endpoint analysis

### Analysis of titres before and after the booster vaccination will be done in the same way as the analysis after primary vaccination. In addition, the geometric mean fold change between time points will be calculated with 95% confidence intervals.

For the safety end-points analysis will be As Treated (according to vaccine received) with proportions having each safety endpoint calculated with 95% exact confidence intervals. These proportions will be calculated combining across the two schedules except for when MenB is not given to group 1. Proportions will be according to the most severe level of the adverse event reached across the 72-hour, 7-day or 28 day follow up after each dose and will be by levels of any and severe as indicated on the diary card.

###  16.4.3 Randomisation

Two computerised block randomisation lists (one for gestational age<30 weeks and one for 30-34+6 weeks) will be produced by the statistician at Public Health England. The appropriate group number will be placed inside an opaque envelope bearing the corresponding participant number by a team of staff from SGUL who are not otherwise involved in the study. Each centre will be allocated blocks of sequential numbers in accordance with the block size used for randomisation and will be provided with the necessary envelopes On recruitment to the study at Visit 1, each participant will be allocated, in order of inclusion, the next available participant number from the appropriate list depending on gestation. The local study team will then open the envelope and reveal the group number. This will define the group to which the baby is assigned and, therefore, the vaccination schedule the baby will receive. The randomisation procedure must take place at the first visit.

## Interim analysis

As all vaccines used in this clinical trial are licensed for routine use in infants, interim analysis will not be performed. All data will be analysed at the overall end of the study.

# Committees involved in the trial

A Trial Management Group (TMG) will be formed consisting of the CI, the study coordinator, the PIs and sub investigators at each site and the trial statistician. The TMG will supervise the trial on a day-to-day basis. The TMG meetings will be considered to be quorate if at least five members are able to attend. Information about the meetings will be circulated by the study coordinator or their delegate and the meetings will take place by teleconference at intervals of 3 months to discuss the progress of the study. The initial meeting will focus on the logistics of study set up and subsequent meetings will cover issues around recruitment, retention, protocol deviations and adverse events. Minutes will be taken by the study coordinator or their delegate and these will be distributed following the meeting. As all vaccines used within this study are part of routine care in the UK an Independent Data Monitoring Committee (IDMC) is not required.

# Direct access to source data

The PI and their institutions will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

# Site approval and ongoing Regulatory compliance

Before any site can enrol patients into the trial, the Principal Investigator must ensure that written permission to proceed is in place and that confirmation of capacity and capability has been granted by that local Trust Research & Development (R&D) department. The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the regulatory authorities as appropriate, and which was given favourable opinion by the Research Ethics Committee (REC) and Health Research Authority (HRA)

The Chief Investigator will be provided (via the Sponsor) with file indexes i.e. JREODOC0003 TMF index and JREODOC0004 ISF index for use with SOP JREOSOP0019 ‘Preparation and Maintenance of the TMF’ The CI will be responsible for the maintenance of the TMF and will delegate the responsibility of ISF file maintenance to the PI at each participating site.

It is the responsibility of the PI at each site to ensure that all subsequent REC-approved amendments gain the necessary local R&D approvals. Refer to JREOSOP0011 ‘Management of Amendments’. This does not affect the individual clinician’s responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

Within 90 days after the overall end of the trial, the CI and Sponsor will ensure that the REC and the MHRA are notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. Refer to JREOSOP0015 ‘End of study declaration’

The CI will supply an End of Study report of the clinical trial to the MHRA and REC within 1 year after the overall end of the trial. The Sponsor can provide JREODOC0059 End of study Report template. An End of Study report will be supplied to GSK and Meningitis Now within 60 days of study completion.

# Monitoring plan for the trial

The CI will be requested to complete the JREODOC0032 Risk Assessment Questionnaire and forward to the Sponsor to facilitate appropriate costing and Sponsorship in Principle to be issued prior to REC application.

The trial will be monitored according to the risk-based monitoring plan JREODOC0030 agreed by the Sponsor. It is the responsibility of the CI to ensure that the Sponsor’s self-monitoring template is completed and submitted as instructed (refer to the Study Monitoring Plan for detail). The JREO governance team will determine the initial project risk assessment and justify change as the study progresses.

The PI at each collaborating site in addition to permitting and facilitating site monitoring visits may also be required to complete self-monitoring form(s) and must return the form to the Sponsor for review and action. Failure for any PI to comply with reasonable requests on behalf of the Sponsor may be escalated in accordance with JREOSOP0031 Escalation Procedure; the site may also be selected for a GCP audit.

It is the Sponsor’s responsibility to ensure that any findings identified in any monitoring report are actioned appropriately and in a timely manner and that any violations of GCP or the protocol are reported to the CI & Sponsor representative. Any serious breach will be handled according to JREOSOP00032 Serious Breach Reporting

Any urgent safety measures at either the CI or a PI site must be reported by that site Investigator within 3 days, as per UK Regulations.

The CI will be provided with a copy of the study monitoring plan during the Trial Initiation monitoring visit.

# Finance

This study is funded by Meningitis Now and GSK.

# Insurance and indemnity

St George’s University of London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that SGUL has been negligent. This includes negligence in the writing of the protocol, or selection of trial resources.

Where the Trial is conducted in a hospital, the hospital has a duty of care to participants. St George’s University of London will not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of hospital employees. Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to St George’s University of London, upon request.

Participants may be able to claim compensation for injury caused by participation in this Trial without the need to prove negligence on the part of St George’s University of London or another party.

If a participant indicates that they wish to make a claim for compensation, this needs to be brought to the attention of St George’s University of London immediately.

Failure to alert St George’s University of London without delay and to comply with requests for information by the Sponsor or any designated Agents may lead to a lack of insurance cover for the incident.

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

# IP and development policy

Unless otherwise specified in agreements, the following guidelines shall apply: All Intellectual Property Rights and Know How (IP) related to the Protocol and the Trial are and shall remain the property of the Sponsor excluding

1) pre-existing IP related to clinical procedures of any Hospital.

2) pre-existing IP related to analytical procedures of any external laboratory.

All contributors shall assign their rights in relation to all Intellectual Property Rights and in all Know How, not excluded above to the Sponsor and at the request and expense of the Sponsor, shall execute all such documents and do all such other acts as the Sponsor may reasonably require in order to vest fully and effectively all such Intellectual Property Rights and Know How in the Sponsor or its nominee.

All contributors shall promptly disclose to the Sponsor any Know How generated pursuant to this Protocol and not excluded above and undertake treat such Know How as confidential information jointly owned between it and the Sponsor

Nothing in this section shall be construed so as to prevent or hinder any medical professional from using Know How gained during the performance of the Trial in the furtherance of its normal business activities, to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Right of the Sponsor.

# Publication policy

Publication: “Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations.”

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

## Before the official completion of the Trial,

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the Trial Management Group/the Funders shall have the final say.

Exempt from this requirement are student theses that can be submitted for confidential evaluation but are subject to embargo for a period not shorter than the anticipated remaining duration of the trial.

## Up to 180 days after the official completion of the Trial

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

The Authorship of the primary results manuscript (‘Main Publication’) arising will comprise all who have made a substantial intellectual contribution to the study (including the research question, design, analysis, interpretation), and so is expected to include all local PIs contributing to this study providing that they fulfil all four criteria of the ICMJE recommendations for authorship ([www.icmje.org](http://www.icmje.org)). The initial drafting of the paper will be the responsibility of the CI. All other contributors to the trial will be listed at the end of the manuscript, with their contribution identified and acknowledged.

* The Chief Investigator shall be senior and corresponding author of the Main Publication.
* Insofar as compatible with the policies of the publication outlet and good academic practice, the other Principal Investigators shall be listed in alphabetic order.
* Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.
* Members of the Trial Management Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
* If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Trial Management Group to arbitrate.

## Beyond 180 days after the official completion of the Trial

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least 60 days prior to submission for publication, public dissemination, or review by a publication committee. The Sponsor’s reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

# Statement of compliance

The trial will be conducted in compliance with the protocol, Sponsor’s SOPs, GCP and the applicable regulatory requirements.

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Human Medicines Regulations 2012, the Medicines for Human Use (Clinical Trial) Regulations 2004, and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP, the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the UK Policy Framework for Health and Social Care Research (Version 3.2, October 2017).

This study will be conducted in compliance with the protocol approved by the REC, HRA and according to GCP standards and UK Clinical Trials Regulation. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor, HRA and REC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and REC as soon as possible.

# List of Protocol appendices

Appendix 1 Protocol Amendment/Revision History (chronological order) or a statement “There are currently no amendments”

Appendix 2 Summary chart of study assessments

Appendix 3 Paracetamol administration record

# References

Campbell H, Amirthalingam G, Andrews N et al. Accelerating control of pertussis in England and Wales. Emerg Infect Dis 2012; 18: 38-47.

Heath PT, Booy R, McVernon J, et al. Hib vaccination in infants born prematurely. Arch Dis Child. 2003; 88:206-10

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Parikh SR, Andrews NJ, Beebeejaun K, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. Lancet 2016; 388: 2775-2782

Robinson MJ, Heal C, Gardener E, et al. Antibody response to diphtheria-tetanus-pertussis immunization in preterm infants who receive dexamethasone for chronic lung disease. Pediatrics 2004; 113: 733–7

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**Appendix 1**

Protocol amendment /Revision History

|  |  |
| --- | --- |
| **Amendment ID/Protocol Version and Date**  | **Justification for change/affected Protocol Sections**  |
| Amendment ID SAM01\_AM04 | Sponsor Representative changed |
| Amendment ID SAM02\_AM05 Protocol Version 2.0, 21.03.18  | Change of contact at central laboratory due to a change in staff. 2. Roles and responsibilities. |
| Addition of ‘child in care’ to exclusion criteria at request from funder. 3. Study synopsis and 9.2 participant selection criteria.  |
| Clarification of new vaccine schedule because of a change in UK policy in August 2017. 6. Background and 8.4 Name and description of each non-IMP (NIMP). |
| Change to adverse event recording so only those events which are not captured in the diary need to be recorded as adverse events and logged. This is to reduce the burden to sites of double reporting. 6. Background- assessment and management of potential risk. 13.2 Investigator responsibilities relating to safety reporting.  |
| Addition of wording clarifying the requirements for prescription of Bexsero. Clarifying existing practice. 6. Background-assessment and management of potential risk. |
| Clarification of how alternative accountability arrangements are to be agreed with the Sponsor for clarity. 8.2 Accountability procedures for the IMPs and NIMPs.  |
| Addition of Palivizumab to concomitant medication of interest. 8.5 Concomitant medication.  |
| Addition of twitter account to allow parents to follow progress of study. 10. Subject/Patient Recruitment process. |
|  | Clarification that randomisation must take place at first visit- no change to existing practice, just to reinforce. 11.2 Randomisation procedure and 16.4.3 Randomisation.  |
| Change to allow participants to be replaced if they are withdrawn from the study before receiving their first vaccination as no study procedure other than randomisation will have taken place. 11.2 Randomisation procedure. |
| Change to allow hospital prescription of vaccines to be performed by a member of the clinical team not on the delegation log providing a member of the study team has prescribed the vaccine on the study prescription chart. This is to reduce obstacles in sites where the study team are not members of the inpatient clinical team and to ensure appropriate study and hospital records can be maintained. 11.3 Prescribing and Dispensing of IMP. |
| Addition of information about the procedure which should be followed if a baby is temporarily transferred to another site (for example for surgical management). 11.6 Participant transfers.  |
| Clarification about the requirement to record physical examination in response to questions from sites. 12.1 Screening assessments.  |
| Change to allow inpatient administration of vaccine by a member of the clinical team who is not on the delegation log providing that a member of the study team is present and the PI is willing to take responsibility for the individual. This is to reduce obstacles in sites where the study team are not members of the inpatient clinical team. 12.3 Treatment procedure. |
| Addition of more detail about administration of paracetamol following Bexsero to provide more information for sites. Inclusion of updated paracetamol administration record. 12.3 Treatment procedure and appendix 3.  |
| Change in amount of serum placed in cryovial to be sent to the central laboratory to 0.5mls in response to comments from the lab. 12.6.2.2 Processing samples at SGUL. |
| Change to allow CRFs to be emailed as well as posted to facilitate the return of CRFs. 14.3 Data handling and analysis.  |
| Amendment ID NSAM01\_ Protocol Version 2.1, 02.08.18 | Change of primary completion date to March 2020 |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Procedures** | **Screening** | **V1****2 months** | **V2****3 months** | **V3****4 months** | **V4****5 months** | **V5****12 months** | **V6****13 months** |
| Informed consent | ✓ | ✓ |  |  |  |  |  |
| Eligibility check | ✓ | ✓ |  |  |  |  |  |
| Medical history |  | ✓ |  |  |  |  |  |
| Concomitant medication |  | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Record of physical examination |  | ✓ |  |  |  |  |  |
| Randomisation |  | ✓ |  |  |  |  |  |
| Dispensing of vaccines |  | ✓ | ✓ | ✓ |  | ✓ |  |
| Administration of vaccinations |  | ✓ | ✓ | ✓ |  | ✓ |  |
| Observation following vaccine administration |  | ✓ | ✓ | ✓ |  | ✓ |  |
| Completion of red book and letter to GP |  | ✓ | ✓ | ✓ |  | ✓ |  |
| Blood sampling |  |  |  |  | ✓ | ✓ | ✓ |
| Processing blood samples |  |  |  |  | ✓ | ✓ | ✓ |
| Distribution of diary card |  | ✓ | ✓ | ✓ |  | ✓ |  |
| Checking diary card with parents |  |  | ✓ | ✓ | ✓ |  | ✓ |
| Checking for AEs/SAEs |  |  | ✓ | ✓ | ✓ | ✓ | ✓ |

**Appendix *2.* Summary chart of study assessments**

Appendix 3. Paracetamol administration record