

SHORT TITLE/ACRONYM LION MenB

IRAS Number: 265199



FULL/LONG TITLE OF THE STUDY	Early Protection against meningococcal disease B in infants
SHORT STUDY TITLE / ACRONYM	LION MenB (early protectiOn agaiNst Meningococcal B disease in infants)
PROTOCOL VERSION NUMBER AND DATE	10.0 10.09.2024
Study Type / Phase:	Phase IV randomisation study of different Men B vaccine primary immunisation schedules in UK infants
IRAS Number:	265199
Clinical Studies registry number (ISRCTN Number / Clinical trials.gov Number) :	52318758
JRES (sponsor) Reference Number	2020.0027

This protocol has regard for the HRA guidance and order of content

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor’s (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

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

For and on behalf of the Trial Sponsor:

Signature:

DocuSigned by:

Subhi Bedi

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Name (please print): Subhi Bedi

Position: Head of Research Gov and Delivery

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Chief Investigator:

Signature:

DocuSigned by:

Dr. Paul Heath

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Name: (please print): Dr. Paul Heath

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ii. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

ii. LIST OF ABBREVIATIONS

AE	Adverse Events
AR	Adverse Reaction
AESI	Adverse Events of Special Interest
CHIS	Child health information systems
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
GMT	Geometric mean titers
hSBA	Serum bactericidal assay using human complement
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IRAS	Integrated Research Approval System
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
JRES	Joint Research Enterprise Service
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group

iii. TRIAL SUMMARY

iii. TRIAL SUMMARY	
Trial Title	Early Protection against meningococcal disease in infants
Clinical Phase	Phase IV
Trial Design	Phase IV randomisation study of different Men B vaccine primary immunisation schedules in UK infants
Trial Participant Population	Term infants (born ≥ 37 weeks gestation)
Eligibility Criteria:	Inclusion: <ul style="list-style-type: none"> • Term infants born at ≥ 37 weeks gestation • Aged ≥ 56 days to ≤ 70 days on the day of first visit • No contraindications to vaccination according to the 'Green Book' • Willing and able to comply with study procedures • Written informed consent
	Exclusion: <ul style="list-style-type: none"> • Contraindication to vaccination according to the Green Book • Life-limiting congenital abnormality or condition • Prior diagnosis of an immunodeficiency syndrome • Previous vaccination against meningococcal disease • History of <i>Neisseria meningitidis</i> infection, confirmed either clinically, serologically, or microbiologically • Considered unlikely to complete expected follow up until the end of the study • Child in care
Planned Sample Size/Target	220 infants will be randomised 1:1 to one of two 4CMenB schedules. Group 1: 4CMenB at 2 and 3 months of age; PCV13 at 4 months of age. Group 2: 4CMenB at the currently recommended schedule at 2 and 4 months of age; PCV13 at the currently recommended schedule at 3 months of age. Both groups will receive a 4CMenB booster at 12 months of age. Both groups will receive the rest of routine paediatric vaccines according to the UK immunisation schedule.
Treatment duration	10 months (from 2 months of age to 12 months of age)
Follow up duration	follow up visit 1 month after 4CMenB booster

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Planned Trial Period	April 2021- 31 st October 2024
Participating sites:	<p>City St George's, University of London Cranmer Terrace, Tooting, London, SW17 0RE Principal Investigator: Professor Paul Heath Professor of Paediatric Infectious Diseases</p> <p>University of Oxford Wellington Square, Oxford, OX1 2JD Principal Investigator: Dr. Dominic Kelly Consultant in Paediatrics and Vaccinology</p> <p>Royal Cornwall Hospitals NHS Trust Treliske, Truro, TR1 3LJ Principal Investigator: Dr. Charlotte Lea Paediatric Registrar (ST8)</p> <p>Portsmouth Hospitals NHS Trust Cosham, Portsmouth, PO6 3LY Principal Investigator Dr. Tim Scorrer Consultant in neonatal medicine</p> <p>Sheffield Children's NHS Foundation Trust Clarkson St, Broomhall, Sheffield, S10 2TH Principal Investigator: Dr. Fiona Shackley Consultant in paediatric immunology/allergy/infectious diseases</p> <p>University Hospital Southampton NHS Foundation Trust SOUTHAMPTON GENERAL HOSPITAL, TREMONA ROAD, Southampton, SO16 6YD Principal Investigator: Dr. Katrina Cathie Consultant in paediatric medicine Co-Principal Investigator: Dr Dan Owens Clinical Research Fellow</p>

	Objectives	Outcome Measures
Primary	To compare the immunological responses of UK infants between two different primary immunisation schedules of 4CMenB (2 and 3 versus 2 and 4 months of age).	<ul style="list-style-type: none"> Antibody geometric mean titers (GMTs) against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by serum bactericidal assay using human complement (hSBA) 4 weeks after 2nd dose of 4CMenB (at 4 months of age for Group 1 versus 5 months of age for Group 2). The proportion of infants with antibody titers $\geq 1:4$ against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by hSBA assessed at 4 weeks after 2nd dose of 4CMenB (at 4 months of age for Group 1 versus 5 months of age for Group 2).
Secondary	To compare the persistence of immunological responses to 4CMenB at 12 months chronological age after two different primary immunisation schedules of 4CMenB (2 and 3 versus 2 and 4 months of age).	<ul style="list-style-type: none"> GMTs against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by hSBA at 12 months of chronological age (pre-booster). The proportion of infants with antibody titers $\geq 1:4$ against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by hSBA at 12 months of chronological age (pre-booster).

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Secondary	To compare the immunological responses one month after the 12-month 4CMenB booster in infants who received two different primary immunisation schedules of 4CMenB (2 and 3 versus 2 and 4 months of age).	<ul style="list-style-type: none"> • GMTs against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by hSBA at 13 months of chronological age (post-booster) • The proportion of infants with antibody titers $\geq 1:4$ against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by hSBA at 13 months of chronological age (post-booster).
Secondary	To compare the persistence of immunological responses to PCV13 at 12 months chronological age after two different primary immunisation schedules of PCV13 (3 versus 4 months of age).	<ul style="list-style-type: none"> • Serotype specific GMCs against PCV13 serotypes at 12 months of age (pre PCV13 booster). • The proportion of infants with serotype-specific GMCs $\geq 0.35 \mu\text{g/ml}$ against PCV13 serotypes at 12 months of age (pre PCV13 booster).
Secondary	To compare the persistence of immunological responses to the booster dose of PCV13 given at 12 months in infants who received two different primary immunisation schedules of PCV13 (3 versus 4 months of age).	<ul style="list-style-type: none"> • Serotype specific GMCs against PCV13 serotypes at 13 months of age (4 weeks post PCV13 booster). • The proportion of infants with serotype-specific GMCs $\geq 0.35 \mu\text{g/ml}$ against PCV13 serotypes at 13 months of age (4 weeks post PCV13 booster).
Observational	<p>Safety</p> <ol style="list-style-type: none"> 1. To describe the safety of 4CMenB when given concomitantly with routine vaccines at 2 and 3 months of age (Group 1). 2. To describe the safety of 4CMenB when given concomitantly with routine vaccines at 2 and 4 months of age (Group 2). 3. To describe the safety of PCV13 when given 	<ul style="list-style-type: none"> • Occurrence, nature, time of onset, duration, intensity, action taken and whether the event led to early termination from the study, of any solicited AEs within 7 days after each vaccination(s). • Occurrence, nature, time of onset, duration, intensity, action taken and whether the event led to early

	<p>concomitantly with routine vaccines at 3 months of age (Group 2).</p> <p>4. To describe the safety of PCV13 when given concomitantly with routine vaccines at 4 months of age (Group 1).</p> <p>5. To describe the safety of 4CMenB booster when given concomitantly with routine vaccines at 12 months of age (Group 1 and 2).</p> <p>6. To describe the safety of PCV13 booster when given concomitantly with routine vaccines at 12 months of age (Group 1 and 2).</p>	<p>termination from the study, of any unsolicited AEs within 28 days after each vaccination(s).</p> <ul style="list-style-type: none"> • Occurrence, nature, time of onset, duration, intensity, action taken and whether the event led to early termination from the study, of any medically attended AEs for the whole duration of the study. • Occurrence, nature, time of onset, duration, intensity, action taken, relationship to vaccination, outcome and whether the event led to early termination from the study, of any SAEs and AESIs for the whole duration of the study.
Investigational Medicinal Product(s) Or Device Name	4CMenB; Bexsero® (Manufactured by GlaxoSmithKline in Italy): a four component vaccine that protects against <i>Neisseria meningitidis</i> serogroup B	
Formulation, Dose, Route of Administration	4CMenB; Bexsero: 0.5mL intra-muscularly; three doses administered at 2-3-12 months of age or 2-4-12 months of age. Each dose of vaccine contains recombinant <i>Neisseria meningitidis</i> group B NHBA fusion protein (50 micrograms); recombinant <i>Neisseria meningitidis</i> group B NadA protein (50 micrograms); recombinant <i>Neisseria meningitidis</i> group B fHbp fusion protein (50 micrograms) and Outer membrane vesicles (OMV) from <i>Neisseria meningitidis</i> group B strain NZ98/254 (25 micrograms measured as amount of total protein containing the PorA P1.4) adsorbed on aluminium hydroxide (0.5 mg Al3+).	

iv. FUNDING

This study is funded by GlaxoSmithKline. This body has 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.

v. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITTEES/GROUPS & INDIVIDUALS

A Trial Management Group (TMG) will be formed consisting of the CI, the study coordinator, the study manager, the trial statistician, the reference laboratory representative, the PIs and sub investigators at each site. The TMG will supervise the trial on a day-to-day basis. The TMG meetings will be considered to be quorate if at least three 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 1 to 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 (DMC) is not required.

vi. PROTOCOL CONTRIBUTORS

Shamez Ladhani conceived the study. Kostas Karampatsas developed the study protocol with Shamez Ladhani. Paul Heath is the grant holder. Nick Andrews provided statistical expertise in clinical trial design. All authors contributed to refinement of the study protocol and approved the final manuscript

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vii. TRIAL FLOW CHART

Visits	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Approximate age of participants		2 months	3 months	4 months	5 months	12 months	13 months
Trial timeline (days)		Day 0	Visit 1 + 28 days	Visit 2 + 28 days	Visit 3 + 28 days		Visit 5 + 28 days
Time windows (days)			+14 days	+14 days	+14 days	+21 days	+21 days
Discuss study with parent/guardian	✓						
Eligibility check	✓	✓					
Informed consent	✓ (can be done at screening or visit 1)	✓					
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/set-up e-diary		✓	✓	✓		✓	
Checking diary card with parents			✓	✓	✓	✓	✓
Checking for AEs/SAEs			✓	✓	✓	✓	✓

1 BACKGROUND

Neisseria meningitidis (meningococcus) is a bacterium which causes meningitis and septicaemia. There are 12 serogroups of meningococcus, 6 (A, B, C, W, X and Y) cause most disease of which MenB is the most common cause of meningococcal disease in the UK. Infants have the highest incidence of MenB disease in the UK and across Europe, with the main burden of disease falling in the second 6 months of life.

4CMenB offers protection against invasive MenB disease in infants, but only after at least two priming doses. In infants, the 4CMenB is licensed as a three-dose infant priming schedule starting at 2 months of age with an interval of one or two months between the doses (e.g. 2-3-4 or 2-4-6 months) or, alternatively, as a two-dose priming dose starting at 3 months of age with a two-month interval between the doses.

In 2015 the UK became the first country in the world to introduce Men B vaccination with 4CMenB (Bexsero®) into its routine schedule, with a two-dose priming regime at 2 and 4 months with a booster at 12 months (Table 1). The vaccine has proved to be very effective in preventing invasive MenB disease in immunised infants (Parikh et al, 2016). This study also showed that a single dose of 4CMenB however, was not effective. Half the MenB cases diagnosed after 16 weeks of age in the vaccine-eligible infant cohort were either unvaccinated or partially vaccinated (i.e. received only a single dose of 4CMenB). Such cases could potentially have been prevented through timely or, preferably, earlier completion of the primary immunisation schedule.

Table 1: UK infant vaccination schedule (from January 2020)

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®				✓

2 RATIONALE

This study is being undertaken to compare the immune responses of UK infants who receive their routine immunisations alongside two different 4CMenB primary immunisation schedules. Completing the primary 4CMenB schedule by 3 months could provide infants earlier protection against MenB disease since cases peak at 5 months of age and remain high in the second half of the first year before starting to decline (Ladhani et al., 2012).

There are no data on the immunogenicity of a two-dose 4CMenB schedule given one month apart in infants. Since this is a protein-based vaccine, it is anticipated that the immunogenicity of the 2-3 month schedule will be similar to the 2-4 month schedule, unlike some conjugate vaccines, where there is some evidence of increased immunogenicity with longer intervals between doses in infants. The blood sample at 4 months of age will allow assessment of any early protection offered by two doses compared to a single dose of 4CMenB. The blood sample at 5 months of age will allow comparison of vaccine responses against the currently recommended national immunisation schedule. Even if the 2-3 month schedule is a little less immunogenic than the 2-4 month schedule, the benefits of earlier protection with the 2-3 month schedule would likely outweigh the lower antibody concentrations. The blood sample at 12 months will allow assessment of waning of immunity before the booster.

The blood sample at 13 months will allow comparison of the post-booster antibody responses. We anticipate that the 12-month booster will provide similar protection for both groups.

Additionally, the UK recently announced a change in the childhood pneumococcal immunisation programme from the current 2+1 schedule of the 13-valent pneumococcal conjugate vaccine (PCV13) at 2 and 3 months of age followed by a booster at 12 months, to a single PCV13 infant dose at 3 months of age followed by the 12-month booster. This decision was made on the basis of near elimination of pneumococcal disease caused by the PCV13 serotypes in the UK. Infants will be protected by a combination of direct protection afforded by the single dose of PCV13 and the excellent indirect (herd) protection, which will continue to be maintained by the 1+1 schedule (Goldblatt et al., 2018). Since pneumococcal disease associated with PCV13 strains is so rare in infants across the UK, the 2-3 month group in this clinical trial will receive PCV13 at 4 months instead of 3 months. This will ensure that all infants will only receive 2 injections at each primary immunisation visit, thus providing an optimal schedule in terms of vaccine policy and implementation.

We will therefore compare the immunogenicity of this new PCV13 schedule (single dose at 4 months instead of 3 months) by measuring antibodies against the PCV13 vaccine serotypes at 12 months of age (pre-booster) and 13 months of age (post-booster).

If this clinical trial shows comparable immunogenicity for the main 4CMenB antigens using the two different schedules, then the results could change UK national immunisation policy to offer infants earlier protection against this devastating disease and could potentially be adopted by other countries worldwide.

2.1 Assessment and management of risk

2.1.1 Vaccination

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 the routine vaccinations with a shorter interval for 4CMenB, at 2-3 months instead of 2-4 months. Because the infants enrolled in the study will receive the same vaccines as part of their routine immunisation, this study is unlikely to be associated with any additional risk of adverse events.

There is always a small risk of an adverse reaction following any vaccination and this will be explained to parents, but the risk per dose will be the same for infants in this study compared to those who receive their routine vaccinations. 4CMenB is particularly associated with fever when administered with routine vaccinations, but this can be mitigated with prophylactic paracetamol at the time of 4CMenB vaccination, which is recommended nationally.

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.

Parents/legal guardians will receive a diary card following vaccination and will be given instructions about how this should be completed for the seven days following vaccination. Alternatively, we will offer the opportunity to set-up an electronic diary. 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. In addition, they will 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 (including seizures, febrile episodes requiring admission, nodule at the site of injection, cellulitis). In addition, all illnesses will be enquired about at each study visit so that all serious adverse events can be recorded. Information about all SAEs and AESIs occurring at any time within the study period (i.e. after consent has been taken) will be collected.

2.1.2 Blood collection

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 infants of 75 mL/kg.

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).

2.1.3 COVID-19 Risk Assessment and Management Strategy

All research staff are required to complete an ongoing COVID-19 risk assessment prior to undertaking any research activity. This process is continuously monitored by the responsible line manager.

The Research Team will contact parents of research participants ahead of scheduled study visits to check for COVID-19 symptoms and the symptom check will be repeated at the study visit.

Parents will receive information regarding the extra precautions that will be taken in light of the COVID-19 pandemic in the Patient Information Sheet. This will detail steps they should take if they have concerns about exposure to COVID-19 through participating in the research, or believe that they are symptomatic or have been in close contact with another person believed to be symptomatic. The Patient Information Sheet will also have contact details for the Research Team for parents to get in touch if they have any concerns or queries about this.

All research personnel are expected to comply with the NHS Trust and University policies on COVID-19.

All parents bringing their children to the hospital site for research visits will be expected to abide by the NHS Trust and University policies on COVID-19 which include wearing suitable PPE (provided by the NHS Trust on arrival), adhering to the visitor policy on social distancing and following the one-way routing systems whilst on site.

The schedule of study assessments has been designed so that they align with the current routine national immunisation schedule; therefore, research participants and site staff are not perceived to be at any additional risk of exposure to COVID-19 through participation in this research study.

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective		
To compare the immunological responses of UK infants at 4 months of age between two different primary immunisation schedules of 4CMenB (2 and 3 versus 2 and 4 months of age).	1. Antibody geometric mean titers (GMTs) against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by serum bactericidal assay using human complement (hSBA) 4 weeks after 2nd dose of 4CMenB (at 4 months of age for Group 1	Blood sampling at 4 months of age for Group 1 and 5 months of age for Group 2.

	<p>versus 5 months of age for Group 2).</p> <p>2. The proportion of infants with antibody titers $\geq 1:4$ against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by hSBA assessed at 4 weeks after 2nd dose of 4CMenB (at 4 months of age for Group 1 versus 5 months of age for Group 2).</p>	
Secondary Objectives		
To compare the persistence of immunological responses to 4CMenB at 12 months chronological age after two different primary immunisation schedules of 4CMenB (2 and 3 versus 2 and 4 months of age).	<p>1. GMTs against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by hSBA at 12 months of chronological age (pre-booster).</p> <p>2. The proportion of infants with antibody titers $\geq 1:4$ against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by hSBA at 12 months of chronological age (pre booster).</p>	Blood sampling at 12 months of chronological age (pre-booster) for Groups 1 and 2.
To compare the immunological responses one month after the 12-month 4CMenB booster in infants who received two different primary immunisation schedules of 4CMenB (2 and 3 versus 2 and 4 months of age).	<p>1. GMTs against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by hSBA at 13 months of chronological age (4 weeks post-booster).</p> <p>2. The proportion of infants with antibody titers $\geq 1:4$ against relevant 4CMenB antigens (fHbp, NadA and PorA) measured by hSBA at 13 months of chronological age (4 weeks post booster).</p>	Blood sampling at 13 months of chronological age (4 weeks post booster) for Groups 1 and 2.
To compare the persistence of immunological responses to PCV13 at 12 months chronological age after two different primary immunisation schedules of PCV13 (3 versus 4 months of age).	<p>1. Serotype specific GMCs against PCV13 serotypes at 12 months of age (pre PCV13 booster).</p> <p>2. The proportion of infants with serotype-specific GMCs ≥ 0.35 $\mu\text{g/ml}$ against PCV13 serotypes</p>	Blood sampling at 12 months of chronological age (pre-booster) for Groups 1 and 2.

	at 12 months of age (pre PCV13 booster).	
To compare the immunological responses to the booster dose of PCV13 given at 12 months in infants who received two different primary immunisation schedules of PCV13 (3 versus 4 months of age).	<ol style="list-style-type: none"> 1. Serotype specific GMCs against PCV13 serotypes at 13 months of age (4 weeks post PCV13 booster). 2. The proportion of infants with serotype-specific GMCs ≥ 0.35 $\mu\text{g/ml}$ against PCV13 serotypes at 13 months of age (4 weeks post PCV13 booster). 	Blood sampling at 13 months of chronological age (4 weeks post booster) for Groups 1 and 2.
Observational Objectives		
<ol style="list-style-type: none"> 1. To describe the safety of 4CMenB when given concomitantly with routine vaccines at 2 and 3 months of age (Group 1). 2. To describe the safety of 4CMenB when given concomitantly with routine vaccines at 2 and 4 months of age (Group 2). 3. To describe the safety of PCV13 when given concomitantly with routine vaccines at 3 months of age (Group 2). 4. To describe the safety of PCV13 when given concomitantly with routine vaccines at 4 months of age (Group 1). 5. To describe the safety of 4CMenB booster when given concomitantly with routine vaccines at 12 months of age (Group 1 and 2). 6. To describe the safety of PCV13 booster when given concomitantly with routine vaccines at 12 months of age (Group 1 and 2). 	<ol style="list-style-type: none"> 1. Occurrence, nature, time of onset, duration, intensity, action taken and whether the event led to early termination from the study, of any solicited AEs within 7 days after each vaccination(s). 2. Occurrence, nature, time of onset, duration, intensity, action taken and whether the event led to early termination from the study, of any unsolicited AEs within 28 days after each vaccination(s). 3. Occurrence, nature, time of onset, duration, intensity, action taken and whether the event led to early termination from the study, of any medically attended AEs for the whole duration of the study. 4. Occurrence, nature, time of onset, duration, intensity, action taken, relationship to vaccination, outcome and whether the event led to early termination from the study, of any SAEs and AESIs for the whole duration of the study. 	<p>Subjects will be monitored in person for 20 minutes post-vaccination.</p> <p>Parents/legal guardians will receive a diary card (electronic or paper) following vaccination and will be given instructions about how this should be completed for the 28 days following vaccination. 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.</p> <p>In addition, they will 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.</p> <p>At each visit, the Investigator or a</p>

		delegate will ask parents/legal guardians about any AEs recorded in the diary card (paper or electronic), as well as about any other AEs that may have occurred since the previous visit.
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4 TRIAL DESIGN

This will be an open label, phase IV study. After appropriate consent, 220 term infants (born at ≥37 weeks gestation) will be randomised to one of the two 4CMen B schedules. All infants will remain in the study from recruitment to around 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.

5 TRIAL SETTING

This is a multicentre study which will take place across several sites in England.

6 PARTICIPANT ELIGIBILITY CRITERIA

There will be no exceptions (waivers) to eligibility criteria prior to participant inclusion into the study. Any questions raised about eligibility will 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 about vaccinating infants in general. It is, therefore, important 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 and enrolment log 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 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

6.1 Inclusion criteria

- Term infants born at ≥37 weeks gestation
- Aged ≥56 days to ≤ 70 days on the day of first visit
- No contraindications to vaccination according to the ‘Green Book’
- Willing and able to comply with study procedures
- Written informed consent

6.2 Exclusion criteria

- Contraindication to vaccination according to the Green Book
- Life-limiting congenital abnormality or condition

- Prior diagnosis of an immunodeficiency syndrome
- Previous vaccination against meningococcal disease
- History of *Neisseria meningitidis* infection, confirmed either clinically, serologically, or microbiologically
- Considered unlikely to complete expected follow up until the end of the study
- Child in care

7 TRIAL PROCEDURES

Group 1: 4CMenB Bexsero® at 2, 3 and 12 months of age; PCV13 at 4 months of age

Group 2: 4CMenB Bexsero® at 2, 4 and 12 months of age; PCV13 at 3 months of age

Table 2. Study Procedures - Group 1

Visits	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Approximate age of participants		2 months	3 months	4 months	12 months	13 months
Trial timeline (days)		Day 0	Visit 1 + 28 days	Visit 2 + 28 days		Visit 5 + 28 days
Time windows (days)			+14 days	+14 days	+21 days	+21 days
Discuss study with parent/guardian	✓					
Eligibility check	✓	✓				
Informed consent	✓	✓				
Collection of demographic data		✓				
Medical history		✓				
Concomitant medication		✓	✓	✓	✓	✓
Record of physical examination		✓				
Measurement of temperature		✓	✓	✓	✓	
Randomisation		✓				
Dispensing of vaccines		✓	✓	✓	✓	
Vaccination with Bexsero®		✓	✓		✓	

SHORT TITLE/ACRONYM LION MenB

IRAS Number: 265199

Vaccination with PCV13				✓		
Vaccination with routine vaccines*		✓	✓	✓	✓	
Observation following vaccine administration		✓	✓	✓	✓	
Completion of red book and letter to GP		✓	✓	✓	✓	
Review of temporary contraindications for blood sampling				✓	✓	✓
Blood sampling				✓	✓	✓
Processing blood samples				✓	✓	✓
Distribution of diary card/set-up e-diary		✓	✓	✓	✓	
Checking diary card with parents (paper/electronic)			✓	✓		✓
Checking for AEs/SAEs			✓	✓	✓	✓

* Routine paediatric vaccines will be given to participants in all groups according to the UK immunisation schedule (Table 1)

Table 2. Study Procedures - Group 2

Visits	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Approximate age of participants		2 months	3 months	4 months	5 months	12 months	13 months
Trial timeline (days)		Day 0	Visit 1 + 28 days	Visit 2 + 28 days	Visit 3 + 28 days		Visit 5 + 28 days
Time windows (days)			+14 days	+14 days	+14 days	+21 days	+21 days
Discuss study with parent/guardian	✓						
Eligibility check	✓	✓					

SHORT TITLE/ACRONYM LION MenB

IRAS Number: 265199

Informed consent	✓	✓					
Collection of demographic data		✓					
Medical history		✓					
Concomitant medication		✓	✓	✓	✓	✓	✓
Record of physical examination		✓					
Measurement of temperature		✓	✓	✓		✓	
Randomisation		✓					
Dispensing of vaccines		✓	✓	✓		✓	
Vaccination with Bexsero®		✓		✓		✓	
Vaccination with PCV13			✓				
Vaccination with routine vaccines*		✓	✓	✓		✓	
Observation following vaccine administration		✓	✓	✓		✓	
Completion of red book and letter to GP		✓	✓	✓		✓	
Review of temporary contraindications for blood sampling					✓	✓	✓
Blood sampling					✓	✓	✓
Processing blood samples					✓	✓	✓
Distribution of diary card/set-up e-diary		✓	✓	✓		✓	
Checking diary card (electronic or paper) with parents			✓	✓	✓		✓
Checking for AEs/SAEs			✓	✓	✓	✓	✓

* Routine paediatric vaccines will be given to participants in all groups according to the UK immunisation schedule (Table 1)

7.1 Recruitment

7.1.1 Participant identification

220 participants will be recruited from suitable participating sites. A variety of recruitment strategies will be used by the different participating centres to recruit eligible participants. Some centres may choose to advertise the study on institutional websites or newsletters, or on posters in the hospital or the community (e.g. in GP practices).

Participant Identification Centres will be used as part of the recruitment strategy. NHS centres (hospitals, GP practices etc.) will be provided with the study inclusion and exclusion criteria so they can screen their patient database for potential recruits. PIC's will be asked to advertise the study via posters and send out text messages to potential participants, informing them of their local recruiting site. Participants may also be approached during routine visits and be provided with information about the study, including the PIS. NHS and non-NHS sites which are not acting as PICs will display posters for the study.

Eligible infants may also be identified through the local child health information systems (CHIS) and initially contacted by post. Families expressing an interest in participating in the study by post, email, text or phone will then be approached by the study team.

The study will be publicised by local media outlets and national charities, which could be in the form of social media posts, news articles and website postings etc.

7.1.2 Screening

The eligibility of an individual to participate in this study will be assessed by any trained member of the research team by checking against the inclusion and exclusion criteria. There are no further screening requirements.

7.1.3 Payment

Participants will be reimbursed for their travel expenses if they attend appointments in hospital/university.

7.2 Consent

All trial personnel/staff undertaking the informed consent process will have signed the Sponsor's Delegation of Responsibilities Log to ensure that the person has been delegated the responsibility by the study CI/PI. All personnel taking informed consent will be GCP trained.

Informed consent from a parent or legal guardian will be obtained following explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific procedures are performed. 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 then be retained in the investigator site file and a copy will be filed in the medical notes along with the corresponding version of the PIS. A copy of the PIS will be sent to the infant's general practitioner (GP) along with a covering letter explain the child's participation in the clinical trial.

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.

7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Parents/guardians of all participants will be asked if they agree for any remaining samples to be retained for future related and ethically approved research. Consent to this will not be required for participation in the main study. Residual samples will be stored with individual study identification numbers until the conclusion of this study after which point they will be de-identified and stored anonymously. Prior to the de-identification, participants can choose to withdraw from further research and have their samples destroyed. After de-identification this will not be possible.

7.3 The randomisation scheme

Participants will be randomised in a 1:1 ratio to the two groups. **Group 1:** 4CMenB Bexsero® at 2, 3 months and at 12 months of age. **Group 2:** 4CMenB Bexsero® at 2, 4 months and at 12 months of age.

7.3.1 Method of implementing the randomisation/allocation sequence

A computerised block randomisation list will be produced for each site. This 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 provided with the necessary envelopes. Upon recruitment, each participant will be allocated, in order of inclusion, the next available participant number from the randomisation. 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 infant 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.

7.4 Blinding

This study is not blinded. The two groups will receive 4CMenB in different timings and it is not possible to blind either the participants or the research team to the group allocation. However, the laboratory staff testing the vaccine responses will be blinded to the allocation of the trial participants until the end of the study.

7.5 Baseline data

Baseline information collected about participants will include demographic information, past medical history, concomitant medication and vaccination history of the infant, contact details for the family and for the GP.

7.7 Trial assessments

Baseline 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.

Vaccination

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. All vaccine doses administered to participants will be either in hospital/university 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 $\geq 38.0^{\circ}\text{C}$, or if there is acute illness on the day of vaccination.

The vaccines will be administered by intramuscular injection into the antero-lateral thighs, apart from Rotarix® which is an oral vaccine. All vaccines should be given according to the practice outline in The Green Book. If needles are provided with the vaccine these will be used, if needles are not provided, the person giving the vaccine will use a 25mm 23G (blue) or 25mm 25G (orange) needle. For the primary immunisations, 4CMenB will be given in the left thigh, 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 booster, 4CMenB 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 90° 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. Parents/legal guardians will receive a diary card (paper or electronic) following vaccination and will be given instructions about how this should be completed for the seven days following vaccination. 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. In addition, they will 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

Immunisations given to infants participating in this study still count for primary care target and remuneration purposes as though they had been given by the practice of the infant's 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.

Paracetamol administration following vaccination

Parents will be advised to give three doses of paracetamol during visits where 4CMenB is administered with routine immunisations. The first dose of paracetamol will be given around the time of vaccination, with two additional doses at 4-6 hourly intervals according to UK guidance. Parents may be provided with an information sheet about the use of paracetamol with 4CMenB vaccination.

Subsequent assessments







Prior to administering subsequent doses of vaccines, parents will be asked about any episodes of illness since the previous visit. The diary cards will be collected (or electronic diaries checked). 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. AEs and SAEs and AESIs 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.

Blood collection

Blood sampling will be performed by appropriately trained members of the research team. 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. Blood sampling will be obtained by venepuncture where possible. There will be a maximum of two venepuncture attempts. 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 at the time of intended venepuncture site to minimise discomfort. Up to 3 mL of blood will be collected into a 5 mL serum separating tube. 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.

Table 4. Timing of vaccinations and blood sampling

Visit Number	1	2	3	4	5	6
Age	2 months	3 months 28 (+14) days days after V1	4 months 28 (+14) days after V2	5 months 28 (+14) days after V3	12 months +21 days	13 months 28 (+21) days after V5
Group 1	4CMenB DTaP/IPV/Hib/HepB Rotavirus	4CMenB DTaP/IPV/Hib/HepB Rotavirus	PCV13 DTaP/IPV/Hib/Hep B 		4CMenB PCV13 MCC-TT/Hib-TT MMR 	
Group 2	4CMenB DTaP/IPV/Hib/HepB Rotavirus	PCV13 DTaP/IPV/Hib/HepB Rotavirus	4CMenB DTaP/IPV/Hib/Hep B		4CMenB PCV13 MCC-TT/Hib-TT MMR 	

 = Blood sampling

Ages of scheduled vaccination refer to chronological ages.

7.8 Withdrawal criteria

Because this study only involves licensed vaccines that would be routinely offered to infants as part of the national 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 as 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.

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 infant will have no impact on any aspect of their infant's continuing care. If parents choose to withdraw their infant from trial participation, permission will be sought to complete data collection and use data up to the point of withdrawal from the trial.

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.

7.9 Storage and analysis of clinical (biological) samples

7.9.1 Obtaining, labelling, storing at local site

- a. 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.

7.9.2 Processing samples at SGUL and at sites

- a. All sites will process and store their own samples.
- b. Samples will be centrifuged within 4 hours of being received by the study staff and the serum will be pipetted into cryovials. Approximately 0.5 mL of serum will be placed in a cryovial for transfer to PHE laboratory, Manchester, and the remainder will be retained at site 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 -80°C freezer.
- c. A log will be kept of samples being stored in this freezer

7.9.3 Transporting samples to PHE Manchester

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

7.9.4 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 utilising human complement (hSBA). Serotype specific pneumococcal IgG antibodies will be measured using an ELISA.

7.10 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.

7.10.1 Notification of results to parents

At the end of the trial, following the laboratory analysis of serum samples, parents will be provided with an information letter about their baby's blood results. This letter will confirm, if the baby has adequate or inadequate protection against meningitis B and against pneumococcal serotypes, included in PCV13 vaccine after the booster dose given at 12 months.

If the antibody levels are below what is considered a protective level, we will recommend another dose of 4CMenB or PCV13 vaccine and contact the family to discuss the options.

8 TRIAL TREATMENTS

8.1.1 Name and description of investigational medicinal product (IMP)

Bexsero® (4CMenB vaccine-GSK) 0.5mL intra-muscularly; two doses administered 1 to 6 months apart. Each dose of vaccine contains recombinant *Neisseria meningitidis* group B NHBA fusion protein (50 micrograms); recombinant *Neisseria meningitidis* group B NadA protein (50 micrograms); recombinant *Neisseria meningitidis* group B FHbp fusion protein (50 micrograms) and Outer membrane vesicles (OMV) from *Neisseria meningitidis* group B strain NZ98/254 (25 micrograms measured as amount of total protein containing the PorA P1.4) adsorbed on aluminium hydroxide (0.5 mg Al₃⁺).

8.1.2 Name and description of non-investigational medicinal product (NIMP)

Infanrix hexa® (Combined Diphtheria-Tetanus-acellular Pertussis [DTPa], Hepatitis B, Inactivated Poliovirus and *Haemophilus influenzae* type b Vaccine; DTPa-HBV-IPV+Hib) at 2, 3, and 4 months of age

Rotarix® (rotavirus vaccine; RV) at 2 and 3 months of age

Prevenar 13® (pneumococcal 13-valent conjugate vaccine; PCV13) at 3 or 4 months and 12 months of age

Menitorix® (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; MCC-TT/Hib-TT) at 12 months of age

Priorix® (live attenuated vaccine against measles, mumps and rubella; MMR) at 12 months of age

8.2 Regulatory status of the drugs

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).

8.3 Drug storage and supply

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. 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 require transport in ‘cool-boxes’ able to maintain temperatures between 2 – 8 degrees Celsius. Minimal cold chain deviations should be managed as outlined in the clinical study plan which reflects manufacturer’s stability data.

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. 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 for that task. A sample signature of all delegated prescribers must be provided for the Pharmacy Site File prior to receipt of the first trial prescription.

8.4 Trial restrictions

Participants may take part in this study if they are already involved in research providing that, in the opinion of the Principal Investigator, this involvement will not adversely affect the conduct or outcomes of the study.

9 PHARMACOVIGILANCE

9.1

Term	Definition
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)	<p>An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.</p> <p>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.</p> <p>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. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.</p>
Serious Adverse Event (SAE)	<p>A serious adverse event is any untoward medical occurrence that:</p> <ul style="list-style-type: none"> • 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 <p>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.</p> <p>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.</p>
Serious Adverse Reaction (SAR)	<p>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.</p>
Suspected Unexpected Serious Adverse Reaction (SUSAR)	<p>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 reference safety information:</p> <ul style="list-style-type: none"> • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question
Adverse Events of Special Interest (AESIs)	<p>Adverse events of special interest (AESIs) are predefined (serious or non-serious) adverse events of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate, because such an event might warrant further investigation in order to characterize and understand it. The following AEs will be captured as AESIs throughout the study:</p>

	<ul style="list-style-type: none"> • Febrile seizures <p>Cases of febrile seizures will be defined according to the Brighton Collaboration Working Group (BCWG) case definition (Bonhoeffer et al, 2004)</p> <ul style="list-style-type: none"> • Arthritis <p>Cases of arthritis will be defined as:</p> <ul style="list-style-type: none"> -Presence of a physical exam findings of swelling, redness, heat, or limitation in range of motion and/or -Presence of a diagnostic imaging studies interpreted by a health care provider as demonstrating evidence of joint inflammation and/or arthrocentesis results evidencing inflammation. <p>Due to the heterogeneity of the presentation of arthritis which can be either acute or chronic, the threshold of duration of 6 weeks will be used.</p>
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9.2 Recording and reporting of SAEs, AESIs, SARs AND SUSARs

All solicited AEs which occur within 7 days of vaccination and 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.

All AESIs (both serious and non-serious) should be reported to the CI and sponsor according to the SAE reporting procedure.

SAEs, AESIs and SARs will be recorded throughout the study and must be notified to the CI and Sponsor within 24 hours of the investigator becoming aware of the event. Ensure the completed SAE form is sent to the CI and sponsor via email to pheath@sgul.ac.uk and adverseevents@sgul.ac.uk. SAEs, AESIs, SARs and SUSARs should be recorded on the AE log.

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, AESIs 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 CI and 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 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 the CI and Sponsor for review upon request and/or every 2 months.

SAEs and SUSARs will be reviewed by the CI. The project management team will return the reviewed SAE to the study team. Any queries raised by the CI/project management team/sponsor should be responded to as soon as

possible. Follow up reports must continually be completed within acceptable time-frames and sent to the CI and sponsor as detailed above until the reportable event is considered resolved.

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, AESIs 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 and AESIs will be communicated to GSK within 24 hours of the CI's first awareness of the event by the project management team at SGUL. Follow up information on safety reports will be provided for any medically relevant request. Any emerging safety issues related to 4CMenB Bexsero® and in connection with the study will be communicated to GSK within 48 hours of the CI and Sponsor becoming aware of them.

9.3 Responsibilities

The Chief Investigator will provide clinical oversight of the safety of participants in the trial, including an ongoing review of the risk / benefit. The CI will immediately review all reports of SUSARS and will review all SAE reports as these become available throughout the study. The SGUL project management team will be responsible for communicating queries to sites and communicating reported events to GSK. The sponsor will maintain overall oversight through receipt of initial and follow up SAE reports, ensuring all have been reviewed as per the protocol. The sponsor will compile the reported SAEs into a database for data consolidation.

Principal Investigators will ensure that information is being collected at local sites about (S)AEs. They will ensure that all SAEs and AESIs are recorded and reported to the CI and Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. They will ensure that SAEs and AESIs are chased with the Sponsor if a record of receipt is not received within 2 working days of initial reporting.

They will ensure that AEs are recorded as specified in section 9.3 of the protocol and that the AE log is sent to the Sponsor at upon request and/or at two monthly intervals throughout the study.

The Sponsor will ensure that central data collection and verification of AEs, ARs, SAEs, AESIs, SARs and SUSARs is conducted according to the trial protocol onto a database, that safety information is communicated to the CI and that investigators are informed of any SUSARS which occur as part of the study.

9.4 Notification of deaths

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

9.5 Overdose

It is extremely unlikely that a participant will receive an overdose of trial medication. If this happens, advice should be sought from the local Principal Investigator in discussion, if necessary, with the Chief Investigator.

9.6 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.

9.7 The type and duration of the follow-up of participants after adverse reactions.

All vaccinations will be given by trained members of staff who are able to deal with an allergic reaction to the vaccine. All participants will be observed for 20 minutes following vaccine administration to ensure that they remain well. All participants will have access to contact details for the study team which they will be able to use if they have any concerns about adverse events following vaccine administration. This is a licensed vaccine so significant adverse reactions are extremely unlikely. All adverse events which occur within the 28 days after vaccine administration will be recorded on the AE log as well as all medically attended AE which occur at any time during the study.

Any SUSAR will need to be reported to the Sponsor irrespective of how long after vaccine administration the reaction has occurred until resolved.

9.9 Development safety update reports

The Chief Investigator will submit annual Development Safety Update Reports (DSURs) to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

10 STATISTICS AND DATA ANALYSIS

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.

10.1 Sample size calculation

Sample size calculations are complicated because of the multiple components in 4CMenB. We will assess the immune responses to 3 antigens. We propose that a comparison of 2 schedules with respect to doses of 4CMenB 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 log_e units. Therefore, a sample size of 60 per group will allow a 1.67 fold difference between groups to be detectable at 80% power with 5% significance. The detectable difference would be 1.56 with a sample size of 80 infants per arm and 1.49 for a sample size of 100 infants per arm. Based on our experience from previous studies, we expect a drop-out rate of around 10% so we will aim to recruit a total of 220 infants (110 per arm) to detect a 1.5 fold difference between the two groups

10.2 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.

10.3 Statistical analysis plan

10.3.1 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, and relevant concomitant medications or vaccines.

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.

10.3.2 Primary outcome 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. 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 $\geq 1:4$ 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.

10.3.3 Secondary outcome analysis

It will be done in the same way as the primary outcome analysis described in 10.3.2. In addition, the geometric mean fold change between time points will be calculated with 95% confidence intervals.

10.4 Interim analysis and criteria for the premature termination of the trial

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 end of the study.

10.5 Procedure(s) to account for missing or spurious data

There will be no imputation of missing data.

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

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

Case report forms

In this study, paper CRFs will be used as source documents, with retrospective data entry into the InferMed Macro 4 EDC system.

All CRFs and data which is entered into the InferMed Macro 4 EDC system will be identified using the unique participant identification number. Local sites will be able to match the CRFS with participating individuals using their list of participants, but this information will not be shared with the central team.

Other material

Local sites will have paper copies of the participant contact details, consent forms and a copy of the participant information sheet. These will be retained by the local site and will not be shared with the central team. Paper copies of the CRFs that are used by the members of the study team will be signed and initialled.

Web-based EDC system

A web based electronic data capture (EDC) system will be designed, using the InferMed Macro 4 system. The EDC will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

The CI or delegate will request usernames and passwords from the KCTU. Database access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g Trial Manager) in the first instance.

Participant initials and date of birth will be entered on the EDC, NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the EDC. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial. Source data will be entered by recruiting site staff, typically within 5 working days of data collection by authorised staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the MACRO 4 EDC system. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

Due to a delay in setting up the database for the study, some of the data entry will be carried out several months after the study visit took place. The central team will be available to help sites with the backlog of data entry if required.

The CI team will undertake appropriate reviews of the entered data, in consultation with the project analyst for the purpose of data cleaning and will request amendments as required. No data will be amended independently of the study site responsible for entering the data.

At the end of the trial, the site PI will review all the data for each participant to verify that all the data are complete and correct. At this point, all data can be formally locked for analysis.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

11.2 Archiving

Archiving will be authorised by the Sponsor following submission of the end of trial report. Each site will be responsible for their onsite level study archiving. The trial essential TMF along with any central trial database will be archived in accordance with the Sponsor SOP. All essential documents will be archived for a minimum of 15 years after completion of trial and the study database will be archived for a minimum of 5 years after completion of the trial. Destruction of essential documents will require authorisation from the Sponsor.

12 MONITORING, AUDIT & INSPECTION

The CI will be requested to complete the 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 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 JRES governance team will determine the initial project risk assessment and justify any changes as the study progresses. The JRES team will prepare a monitoring plan based on the determined risk of the study. Monitoring will consist of on-site visits (scheduled and triggered) alongside central monitoring.

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 the sponsor's 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 the sponsor's Serious Breach Reporting SOP.

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.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

- before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters
- substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (note that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites)
- all correspondence with the REC will be retained in the Trial Master File/Investigator Site File
- an annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- it is the Chief Investigator's responsibility to produce the annual reports as required.
- the Chief Investigator will notify the REC of the end of the trial
- if the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination
- within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC

13.2 Public and Patient Involvement

Patient and Public Involvement (PPI) groups and meningitis charities will have been involved in discussions about the conduct of the study and will assist in the dissemination of results.

13.3 Regulatory Compliance

The trial will not commence until Favourable REC opinion has been obtained.

Before any site can enrol patients into the trial, the Principal Investigator must ensure written permission to proceed has been granted by that Trust Research & Development (R&D) office. 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).

For any amendment to the study, the Chief Investigator or designee, in agreement with the Sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

13.4 Protocol compliance

Protocol non-compliances are departures from the approved protocol.

- prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol
- accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.
- deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.
- All protocol deviations (critical, major and minor/other) should be reported to the Chief Investigator and Sponsor immediately. The sponsor will review the deviation and return the form to the site team.

13.5 Notification of Serious Breaches to GCP and/or the protocol

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 sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase
- the sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of
 - (a) the conditions and principles of GCP in connection with that trial; or
 - (b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

The Sponsor should be notified within 24 hours of becoming aware of a serious breach.

13.6 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles.

- **Nature of the processing**

Local sites will collect contact details from participants and will retain consent forms which contain identifiable information. The paper copies of this information will be stored in a secure location in a private office, the digital records of this information will be stored on password protected files on secure university or hospital computers. This information will be used by the local team only and no identifiable information will be shared with the central team. Data for the study will be recorded on paper CRFs, then entered into the InferMed Macro 4 EDC system for analysis. Participants will be identified using a unique participant identification number.

- **Scope of the processing**

We will be collecting information about the participants' demographics- including ethnicity and age- past medical history, obstetric history, details of their current pregnancy and a detailed vaccination history. At each visit we will collect information about whether any adverse events have been experienced. None of this information will be stored alongside any identifiable information. This information will be retained in the study database for five years after the end of the study.

- **Movement of data:**

Data will be entered into the InferMed Macro 4 EDC system and will be available to the central team through this system. No data will leave the UK.

13.7 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator, Principal Investigators and all members of the trial management group will be asked to declare any competing interests. This disclosure will reflect:

- ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
- commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

A record of this disclosure of competing interests will be kept locally in the ISFs and in the TMF

13.8 Indemnity

City St George's, University of London sponsored research:

City 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 City St George's, University of London 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. City 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.

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

Failure to alert City 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.

13.9 Amendments

Amendments can be made whilst the study is ongoing. The decision about the need for an amendment would be made by the Chief Investigator, informed by discussions with the trial management group and the JRES. The decision about whether the amendment is substantial or non-substantial will be made by the Chief Investigator in discussion with the JRES. The amendment will be prepared by a member of the central study team and the JRES and will be submitted to the REC through the IRAS system. Substantive changes will be communicated to all sites by a member

of the central study team or a representative of the JRES and details of the amendment history will be stored in ISFs at sites and in the TMF.

13.10 Post trial care

Infants will receive a vaccine which is part of the national immunisation schedule in the UK. There is no need for any post trial care to be arranged.

13.11 Access to the final trial dataset

All members of the trial management group will have access to the full dataset on request. This will include the principal investigators at all sites.

14 DISSEMINATION POLICY

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 Steering Committee/the Funder 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 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 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 Steering 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 Steering 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

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where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. 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.

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16. APPENDICIES

16.1 Appendix 1-Risk

<p>Risks associated with trial interventions</p> <p>A ≡ Comparable to the risk of standard medical care</p> <p>B ≡ Somewhat higher than the risk of standard medical care</p> <p>C ≡ Markedly higher than the risk of standard medical care</p>
<p>Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):</p> <p>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 the routine vaccinations with a shorter interval for 4CMenB, at 2-3 months instead of 2-4 months. Because the infants enrolled in the study will receive the same vaccines as part of their routine immunisation, this study is unlikely to be associated with any added risk of adverse events.</p> <p>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).</p>

16.2 Appendix 2. Summary chart of protocol amendments.

Amendment History				
Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA01	2.1	13.07.2021	Zsofia Danos	p.3&4 – addition of new names p.8 - addition of new sites p.25 - clarification re maximum number of venepuncture attempts p.35, 36, 38, 39 – change to using paper source document rather than direct data entry
SA02	3.0	02.08.2021	Zsofia Danos	p.8 - change of site name and address for the University of Oxford p.13, 20, 21, 26 – change of time interval between visits from 30 to 28 days.
SA04	4.0	30.03.2022	Natalina Sutton	Key study contacts and Southampton Co-PI updated. Section 7 – More recruitment methods added including the use of PIC sites Section 11 – Data management: details of database to be used added
SA05	5.0	05.08.2022	Natalina Sutton	PIs for Cornwall and Oxford sites updated. Section 11.1 and 13.6 - Small changes to information regarding database.
NSA02	6.0	12.09.2022	Natalina Sutton	Visit window for Visit 5 changed to +21 days.
SA06	7.0	06.12.2022	Zsofia Danos	PI for City St George's, University of London updated P.10 – secondary objective added p.14 – Meningococcus groups changed from 13 to 12
NSA03	8.0	18.04.2024	Jonathan Lewis-Bridgeman	Planned trial period extended to 31 st August 2024.
SAM08	9.0	25.07.2024	Clare Thornbury	Change of Sponsor Representation from St George's to City St George's University of London

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IRAS Number: 265199

NSA04	10.0	10.09.2024	Jonathan Lewis- Bridgeman	A no-cost extension to the planned trial period, extending the study to the 31 st October 2024.
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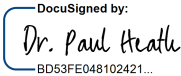
Certificate Of Completion

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Document Pages: 46	Signatures: 2
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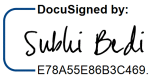
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