Trial Title: Evaluating the effect of immunisation with group B meningococcal vaccines on meningococcal carriage.

Internal Reference Number / Short title: Be on the TEAM: Teenagers against Meningitis

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Department of Health

Pfizer (provision of MenB-fHBP vaccine)

Confidentiality Statement

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

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1. KEY TRIAL CONTACTS

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Statisticians	Dr Caroline Trotter & Dr Hannah Christensen
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	Professor Ray Borrow, Public Health England Dr Caroline Trotter, University of Cambridge Professor Martin Maiden, University of Oxford Professor Adam Finn, University of Bristol Dr Hannah Christensen, University of Bristol Steven Gray, Public Health England Jenny MacLennan, University of Oxford

2. SYNOPSIS

Trial Title	**Evaluating the effect of immunisation with group B meningococcal vaccines on meningococcal carriage.**	
Internal ref. no. (or short title)	**Be on the TEAM; Teenagers against Meningitis**	
Clinical Phase	Phase IV: Post Licensure	
Trial Design	Clinical Trial	
Trial Participants	Adolescents aged 16 to 19 years, enrolled in school year 12/S5 (or equivalent).	
Planned Sample Size	A total of 24,000 recruits; 16,000 of these will be in the vaccine groups and receive either 4CMenB (Bexsero) or MenB-fHBP (Trumenba). 8,000 in the unimmunised control group (will receive 4CMenB at the conclusion of the study).	
Treatment duration	6 months	
Follow up duration	12-18 months	
Planned Trial Period	March 2018 – December 2023 (end of trial date)	
	Objectives	Outcome Measures
Primary	To determine if immunisation with 4CMenB (Bexsero) or MenB-fHBP (Trumenba) influences the carriage of pathogenic meningococci.	Rates of carriage prevalence of any of meningococci genogroup B, C, W, Y and X before and after immunisation in both immunisation cohorts, compared with unimmunised controls

Secondary	To determine the broader impact of immunisation with either 4CMenB (Bexsero) or MenB-fHBP (Trumenba) on meningococcal species	Rates of carriage prevalence of particular *Neisseria* before and after immunisation in both immunisation cohorts, compared with controls, specifically: a. genogroup B meningococci b. Hyper-invasive meningococcal strains c. All meningococcal strains d. Other Neisseria species e. Meningococci of other genogroups and capsule null meningococci f. Meningococci expressing antigens contained in 4CMenB and MenB-fHBP The difference in acquisition of carriage of all *N. meningitidis* over a 12 month period in both immunised cohorts compared to unvaccinated participants
Exploratory Objectives	To explore the impact on carriage of the UK Adolescent MenACWY immunisation programme	Comparison of pre-intervention carriage using the 2014/15 UK 'MenCar4'[4] carriage survey with this current study forming post-intervention measure of carriage prevalence
Investigational Medicinal Product(s)	4CMenB licensed vaccine (Bexsero® –GSK); or MenB-fHBP (Trumenba® – Pfizer), two doses administered 6 months apart.	
Formulation, Dose, Route of Administration	4CMenB vaccine (Bexsero® -GSK) 0.5mL intra-muscularly; two doses administered at least 5 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 Al^{3+}). MenB-fHBP (Trumenba® – Pfizer) 0.5mL intramuscularly; two doses administered at least 6 months apart. Each dose of the vaccine contains *Neisseria meningitidis* serogroup B fHBP subfamily A (60 micrograms); and *Neisseria meningitidis* serogroup B fHBP subfamily B (60 micrograms) adsorbed on aluminium phosphate (0.25 milligram aluminium per dose).

3. ABBREVIATIONS

4CMenB	Four component Meningococcal capsular group B vaccine, trade name Bexsero ®. Manufactured by GlaxoSmithKline.
AE	Adverse event
AR	Adverse reaction
caPCR	Culture-amplified PCR
CCVTM	Centre for Clinical Vaccinology and Tropical Medicine
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials and Research Governance
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
DSUR	Development Safety Update Report
fHBP	Factor H binding protein
GCP	Good Clinical Practice
GP	General Practitioner
GSK	GlaxoSmithKline

GTAC	Gene Therapy Advisory Committee
HRA	Health Research Authority
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MenB	Capsular group B meningococcus
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NRES	National Research Ethics Service
OMV	Outer Membrane Vesicles
OVG	Oxford Vaccine Group
OXTREC	Oxford Tropical Research Ethics Committee
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
MenB-fHBP	Meningococcal serogroup B vaccine, trade name Trumenba. Manufactured by Pfizer.
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
STGG	Skim-milk-tryptone-glucose-glycerin
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSG	Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group

4. BACKGROUND AND RATIONALE

Neisseria meningitidis is a normal human commensal bacterium frequently found in the upper respiratory tract. It also has the capability to cause invasive meningococcal disease (IMD), which is rapidly progressive with a high fatality rate and often devastating outcomes in survivors. The United Kingdom was the first country in the world to introduce the 4CMenB programme in September 2015. In this programme, the vaccine 4CMenB (Bexsero) was offered to all children born after the 1st May 2015. This programme has subsequently been estimated to be 83% effective at preventing invasive *Neisseria meningitidis* genogroup B (MenB) disease[1]; however, this campaign has had no impact on the rates of MenB disease in unimmunised cohorts. This is in keeping with mathematical modelling before the introduction of the vaccine, which predicted that infant immunisation alone could prevent a maximum of 26.3% of meningococcal infections within the first five years of introduction[2]. The same paper noted that, assuming 4CMenB immunisation were to reduce meningococcal carriage by 30%, long term maximal reduction would be achieved by combining infant and adolescent immunisation, reducing annual cases by 48.8% at 10 years (and 59.7% at 20 years), providing maximal impact in a more cost-effective manner.

However, the critical assumption that 4CMenB immunisation can reduce MenB carriage is unproven. An attempt to address this question was made in a randomised controlled trial enrolling 2954 UK university students[3], in which carriage of all meningococci was reduced by 18.2% from 3 to 12 months following immunisation with 4CMenB compared with controls. This reduction was mostly accounted for by a fall in carriage of capsular groups C, W and Y meningococci (29.6% reduction), with a non-significant fall of 15.6 % observed for MenB. This study had an inherent limitation, as only a small minority of students at any institution received the vaccine, minimising any impact on circulation of bacteria that might have been observed. Since this study commenced, The 'B Part of It' randomised controlled trial of 24269 teenagers did not show a reduction in carriage of the pathogenic genogroups A, B, C, W, Y, or X at 12-months following vaccination 4CMenB, one of the vaccines in this current study protocol.[4]

The impact of a more recently licensed MenB vaccine, (MenB-fHBP, 'Trumenba') on meningococcal carriage is unknown.

Therefore, this study will evaluate the carriage of pathogenic *N. meningitidis* species in adolescent populations being immunised with either 4CMenB or MenB-fHBP, when compared with those receiving no vaccine.

The proposed study will also be informed by the MenCar4 study (REC ref 14/SC/1163) in which oropharyngeal swabs were taken from 21 000 teenagers, providing detailed information on current carriage prevalence in UK adolescents[5]. Provisional data from this study has provided phenotypic information on the serogroup and, through whole genome sequencing, genetic information on the genogroup, vaccine matched antigens ('BAST') and clonal complexes. These data have proved crucial to the design of this new study, and further information on the BAST approach to predicting 'coverage' provided by the 4CMenB vaccine[6].

Study design:

This study will evaluate the prevalence of pharyngeal carriage of pathogenic meningococci in year 12/S5 (or equivalent) students in immunised and unimmunised cohorts on the date of enrolment and

at 12 months (6 months following second vaccine dose in the immunised cohorts) to determine:

(i) Rates of 'baseline' and '12 month' carriage of genogroup B, C, W, X and Y meningococcal strains in immunized and unimmunized cohorts testing the hypothesis that immunisation with MenB-fHBP (Trumenba) or 4CMenB (Bexsero) reduces carriage rates in immunised cohorts.

(ii) Rates of carriage of particular Neisseria before and after immunisation in both cohorts, specifically
   a. genogroup B meningococci
   b. Hyper-invasive meningococcal strains
   c. All meningococcal strains
   d. Other Neisseria species
   e. Meningococci of other genogroups and capsule null meningococci
   f. Meningococci expressing antigens contained in 4CMenB and MenB-fHBP;

This will test the hypothesis that any effect seen in (i) is specific to particular Neisseria.

(iii) Evaluation of the rates of acquisition in immunised and unimmunised cohorts of each of the Neisseria mentioned in (ii) ,

To evaluate this the prevalence of oropharyngeal carriage of invasive meningococcal isolates will be surveyed in 24,000 secondary-school students. One third of these participants will receive 2 doses of MenB-fHBP at least six months apart, another third will receive two doses of 4CMenB at least 5 months apart, and the remaining third 4CMenB at the end of the study. Meningococcal carriage will be re-evaluated in all participants approximately 12 months after their first swab to determine if immunisation with MenB-fHBP or 4CMenB has reduced the prevalence of invasive meningococci. This study will be delivered across at least 14 sites, each recruiting through multiple secondary schools/colleges, and allocation to MenB-fHBP/4CMenB/control groups will be on a regional basis.

In March 2020, the SARS-CoV-2 pandemic required temporary suspension of the study due to school closures and NIHR research priority directives. In September 2020, following consultations with the Department of Health and Social Care, the Research Ethics Committee, the study sponsor and the Scientific Advisory Board the decision was made not to resume the study visits. This reflected concerns regarding the disruption to study visit timelines, potential risk of SARS-CoV02 transmission during study visits, the feasibility of ongoing study visits in the context of restricted access to schools, and diversion of resources away from COVID-19 vaccine studies.

Characteristics of the licensed vaccines:

4CMenB(Bexsero) was licensed in 2013 in Europe and North America and in various other jurisdictions. The UK introduced this vaccine into its routine infant immunisation programme in 2015 in a 2, 4 and 12 month schedule. During clinical development, the vaccine was evaluated in adolescents, and it was demonstrated that two doses of 4CMenB induced robust immune responses against the vaccine antigens [7 8]. The vaccine was well tolerated, and no safety concerns were identified (reviewed in [9]).

MenB-fHBP (Trumenba) is licensed for use in those aged 10 to 25 years of age. It is composed of surface factor H binding protein (fHBP) from two subgroups of capsular group B *N. meningitidis*, and is produced in *Escherichia coli* cells by recombinant DNA technology and adsorbed on aluminium phosphate. MenB-fHBP has been found to be safe and generally well tolerated, with the main side effects reported as fatigue, headache and muscle pain[10]. These are not dissimilar to the side-effects reported after 4CMenB. MenB-fHBP is licensed for use in the U.K. but is not currently on the routine vaccine schedule.

Full details of the immunogenicity and side effect profile of 4CMenB and MenB-fHBP are available in the relevant summary of product characteristics.

Description of the population to be studied.
This study will recruit adolescents attending school/college in year 12 (or equivalent) aged between 16 and 19 years of age. As in MenCar4 a network of at least 14 study sites will be employed, with a 'site' being a geographically distinct research team and Principal Investigator. (In MenCar4 these sites were based in Bristol, Cardiff, Glasgow, South London, Maidstone, Stockport, Manchester, Oxford, Plymouth, Preston, Stockport and Wigan; all these sites will be approached to take part in this new study, along with additional sites to facilitate recruitment). Each of these sites will recruit through multiple schools/colleges, and study visits will be conducted at schools, except for select circumstances where visits 2 to 4 may potentially require community visits for participants that have left school (see section 6).

Known potential risks and benefits to participants:
Potential Benefit to Participants:

Vaccine recipients will have the benefit of receiving licensed vaccines against MenB disease not currently administered to adolescents in the routine UK immunisation schedule, directly reducing the chance of invasive meningococcal disease (IMD).

Potential Risk to Participants:

1. Collection of oropharyngeal swabs

Collection of swabs can be uncomfortable, but should cause minimal distress to participants.

2. Vaccination

Both vaccines are licensed for use in Europe. The most common reported side effect in adolescents and young adults following vaccination with 4CMenB or MenB-fHBP is pain at the injection site, headache, and generally feeling unwell. Other possible side effects include fever, feelings of tiredness and nausea. As with all vaccines, there is a small chance of an allergic reaction to the vaccine including a severe allergic reaction, or anaphylaxis (risk less than 1 in a million doses for existing vaccines)[11].

Route of administration, dosage, dosage regimen, and treatment period: The route of administration and dosage will follow the license of these products. Both vaccines (4CMenB and

MenB-fHBP)) will be given intramuscularly into the deltoid muscle of the non-dominant upper arm. Both vaccines will be given as two doses, for MenB-fHBP this will be a minimum 6 month interval, for 4CMenB this will vary between 5 to 6 months (4CMenB group), and 1 to 6 months (control group).

5. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective To determine if immunisation with 4CMenB (Bexsero) or MenB-fHBP (Trumenba) influences the carriage of pathogenic meningococci.	Rates of carriage prevalence of any of meningococci genogroup B, C, W, Y and X before and after immunisation in both immunisation cohorts, compared with unimmunised controls	Oropharyngeal swabs taken at day 0 and 12 months (range 11-17 months).
Secondary Objectives To determine if the effect of immunisation with either 4CMenB (Bexsero) or MenB-fHBP (Trumenba) is specific to a particular *Neisseria*.	Rates of carriage prevalence of particular *Neisseria* before and after immunisation in both immunisation cohorts, compared with controls, specifically: a. genogroup B meningococci b. Hyper-invasive meningococcal strains c. All meningococcal strains d. Other Neisseria species e. Meningococci of other genogroups and capsule null meningococci f. Meningococci expressing antigens contained in 4CMenB and MenB-fHBP The difference in acquisition of carriage of all *N. meningitidis* over a 12 month period in both immunised cohorts compared to unvaccinated participants	Oropharyngeal swabs will be taken on day 0 and 12 months (range 11-17 months).

Exploratory Objectives To explore the impact on carriage of the UK Adolescent MenACWY immunisation programme	Comparison of pre-intervention carriage using the 2014/15 UK 'MenCar4'[4] carriage survey with this current study forming post-intervention measure of carriage prevalence	

6. TRIAL DESIGN

This study will be an open-label clinical trial with regional allocation to one of three study arms, as outlined below.

Population and study sites.

We will enrol 24,000 year 12/S5 (or equivalent) pupils attending schools and 6th form colleges in England, Scotland and Wales. The study will designate each site (geographical area) as a vaccine or control site according to local capacity and expertise (e.g. previous experience of conducting vaccine clinical trials).

All study procedures will happen at participant's schools/colleges, with the exception of sites in Scotland (due to the structure of the academic year), or selected sites following discussion with the Chief Investigator where community visits may be more feasible to complete Visits 2 to 4. Community visits are defined as non-school visits and may include hospitals or other health facilities subject to local approvals. Participants will be assessed for carriage of meningococcus by an oropharyngeal swab at the first visit. At the vaccine sites, participants will also receive their first dose of vaccine, and will have a second dose of vaccine administered after an interval of at least 6 months (MenB-FHBP) or at least 5 months (4CMenB). Approximately twelve months after the time of the first visit, (6 months after the second dose of vaccine at vaccine sites) a second oropharyngeal swab will be taken from all participants. A course of 4CMenB will be offered to all participants in the control centres after the '12 month' swab has been taken but is not a study requirement.

Table 1: study design

	Visit 1 (Baseline)	Visit 2 (Month 6)	Visit 3 (Month 12)	Visit 4 (Month 13 to 18)
Visit timing	NA	5 to 8 months after Visit 1 (4CMenB group) 6 to 8 months after Visit 1 (MenB-fHBP group) *	5.5 to 9 months after visit 2 and 11 to 17 months after Visit 1 (4CMenB and MenB-fHBP groups) 11 to 17 months after visit 1 (Control group)	1 to 6 months after visit 3, but no more than 18 months after Baseline**
Group 1 4CMenB arm (n = 8000)	Swab 4CMenB Questionnaire distribution	4CMenB	Swab	NA
Group 2 MenB-fHBP arm (n= 8000)	Swab MenB-fHBP Questionnaire distribution	MenB-fHBP	Swab	NA
Group 3 Control arm (n=8000)	Swab Questionnaire distribution	NA	Swab 4CMenB	4CMenB**

* the second dose of MenB-fHBP must be at least 6 months after the 1st dose.

** For most participants this second dose will be given at approximately 1 month after the first dose. For participants recruited in September 2018 this second dose would ideally be delayed until 5 to 6 months after their first dose, i.e. until March 2020, to minimise any potential impact on carriage rates on future Year 12 cohorts recruited in subsequent waves at the same school. This course of 4CMenB is optional for participants in the control arm.

Wave 3 and 4 recruited participants with visits impacted by SARS-CoV-2

Of participants enrolled in Wave 3 (March-May 2019) 1310 out of 6413 completed their visit 3, leaving 5103 Year 13 students considered 'lost to follow up'. There were 4173 participants enrolled in Wave 4 (Sep-Nov 2019). No further study visits will occur for these participants.

Frequency and timing of study visits.

In order to deliver the study within the proposed funding period, while maximising the interval between swabs and fitting in with the school exam year, the following 4 wave recruitment strategy is proposed, but is not prescriptive and is adaptable to local circumstances.

- Commencing the 'first wave' of recruitment for year 12/S5 students in March - May 2018, with the 2nd vaccine dose (where applicable) to be given in Sept - Oct 2018, and the final swabs to be taken (and first control vaccine doses given, where applicable) in March - May 2019
- Commencing the 'second wave' of recruitment in September - October 2018 for the new year 12/S5 cohort with the 2nd vaccine dose (where applicable) to be given in March – May 2019 and the final swabs to be taken (and first control vaccine doses given, where applicable) in September – December 2019
- Commencing the 'third wave' of recruitment for year 12/S5 students in March – May 2019, with the second dose of vaccine (where applicable) in September – October 2019, and the final swabs to be taken (and first control vaccine doses given, where applicable) in March – May 2020
- Commencing the 'fourth wave' in September – October 2019 for the next new year 12/S5 cohort with the second dose of vaccine (where applicable) to be given in March – May 2020, and the final swabs to be taken (and first control vaccine doses given, where applicable) in September – October 2020

It will be important to ensure that the timing of recruitment in the immunised and unimmunised groups remains similar to minimise seasonal variation. Using this design it will be possible to recruit to the study across 3 year 12/S5 cohorts, in 4 'waves' over a 19 month period, as shown in the tables below.

Within this adaptable study design, there is the opportunity to extend the 2nd swab visit for wave two. Lengthening the period between the 2nd immunisation dose and the final swab may augment any effect of MenB immunisation on reducing oropharyngeal carriage (3)

Table 2a: Recruitment strategy/ study visit timing: immunisation sites

Year 12 cohort		2018 March/ May	Sept/ Oct	2019 March/ May	Sept/ Oct	2020 March/ May	Sept/ Oct
2017/2018	Wave 1	V S	V	S*			
2018/2019	Wave 2		V S	V	S**		
	Wave 3			V S	V	S*	
(2019/2020)	Wave 4				V S	V	S

*These '12 month' swab visits will need to be completed by April to fit with school exam timetables

** This second swab for wave 2 can be delayed to Nov/Dec or beyond provided the visit remains within the timelines outline within table 1.

V- vaccination S- swabbing

Year 12 cohort		2018 March/ May	Sept/ Oct	2019 March/ May	Sept/ Oct	2020 March/ May	Sept/ Oct
2017/2018	Wave 1	V S	V	S*			
2018/2019	Wave 2		V S	V	S**		
	Wave 3			V S	V	S*	
(2019/2020)	Wave 4				V S	V	S

* These '12 month' swab visits will need to be completed by April to fit with school exam timetables
** This second swab for wave 2 can be delayed to Nov/Dec

Table 2b: Recruitment strategy/ study visit timing: control sites

Year 12 cohort		2018 March /May	Sept/ Oct	2019 March /Apr	Apr	Sept/ Oct	2020 March /Apr	Apr	Sept	Oct
2017/2018	Wave 1	S		S * V	V					
2018/2019	Wave 2		S			S** V	V			
	Wave 3			S			S* V	V		
(2019/2020)	Wave 4					S			S V	V

*'12 month' swab visits for wave 1 and 3 will need to be completed by March to allow for the 2nd dose of vaccine to be administered in April (before the May exam period)

** This second swab for wave 2 can be delayed to Nov/Dec or beyond provided the visit remains within the timelines outline within table 1.

V- vaccination S- swabbing

The indication of visit months given above may be adjusted depending on participant and school/college availability for visits. However, participant's visits will be conducted within the timelines outlined within table 1.

Data from brief questionnaires will be captured electronically where possible. Each participant will be assigned a unique study ID which will be used to label samples and questionnaires to ensure anonymity.

7. PARTICIPANT IDENTIFICATION

7.1. Trial Participants

Participants will be healthy adolescents aged 16-19 years of age, in their penultimate year of school/college, who intend to return for a further year. Participants will therefore be in year 12 or equivalent in selected 6th form colleges in England and Wales and in Scotland participants will be in year S5.

7.2. Inclusion Criteria

- Aged 16-19 years and attending year 12/S5 (or equivalent) at one of the participating schools.

- Participant is willing and able to give informed consent for participation
- In the Investigator's opinion, is able and willing to comply with all trial requirements.
- Willing to have throat swabs, and the bacterial isolates from throat swabs, stored for future research
- Willing to allow their General Practitioner to be contacted to confirm vaccination status if necessary

7.3. Exclusion Criteria

The participant may not enter the trial if the following applies:

- All participants: Evidence of a course of either 4CMenB or MenB-fHBP in the past (documentation or self-report)
- Participants in the **4cMenB or MenB-fHBP groups** may not enter the study; and participants in the **control group may not receive 4cMenB** if they have ANY of the following
    a. History of anaphylaxis to any component of 4CMenB or MenB-fHBP. For 4CMenB only, this includes allergy to latex.
    b. Any other significant disease or disorder which, in the opinion of the investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate. Specific examples are haemophilia or medically diagnosed bleeding disorder, or anticoagulant medication that prohibits the use of intramuscular injections;
    c. Participant is known to be pregnant
- Participants in the **control group** that meet any of the specific criteria *a., b*. or *c.* listed above can participate in the throat swabs and questionnaire but will not be eligible to receive the 4CMenB vaccine after the second throat swab.

7.4. Eligibility assessment at enrolment & reconfirmation at subsequent visits

Appropriately trained medical or nursing staff may be delegated to assess eligibility, based on the inclusion and exclusion criteria and with the oversight of the Principal Investigator. The Principal Investigator is required to sign an 'Eligibility Training and Delegation' form stating that they have trained staff appropriately before this task is assigned on the delegation log. Non-clinical staff may reconfirm ongoing eligibility at visit 3 for the 4CMenB or MenB fHBP groups only where the only study procedure is an oropharyngeal swab. Where there are questions concerning eligibility, study team members checking eligibility will be able to escalate to a medically qualified, delegated staff member or the site PI.

8. TRIAL PROCEDURES

8.1. Recruitment

The Meningitis Research Foundation and Meningitis Now, two national patient representative groups, will be our partners in the study. They will contribute particularly to the recruitment and engagement of pupils to the study, raising awareness of the signs and symptoms of meningitis in all schools. Public

engagement may include Social media platforms. These will be used by University and Hospital 'patient and public involvement and engagement' teams to educate teenagers and families about meningitis and meningitis vaccines, and to provide information about the study.

Schools will be approached directly by the study team, either by email or phone call. Individual participants will not be directly approached by the study teams outside of the school setting other than to being made aware of the study through social media (potentially including answering educational questions and 'signposting' of schools taking part). These platforms will not be used for individual participant recruitment. To identify schools interested in participating, the study team will contact the school principal or other senior teacher, and will inform students and their parents about the study through means such as posters, study flyers and talks in assembly etc. Information about the study will also be provided through study site websites, newsletters and through social media. Students at participating schools will be able to review the participant information sheet and informed consent form in advance of the first study visit. These documents will be provided by various means adapted to the school and site logistics and preference, e.g. through paper versions distributed in schools in association with a school based study presentation, or through email with a link to electronic versions of these documents on the study website. Parents will also have access to information about the study through these means.

8.2. Informed Consent

Information will be presented to students in a school setting detailing the exact nature of the study in the period prior to the first swabbing and/or vaccination visit. This information will also be disseminated to parents through the school, and provided on web and social media platforms.

Written versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal. These Participant information and Informed Consent leaflets will be given to students to take home for the information of parents/legal guardians, and parents will also be advised of the study through school newsletters etc.

Consent will be self-consent, as all participants in this trial will be aged 16 years or over [12]. Consent may be taken by clinical staff (registered doctor or nurse) or non-clinical staff who have had appropriate experience and training and who have been signed off by the site PI on the delegation log. As well as consent for this study, participants will be asked to give optional consent to be contacted about future research studies. For participants entering into the study during wave 4 this will be obtained at the time of initial consent. Additionally, for participants already enrolled in the study attending for Visit 2 or Visit 3 during wave 4, sites may choose to consent participants with a separate informed consent form for permission to contact about future research studies, according to the site's capacity to do so.

Parents/legal guardians will be provided with information about the study through above means, and have the opportunity to discuss their teenager's participation if desired. They will be provided with a

study-specific email address that they can contact for this purpose, or if they wish to discuss the study further.

If the teenager and their parent/legal guardian disagree over participation in the study, the study team members will be available to give information and mediate any discussions, but the decision will ultimately rest with the potential participant themselves.

On the day of the particular school's participation students will have the opportunity to ask study members any questions they might have prior to taking part in any procedures.

Participating schools may have vulnerable students with learning difficulties, and in this case study staff will need to be take extra care that the individual in question is giving informed consent. If there is any doubt then additional input or support from the individual's parents/guardians may be useful to provide this context. If there is ongoing doubt about the individual's ability to provide informed consent then they should not be enrolled in the study.

Allocation of Participant Numbers, confirmation of recruitment and replacement

A participant number will be allocated following signing of the Informed Consent Form, however a participant will not be considered as recruited until they have been confirmed as eligible. If a participant does not meet eligibility criteria or, if a participant refuses all study procedures subsequent to meeting eligibility criteria, then the participant number will not be replaced, but that participant will not count towards the study sample size.

8.3. Randomisation, blinding and code-breaking

The study will not be randomised, but rather allocation into either vaccine arm or the control arm will be on a regional basis, as per the needs and expertise of the local area, and the requirements of the study in order to maintain equal numbers in each study arm. There will not be a formal randomisation process, and the study will not be blinded.

Baseline Assessments

These will occur at the initial visit (Visit 1) after informed consent has been obtained.

Participants will

- Have an oropharyngeal swab taken
- Be immunised with the first dose of 4CMenB or MenB-fHBP (immunisation groups only)
- Complete a brief questionnaire to collect demographic data and risk factors for meningococcal carriage such as smoking and antibiotic use

8.4. Subsequent Visits

Promoting retention of participants

To aid in retaining participants to visits 2 to 4 a number of interventions may be used:

sites may choose to contact participants by text message or mobile phone communications 'app' or email to remind them of their upcoming visit.

Assemblies held within schools/colleges prior to visits occurring to remind participants of the study aims - a PowerPoint presentation and or video may be used and ambassadors from meningitis charities may attend

The study may be promoted through means such as posters and study flyers etc.

Information about the study and upcoming visits may also be provided through study site websites, newsletters and through social media.

Visit 2 (month 6): Vaccine groups only

- Students will be visited in their schools again
- Eligibility criteria will be reconfirmed as per inclusion/exclusion criteria, and students asked for their recall about anaphylaxis after the first dose of vaccine. We will not be recording concomitant medications.
- The second dose of either 4CMenB or MenB-fHBP will be administered as appropriate.
- No swabs will be taken at this visit.

Visit 3 (month 12): All groups

- Participants will be seen again at their schools.
- Eligibility criteria will be reconfirmed and participants will be asked for their recall about anaphylaxis after previous vaccines
- A second oropharyngeal swab will be obtained
- Control group participants will have first dose of 4CMenB administered

Visit 4 (month 13 to 18): Control group only

- Participants will be seen again in their schools
- Eligibility criteria confirmed
- Second dose of 4CMenB administered

We will not be giving specific feedback on swab results at any of the visits, but in the event that we receive an unexpected result, we will make provision for feedback and follow up (see section 11.5).

8.5. Sample Handling

Each participant will have 2 x oropharyngeal swab samples collected, on day 0 and day 365 of the trial.

At each swabbing visit:

- Throat swab taken
- Insert into STGG broth (no direct plating)

Cold chain process:

- Swabs samples will be immediately placed into cooler boxes at 4 degrees Celsius (range 2-8 degrees Celsius). These boxes will be monitored with temperature gauges.
- Cool boxes will be transported to the local laboratory within 4 hours of the first sample collection.

STGG samples will be frozen on arrival to the local site laboratory.
Samples will subsequently be processed according to a standardised process fully described in the laboratory analysis plan. Briefly, either at site or at a regional participating site, samples will be:

- Defrosted and plated out on GC plate, to be read at 24 and 48 hours.
- Potential meningococcal isolates identified by Gram stain and oxidase test
- Isolates of gram negative, oxidase positive diplococci are then frozen, stored in glycerol broth, and sent to Manchester Public Health England Meningococcal Reference Laboratory

The positive lawns (any growth at all) will be harvested, and sent to the University of Bristol for PCR analysis (culture-amplified PCR, caPCR) . Carriage detection using the lawn samples will be determined by PCR of a conserved target of *Neisseria meningiditis* (*eg.* PorA). Capsular group will be determined by genogroup-specific PCRs of the major potentially pathogenic genogroups (eg genogroup B, C, W, and Y).
At Manchester Public Health England Meningococcal Reference Laboratory:

- Further identification of *Neisseria* isolated to establish
    - Identity as *Neisseria meningitidis* or of other *Neisseria* species
    - Phenotypic characterisation (including serogroup)
- Extraction of DNA to be sent to Oxford for subsequent whole genome sequencing

Neisseria isolates and positive 'lawn' cultures (not containing any human tissue) will be stored beyond the end of the study either at the study site or at a central location for potential subsequent analysis by PCR to further address the endpoints of this study. Throat swabs will be retained in an approved HTA licensed facility for use in future research related to oropharyngeal flora.

A representation of the microbiological processing is outlined in Figure 1.

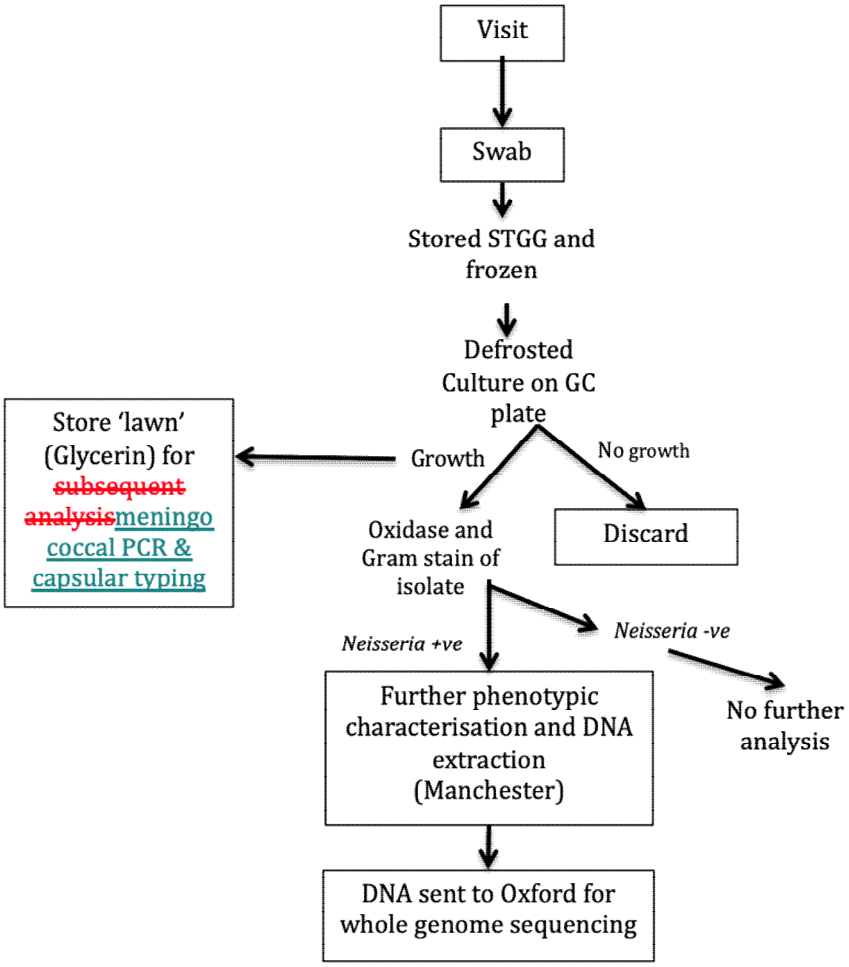

Figure 1: summary of microbiological processing

8.6. Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time.

If a participant withdraws consent for the whole study, no further study procedures should take place. In some circumstances, participants will withdraw consent for specific procedures, or fail to attend a visit, but may still be willing to participate in subsequent visits/ procedures.

In this situation the following guidelines apply:

- If any of the procedures at the first visit are refused then they will be considered as withdrawn from the study, and no further procedures will take place.
  If a participant at an 'immunising site' refuses or doesn't attend for the 2nd immunisation, they can remain in the study for the final swab, and should be encouraged to do so. These participants may be offered their 2nd immunisation ('Visit 2') on the same day as their Visit 3.
- If a participant at a control site refuses the second swab, they can still receive the study vaccine (although this should be discouraged).
- A participant at a control site may decline the course of 4CMenB; this does not count as a study withdrawal as this procedure is optional

In addition, the Investigator may discontinue a participant from the trial at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the trial or retrospectively having been overlooked at screening) However, participants that become ineligible during the trial due to the specific criteria *a., b*. or *c.* listed in section '7.3 Exclusion Criteria' may participate in the second throat swab at visit 3.
- An adverse event which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Disease progression which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures
- Withdrawal of Consent (as above)
- Loss to follow up, but we will still include any data already gathered from the participant in the final analysis, unless consent is withdrawn.

Exclusion from the trial will not result in exclusion of the data already taken for that participant.

The reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

Withdrawn participants will not be replaced.

8.7. Definition of End of Trial

The end of the trial is defined as the date of completion of laboratory analysis of the oropharyngeal swab samples and their culture products.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1. IMP Description

4CMenB vaccine (Bexsero® -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 Al^{3+}).

MenB-fHBP (Trumenba® – Pfizer) 0.5mL intramuscularly; two doses administered 6 months apart. Each dose of the vaccine contains *Neisseria meningitidis* serogroup B fHBP subfamily A (60

micrograms); and *Neisseria meningitidis* serogroup B fHBP subfamily B (60 micrograms) adsorbed on aluminium phosphate (0.25 milligram aluminium per dose).

Both vaccines will be administered into the deltoid muscle of the non-dominant arm.

9.2. Storage of IMP

Supply of 4CMenB will be through the Department of Health. MenB-fHBP will be supplied by Pfizer. 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 to schools 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.

9.3. Compliance with Trial Treatment

Compliance will not be essential to this trial. Participants will be allowed to attend swabbing and vaccination sessions of their own volition, and will not be required to fulfil any trial-related procedures between visits.

9.4. Accountability of the Trial Treatment

4CmenB will be ordered through NHS supplies.

MenB-fHBP will be ordered directly from Pfizer by sites in the MenB-fHBP arm of the trial.

IMPs will be administered according to the protocol or by use of Patient Group Directions (PGDs). No additional labelling of IMPs is required.

9.5. Concomitant Medication

There are no concomitant medications that would result in exclusion from this trial, therefore we will not be recording them.

9.6. Post-trial Treatment

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

10. SAFETY REPORTING

This study is being conducted with licensed products used according to their license, and as such safety monitoring will therefore focus on detecting any suspected, unexpected, serious, adverse reactions, i.e. SUSARs.

10.1. Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

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

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

Any pregnancy which is voluntarily mentioned by a participant and occurring during the clinical trial, and the outcome of the pregnancy, should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious".

10.2. Causality

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

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

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

10.3. Procedures for Recording Adverse Events

Given the scale of this study and the licensed nature of the vaccines no active solicitation of adverse events will occur.

Should investigators become aware of a serious adverse event that is not on the exemption list (see section 10.4) the following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

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

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

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to prevent the participant receiving a second dose of vaccine. A participant may also

voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

10.4. Reporting Procedures for Serious Adverse Events

Given the scale of the study and the fact that the vaccines are being administered according to their licensed indication we will not be actively soliciting Serious Adverse Events.

In addition, the following Serious Adverse Events will be exempted from requiring reporting, unless they result in death or are considered by the investigator to be related to the vaccines or a study procedure.

- Traumatic injuries
- Hospital admissions for intoxication
- Hospital admissions for deliberate self harm (although any underlying mental illness should be reported if considered medically significant as per SAE definitions)
- Planned hospital admission for management of pre-existing conditions (unless in response to a worsening of that condition since study enrolment)

The period of recording SAEs will be from the time of taking informed consent to the last study visit for that participant.

All SAEs (other than those defined in the protocol as not requiring reporting) must be reported on a SAE reporting form to both the Chief Investigator and the Oxford Vaccine Group (mencarriage@ovg.ox.ac.uk) within 24 hours of the Site Study Team becoming aware of the event. The CI or delegate within the OVG will perform an initial check of the report, request any additional information. OVG will forward the SAE form to the Sponsor (CTRG) via the safety reporting mailbox for review by the Medical Monitor and Trial Safety Group. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and emailed to CI or delegate within the OVG who will review and forward updated information to the Sponsor (CTRG). Additionally all SAEs from MenB-fHBP sites will also be reported to Pfizer. Requests for clarification or further information from CTRG or Pfizer will be directed through the OVG via the above study email who liaise with the relevant site.

10.5. Procedure to be followed in the event of an abnormal finding

In the event that the throat swabs grow an unexpected pathogen such as gonococcus, the relevant swab and isolate will be re-analysed to ensure that it not a spurious result. If a growth of gonococcus is confirmed the participant will be informed by a clinical study team member. While all participants will be over 16 years of age, the staff member will have had training in child safeguarding and sexual exploitation. If the participant is agreeable, their GP will be notified in writing. The participant will be referred to the local GUM (genitourinary medicine) unit for follow up and management.

10.6. Expectedness

Expectedness will be determined according to the Summary of Product Characteristics.

10.7. SUSAR Reporting

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

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

10.8. Safety Monitoring Committee

The Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group (TSG) will conduct a review of all SAEs for the trial reported during the quarter and cumulatively. The aims of this committee include:

- To pick up any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

10.9. Development Safety Update Reports

The Oxford Vaccine Group 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.

11. STATISTICS

11.1. Description of Statistical Methods

The statistical methods will be fully described in the statistical analysis plan (SAP), and are briefly outlined here. (Note that the SAP will be reviewed by an independent statistician). All analyses will be performed using Stata software. Analysis of pharyngeal carriage will use a modified intention-to-treat (MITT) population that includes all participants providing an evaluable swab at 12 months. Data will only be excluded if consent for data use has been withdrawn by the student. All analyses will take into account the estimated design effect.

Descriptive analysis

The data will first be described in tables and figures and using summary statistics. Recruitment rates, drop-outs and exclusions will be summarized overall and by site. The percentage of subjects with *N. meningitidis* carriage and the associated 95% Clopper-Pearson confidence intervals (CIs) will be tabulated for each vaccine group and the control group both at baseline and at 12 months. Responses to each of the questions from the questionnaire will be tabulated in one-way tables to provide a descriptive account of the results; for continuous data mean, median and inter-quartile range will be reported. Factors associated with carriage at the first visit will be investigated using multivariable

logistic regression.

Carriage prevalence

The data will be structured so that carriage (a binary outcome) is measured at two time-points (baseline and 12 months) in each group; in the intervention arms these measures are taken before and after vaccination. There are thus repeated measures taken in participants and potential clustering of outcomes within schools (and potentially by site). For all models both vaccine arms will be compared independently to the control arm – there is no planned comparison between vaccine arms. We will first use multivariable logistic regression including baseline carriage status and risk factors as covariates if they are found to differ between study arms at baseline. We will further take into account the timing (month) of the outcomes given several waves of recruitment at different points in the year and school-level vaccine uptake. Odds ratios (ORs) and the associated two-sided 95% CIs will be calculated; carriage reduction will be calculated for the comparisons as (1 – OR) multiplied by 100. We will consider each of the primary and secondary endpoints in turn. Before considering whether any subgroup analyses are warranted we will assess the factors associated with carriage at baseline. We will also use a generalized estimating equation (GEE) approach ((binary response), which are flexible in handling many types of unmeasured dependence between outcomes that may arise in a multi-site study such as this.

Acquisition of carriage

A new acquisition of carriage is defined as the detection of an *N. meningitidis* isolate that was undetected at baseline. The percentage of participants with new acquisitions of *N. meningitidis* carriage will be calculated with two-sided 95% confidence intervals for each vaccine group and the control group at 12 months from baseline. The odds ratio (ORs) of new carriage acquisition by the 12 month visit and any difference in acquisition between control and vaccine arms will be analysed using a logistic regression model including baseline carriage status and risk factors as covariates if they are found to differ at baseline.

Baseline analysis

As the study is organised into several 'waves', with samples processed throughout the study, we have an opportunity to undertake a baseline analysis after wave 2, when approximately 50% of participants have had their first swab.

The primary aim of this baseline analysis is to ascertain whether the assumptions made regarding carriage prevalence in the sample size calculation were reasonable. As the prevalence of carriage is somewhat unpredictable, we may find that we had over or underestimated prevalence or our power to detect an effect. The baseline analysis will thus focus on the prevalence of carriage at the first visit, particularly prevalence of groups B, C, W, Y, X. The serogrouping data from wave 1 and 2 will likely be available March 2019. We will also have an opportunity to examine retention rates from wave 1 (i.e. the proportion of participants who return for a second swab) around the same time to ascertain whether our assumption of 80% retention is realistic.

A baseline analysis report will be prepared by Dr Caroline Trotter and the study Chief Investigator, according to a pre-specified analysis plan and submitted to the independent scientific advisory committee comprising external observers (minimally one member proposed by NIHR and one

experienced statistician). This may give us an opportunity to revise our final sample size and alter recruitment targets for the final wave.

11.2. The Number of Participants

24, 000 participants will be recruited, 16 000 of these will be in vaccine groups and 8,000 in an unimmunised control group.

11.3. Sample Size and the Level of Statistical Significance

Study visits were stopped in March 2020 due to the SARS-CoV-2 pandemic, resulting in the inability to collect the majority of '12 month' throat swabs from participants recruited in wave 3 and wave 4. This has necessitated a re-calculation of the sample size and microbiological methods of carriage detection.

Original sample size estimate

The prevalence of culture-confirmed genogroup B meningococci in the MenCar4 study was 1.6%, that of hyper-invasive meningococci was 2.3%, and the combined prevalence of group B C, W, Y or X meningococci was 4.3%. In this current study, the initial sample size calculations assumed a conservative carriage estimate of 3.43% for genogroup B, C, W, Y or X meningococci. A sample size of 8,000 per immunisation arm would provide 80% power to detect a 30% reduction of these strains assuming a retention rate of 80%, a design effect of 1.5 and a significance level of 0.05..

Revised sample size estimate and effect size calculation

1.Revised estimates of number of participants completing study.

As of the suspension of study visits in March 2020, 11201 participants had completed their second swab at visit 3. The original sample size calculation anticipated study completion by 19200 participants (i.e. assuming 80% retention).

2. Revised estimate of carriage prevalence

The baseline analysis of 13448 participants showed a baseline carriage prevalence of genogroup B, C, W, Y or X of 2.1% (95% CI 1.86 – 2.36) in all participants. However in those that attended Visit 3 (compared with those participants who did not attend their final visit), the baseline carriage rate is lower, at 1.85%. The design effect, accounting for clustering within schools, estimated on baseline carriage is 2.08, higher than the design effect of 1.5 used in the sample size calculations. Current sample processing supports a 50% increase in carriage through to the final swab and this corresponds to an estimated carriage prevalence of 2.77% at the final throat swab. Using the available data from completed participants (n=11201) and using culture/gram stain methods of carriage identification, will detect a 48% reduction in carriage at 80% power.

3. Updated detectable effect size using Culture-amplified PCR lo determine carriage prevalence

Carriage prevalance using caPCR yields approximately double the rate of carriage compared with conventional bacterial techniques [unpublished data Prof A Finn].

Assuming carriage prevalence of 5.55% detected by caPCR, the sample size of completed participants of approximately 3700 per group will detect a 35% reduction between the control and each vaccine group separately at 80% power.

Carriage rates by conventional culture and by caPCR will be reported separately.

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

There will be no imputation of missing data in the primary analysis.

11.5. Inclusion in Analysis

All participants providing an oropharyngeal swab at the first and final study visits will be included in the analysis for carriage prevalence at that time point. Analysis evaluating acquisition of meningococci will only be conducted on participants providing samples at both time points.

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

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

12. DATA MANAGEMENT

12.1. Source Data

Participants will complete questionnaires reporting demographic information relevant to meningococcal carriage prevalence; these will be completed directly by the participants on electronic tablets (direct data entry) or if this option is not available onto anonymous paper records that will subsequently be transcribed.

All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the contact sheet and the signed consent form, the participant will be referred to by the trial participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. Ultimately any meningococcal genome sequence data deriving from the isolates, without participant identifying information, will be made available publicly.

12.3. Data Recording and Record Keeping

Data will be stored on a validated online clinical trial database (e.g. REDCap) developed at the Oxford Vaccine Group and hosted by the University of Oxford servers. This database has restricted access, is password-protected, with accountability tracking, enabling compliance with regulatory guidelines such as FDA 21 CFR Part 11.

Each subject will be given a single, unique study number. Laboratory specimens will be identified with pre-printed, barcoded labels. The name of participants and corresponding study number will be kept on a separate and secure database. Centres will use their preferred method of data capture – paper questionnaires or electronic capture. All identifiable data collected will be stored at the Local Study Site and accessed by research staff, regulatory authorities and monitors. The exception to this is a REDCap database hosted by Oxford University for the school absence survey (as a separate database to the eCRF and questionnaire). This study activity was stopped in protocol version 5.0. This database will include the participant's email address and will be anonymized as soon as practicably able. Participant emails will either be entered directly on to the REDCap database by local study teams, or be transferred using an encrypted file transfer platform and the study data manager will upload in to REDCap. Access to the database will be restricted and controlled by the Study Data Manager at the Oxford Vaccine Group.

Data will be cleaned and analysed using Stata (or other appropriate statistical software if required).

Personal data will be kept until the youngest participant turns 21 years of age. Anonymised research data will be stored indefinitely. Storage of this data will be reviewed every 5 years and destroyed if no longer required.

13. QUALITY ASSURANCE PROCEDURES

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

Regular monitoring will be performed according to GCP and as specified in a risk adapted monitoring plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

An independent scientific advisory committee will be formed to advise on the interpretation of the planned baseline analyses, and provide ad-hoc advice as required.

A management committee comprising of the grant co-applicants, together with Stephen Gray (microbiologist) and Dr Jenny MacLennan will confer monthly during study set up and recruitment periods.

14. SERIOUS BREACHES

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

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

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

(b) the scientific value of the trial".

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

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Declaration of Helsinki

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

15.2. Guidelines for Good Clinical Practice

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

15.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.4. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

15.5. Participant Confidentiality

Participants will be identified only by a participant ID number (+/- participant initials) on all trial documents and on the validated trial database with the exception of the contact sheet, the informed consent form, the password-protected site-specific study management databases (for example Microsoft Access). and the inclusion of a participant email on a secure Oxford University hosted REDCAp database for the school absence survey (commenced but then discontinued in protocol version 5.0). All documents will be stored securely and only accessible by trial staff and authorised

personnel. The trial will comply with the General Data Protection Regulation and Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Given the visits for this study are often occurring in school halls, an awareness amongst study participants and study staff of which students at their school are participating is inevitable. Similarly, school staff may, on their own initiative, record the names of students who are participating in this study, or are interested in doing so, and use this to coordinate study visits. Nevertheless, a participant's medical history and questionnaire responses will be held in strict confidence. The involvement of a student in this study will not be shared beyond that student's school and (if required) the student's general practitioner.

15.6. Expenses and Benefits

As the study team will be making visits to schools to conduct the trial, and no travel will be necessary for the participants, provision will not be made for travel expenses. As part of the student engagement programme, all participants completing the throat swab at visit 3 will be automatically enrolled in a 'Be on the TEAM' prize draw, awarding age appropriate prizes (e.g. headphones), with approximately 1 prize per 1000 participants (drawn proportionally for the recruits in each 'wave'). This will assist in optimising participant retention to maintain the statistical power of the study. Given the impact of SARS-CoV-2, all Wave 3 and Wave 4 participants attending their first visit will be eligible for the prize draw.

15.7. Other Ethical Considerations

The potential for isolation of gonococcus has been considered and the response to this outlined in section 10.5.

One third of participants enrolled into this study will only receive a MenB immunisation at the end of this study, potentially creating concerns that they are at a comparative disadvantage to those enrolled in the vaccine arms. In this respect it is important to bear in mind that adolescent MenB immunisation is not routine in the UK, and that all participants in this study will be receiving an additional immunisation compared to their peers.

16. FINANCE AND INSURANCE

16.1. Funding

The direct research costs of this study are being funded by NIHR Policy Research Programme. The Department of Health have agreed to cover the costs of vaccine administration, and NIHR the NHS service support costs. The vaccine MenB-fHBP (Trumenba) is being provided free of charge by Pfizer.

16.2. Insurance

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

17. PUBLICATION POLICY

Presentation of data and publications arising from this study will be coordinated by the chief investigator.

This study is expected to result in several papers which will be submitted to peer reviewed journals for consideration of publication. Authorship and order of authorship will be agreed upon in advance of development of publications. Publications will include a description of the contributions of each author and how the order has been assigned. This is likely to place the person who took the lead in writing the manuscript or doing the research first, and the most experienced contributor in the field last.

Authorship of publications will include all of those who meet the following criteria:

- substantial contribution to concept and design, acquisition of data, or analysis and interpretation of data
- drafting the article or revising it critically for important intellectual content
- final approval of the version to be published

Other collaborators or members of the research group who may have contributed to some but not all of these criteria will be listed in the acknowledgements.

Results will be disseminated to trial participants via principals and head teachers, via school newsletters, and by informing schools of the publication of trial papers. Given the number of participants enrolling we will not be directly informing trial participants directly about publications.

18. REFERENCES

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19. APPENDIX A: List of study Investigators

Site	Principal Investigator
Oxford Vaccine Group	Dr Matthew Snape
St Georges University Hospitals	Professor Paul Heath
NHS Greater Glasgow & Clyde / University of Glasgow	Dr Andrew Smith
Royal Alexandra Childrens Hospital, Brighton and Sussex University NHS TRUST	Dr Katy Fidler
Bristol Childrens Vaccine Centre	Professor Adam Finn
University Hospital Southampton NHS Foundation Trust	Professor Saul Faust
Royal Manchester Children's Hospital	Dr Stephen M Hughes
Wrightington , Wigan and Leigh NHS Foundation Trust	Dr Christos Zipitis
Stockport NHS Foundation Trust	Dr David Baxter
Imperial Healthcare NHS Trust	Dr Elizabeth Whittaker
Cardiff	Dr Christopher Williams
University of Nottingham Health Service	Dr David Turner
Maidstone and Tunbridge Wells NHS Trust	Dr Rohit Gowda
University of Oxford Dept of Zoology	Professor Martin Maiden
Public Health England Meningococcal Reference Laboratory, Manchester	Professor Ray Borrow
Plymouth Hospitals NHS Trust	Dr Mala Raman
Lancashire Care NHS Foundation Trust	Dr David Orr
Northamptonshire Healthcare NHS Foundation Trust	Dr Sujata Khajuria

20. APPENDIX B: AMENDMENT HISTORY

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

Amendment No. 2

Protocol Version No. 2

Date issued: 10/Aug/2018

Author(s) of changes: J.Carr/M.Snape

Details of Changes made
• Addition of Professor Sir Brian Greenwood as chair of the scientific advisory board, and identification of James Stuart as Deputy chair • Alterations of wording describing study design in background to correct errors and avoid ambiguity • Clarification throughout document that participants recruited in Scotland are recruited at S5 year level • In section 6 (trial design) and elsewhere o Modification on study intervals to allow a reduction of dose 1 to dose 2 interval to 5 months in the '4CMenB' group, and the interval between swab 1 and swab 2 to 11 months (all groups), in order to allow greater flexibility to fit around the school year. • In section 7.1, 7.2 and 7.3 o Modification of inclusion/exclusion criteria to specifically exclude participants with medically diagnosed bleeding disorders and (for (4CMenB) latex allergy o Outline of process by which appropriately trained nurses can assess participant eligibility o Removal of binary specific gender inclusion criteria • In sections 7.2 and 8.6: o Clarification that throat swabs will be stored following the end of the study, as well as bacterial isolates • In section 8.2 o Specification that consent can be taken by doctors, nurses or appropriately trained non clinical staff o Clarification on classification of allocation of participant numbers, vs participants considered 'enrolled' • In section 8.4 o Re-ordering of study procedures • In section 8.7 o Clarification of guidelines for participant withdrawal • In section 10.4 o Reporting of any SAEs to occur following administration of MenB-FHBP to Pfizer • In section 12.3 o Updating of sample handling process • In section 15.5 o Updating of participant confidentiality section to recognize that school staff and students are likely be aware of which students are participating in this study • addition of sites – e.g. Preston, Plymouth

• Update of PIs

Amendment No. 5

Protocol Version 3.0 Dated 14-Dec-2018

Date Issued 19-Feb-2018

Details of Changes Made
In section 4 Background and Rationale • Clarification to state school/college • Refers to Section 6 for community visits In section 6 Trial Design • Additional guidance about community visits • Clarification about voluntary nature of MenB vaccination in control groups (also in table 1: Study Design) In Section 7.3 Exclusion Criteria • Modification of exclusion criteria to allow participation in throat swabs & questionnaire for participants who are medically ineligible to receive immunisation In Section 8.7 Discontinuation / Withdrawal • Clarification about optional nature of immunisation in control groups In Section 9.4 Accountability of the Trial Treatment • Includes statement about the use of Patient Group Directions and labelling of IMPs In Section 10.4 Reporting Procedures for SAEs • Addition of an SAE exemption for planned hospital admissions for management of pre-existing conditions In Section 11.1 Description of Statistical Methods • Removal of interim analysis of vaccine effect after Wave 1 • Clarification of baseline analysis of baseline carriage and retention rates in order to inform potential adjustment of sample size and recruitment in Wave 4 In Section 11.4 Criteria for End of the Trial • Delete early termination of the study because the interim analysis has been removed In Section 14.6 Expenses of Benefits

• Refinement of prize-draw

Amendment No. 7

Protocol Version 4.0

Date Issued 09/08/2019

Details of Changes Made
In Section 5 Objectives and Outcome Measures • added exploratory Objectives: o school absence survey following vaccination o carriage impact of UK Adolescent MenACWY programme In Section 6 Trial Design (Table 1) • expanded window of V3 visits from 15 to 17 months to allow for more time to schedule mop-up visits at schools and the communities • school absence survey added to study schedule (new participants only) In Section 7.4 Eligibility Assessment at enrolment and reconfirmation at subsequent visits • non-clinical staff permitted to reconfirm ongoing eligibility at visit 3 for the 4CMenB or MenB-fHBP groups only where the only study procedure is a throat swab In section 8.2 Informed Consent • Added optional consent to be contact for future research studies (Wave 4 New participants (with a new version of the ICF) and also currently enrolled participant who will sign a specific ICF for consent to store information for future contact) In Section 8.4 Baseline Assessments and 8.5 Subsequent Visits • School absence survey added to study assessments In section 8.7 Discontinuation / Withdrawal • Clarification that participants in the 4CMenB or MenB-fHBP who don't attend Visit 2 (vaccination) may be offered their 2nd immunization on the same day as their Visit 3, In section 10.4 Reporting Procedures

- Changed reporting procedures for SAEs which will first be checked by the Chief Investigator or delegated medical officer at the Oxford Vaccine Group , who will then be responsible for forwarding to CTRG

In Section 12.3 Data Recording and Record Keeping

- Details of REDCap database hosted by Oxford University
- Addition of email for the school absence survey to separate REDCap database
- Clarity in handling anonymized data

In Section 15.5 Patient Confidentiality

- Updates storage of personal information

Amendment No. 8

Protocol Version 5.0

Date Issued 24th Jan 2020

Details of changes made
In section 6 Trial design • Footers of Table 2a and 2b, relating to timing of study visit, updated to reflect all months' final swab may be collected for participants recruited in Wave 2 • Clarity that visits may occur outside of the calendar months named but will be conducted within study timelines outlined within table 1. In section 8.5 Trial producers • modified to outlined additional interventions that may be used to promote retention of participants to visits 2 to 4: texting/emailing to remind participant of upcoming visit, school assemblies, video, posters and flyers, information about the study and upcoming visits provided through study websites, newsletters and social media Sections 8.6 to 8.8 re numbered to accommodate addition of section 8.5 Section 10.4 Clarification of SAE reporting process where request for further information from CTRG or Pfizer is directed to OVG who will liaise with the responsible site Discontinuation of the exploratory objective to determine school absence rates following immunisation due to a low response rate and to focus on primary & secondary objectives

Amendment No. 11

Protocol Version 6.0

Date Issued 13-Oct-2020

Details of changes made

This amendment provides modifications to the study required as a result of the SARS-CoV-2 pandemic, notably stopping of all clinical visits.
 	
• Section 4
  o Update of literature with results of the "B Part of it" RCT
  o All study visits stopped due to impact of the SARS-CoV-2 pandemic
• Section 8.7 revised definition of the end of the trial
• Section 11.3 Revised Sample Size & Power Calculations
  o Updated carriage rates and sample size
• Section 11.3 'criteria for the end of the trial' removed as this is documented in 'definition of the end of the trial' section 8.7
• Section 12.3 & 15.5 minor change to data handling and participant confidentiality sections that clarify that the school absence survey has been discontinued
• Section 16
  o Updated Prize Draw

Amendment No. 12

Protocol Version 6.1

Date Issued 18-Nov-2021

Details of changes made
Extension of end of trial date to 30/11/2022 to allow for completion of laboratory analysis.

Amendment No. 13

Protocol Version 7.0

Date Issued 28-Feb-2022

Details of changes made
Section 8.5, figure 1 and section 11.3 revised laboratory methods and sample size calculations for the addition carriage prevalence determined by culture-amplified PCR. Extension of end of trial date to 31/12/2023 to allow for additional laboratory analysis.