Better Outcomes in Babies with Bacterial meningitis (BOBBi) - a multisite, open-label, two-arm, parallel-group, pragmatic, randomised controlled trial to compare dexamethasone versus no dexamethasone as treatment in babies with suspected bacterial meningitis: the BOBBi Protocol

ISRCTN Number: 17216564

Protocol Version No and Date: V1.0 15 April 2026

Chief Investigator:	Professor Paul Heath City St George's, University of London
Co-Lead Investigator (UK):	Professor Chris Gale Imperial College London
Paediatric Lead (UK):	Dr Ifeanyichukwu Okike University Hospitals of Derby and Burton NHS Foundation Trust
Co-Lead Investigator (Canada):	Professor Manish Sadarangani University of British Columbia
Statistician:	Dr Rema Ramakrishnan University of Oxford

Overarching study sponsor:	City St George's, University of London
Sponsor for UK sites:	City St George's, University of London
UK Sponsor Reference:	2025.0274
Sponsor for Canadian sites:	University of British Columbia
IRAS Number:	1013356
EudraCT Number:	N/A
REC Reference:	26/SC/0146
Funders:	NIHR Health Technology Assessment (HTA) Programme Canadian Institutes of Health Research (CIHR)

Funder References:	NIHR ref:	NIHR166133
	CIHR ref:	PJT-203801

Chief Investigator Signature: Paul T. Heath Apr 21, 2026

Statistician Signature: Rema Ramakrishnan 20/04/26
Rema Ramakrishnan (Apr 20, 2026 14:55:57 GMT+1)

For and on behalf of the UK sponsor signature:
Rebecca Pararajasingam (Apr 20, 2026 15:16:56 GMT+1) Apr 20, 2026

Conflict of interest: There are no conflicts of interest to declare

TABLE OF CONTENTS

1. KEY TRIAL CONTACTS 8
2. PROTOCOL STRUCTURE 9
3. LAY SUMMARY 10
4. TRIAL FLOWCHART 12
5. SYNOPSIS 13
6. ABBREVIATIONS 18
7. BACKGROUND AND RATIONALE 20
   - 7.1. Burden of bacterial meningitis 20
     - 7.1.1. Burden of bacterial meningitis in babies in the UK 20
     - 7.1.2. Burden of bacterial meningitis in babies in Canada 20
   - 7.2. Longer term outcomes of bacterial meningitis 20
     - 7.2.1. Longer term outcomes of bacterial meningitis in babies in the UK 20
     - 7.2.2. Longer term outcomes of bacterial meningitis in babies in Canada 21
   - 7.3. Corticosteroids (steroids) as therapy in bacterial meningitis 21
   - 7.4. Diagnosing bacterial meningitis in babies 21
     - 7.4.1. Relative incidence of viral and bacterial meningitis in babies 22
     - 7.4.2. Outcomes of viral meningitis 22
     - 7.4.3. Differentiating bacterial from viral meningitis 22
     - 7.4.4. Safety of steroids 23
   - 7.5. Aim 23
   - 7.6. Research question 23
8. OBJECTIVES AND OUTCOME MEASURES 24
   - 8.1. Longer-term follow-up 27
9. TRIAL DESIGN 28
   - 9.1. Internal pilot progression criteria 28
     - Table 1: Internal pilot trial progression criteria 28
10. PARTICIPANT ELIGIBILTY CRITERIA 28
    - 10.1. Inclusion criteria 28
    - 10.2. Exclusion criteria 29
    - 10.3. Definitions of meningitis 29
      - 10.3.1. Bacterial meningitis (BM) 29
      - 10.3.2. Non-bacterial meningitis (non-BM) 30
      - 10.3.3. Confirmed viral meningitis 30
11. TRIAL PROCEDURES 30

11.1. Recruitment 30
11.1.1. Trial setting 30
11.1.2. Inter-hospital transfers 30
11.1.3. Participant identification 31
11.1.4. Screening and eligibility assessment 31
11.1.5. Recruitment to other studies 31
11.2. Informed consent 31
11.2.1. Longer-term follow-up beyond 2 years 33
11.2.2. Discharge or death prior to written consent being sought 33
11.2.3. Consent declined 33
11.3. Discontinuation and withdrawal of participants 33
11.3.1. Withdrawal of consent 33
11.3.2. Discontinuation of the intervention 33
11.4. Randomisation 34
11.5. Blinding 34
11.6. Baseline data 34
11.7. Trial assessments 35
11.7.1. Payment 35
11.7.2. Feedback of outcomes to families 35
11.8. Blinded Endpoint Review 35
11.9. Sample handling 36
11.10. Definition of End of Trial 36
12. TRIAL INTERVENTIONS 36
12.1. Trial arms 36
12.2. Investigational Medicinal Product (IMP) 37
12.2.1. Name and description of IMP 37
Table 2: IMP description 37
12.2.2. Regulatory status of the IMP 37
12.2.3. Product characteristics 37
12.2.4. Dosage 37
Table 3: Dosage of IMP for dexamethasone group 37
12.2.5. Blinding of IMP 38
12.2.6. Storage and supply of IMP 38
12.2.7. Preparation and labelling of IMP 38
12.2.8. Administering and prescribing IMP 38

12.2.9. Known drug reactions and interaction with other therapies 38
12.2.10. Concomitant medication 38
12.2.11. Compliance with trial treatment 39
12.3. Other treatments (non-IMPs) 39
12.4. Other interventions 39
12.5. Post-trial treatment 39
13. SAFETY REPORTING 39
13.1. Adverse event definitions 39
13.2. Assessment of causality 40
13.3. Justification of safety reporting requirements 41
13.4. Procedures for reporting adverse events 41
13.5. Requirements for Serious Adverse Event (SAE) reporting 41
13.5.1. From randomisation to 8 weeks from randomisation, only the following events should be reported as SAEs: 41
13.5.2. Where participation is withdrawn before 8 weeks, or parents/carers do not provide deferred consent 41
13.6. Reporting procedures for Serious Adverse Events 41
13.6.1. Procedure for immediate reporting of Serious Adverse Events 42
13.7. Expectedness 42
13.8. SUSAR reporting 42
13.9. Responsibilities 42
13.10. Overdose 44
13.11. Development Safety Update Reports 44
14. STATISTICS 44
14.1. Sample size determination 44
14.2. Statistical Analysis Plan (SAP) 45
14.3. Description of statistical methods 45
14.3.1. Descriptive statistics 45
14.3.2. Comparative analysis 45
14.4. Analysis populations 46
14.5. Data monitoring 46
14.6. Stopping guidelines 46
14.7. The level of statistical significance 46
14.8. Procedure for accounting for missing, unused, and spurious data 46
14.9. Procedures for reporting any deviation(s) from the original Statistical Analysis Plan 46
15. DATA MANAGEMENT 46

15.1. Source data 47
15.2. Access to data 47
15.3. Data recording and record keeping 47
16. QUALITY ASSURANCE PROCEDURES 48
16.1. Risk assessment 48
16.2. Monitoring 48
16.3. Trial committees 48
16.3.1. Project Management Group (PMG) 48
16.3.2. Co-Investigator Group (CIG) 48
16.3.3. Trial Steering Committee (TSC) 48
16.3.4. Data Monitoring Committee (DMC) 49
16.3.5. Blinded Endpoint Review Committee (BERC) 49
16.4. Patient and Public Involvement and Engagement (PPIE) 49
17. URGENT SAFETY MEASURES 49
18. PROTOCOL DEVIATIONS 50
19. DATA BREACHES 50
20. SERIOUS BREACHES 50
21. ETHICAL AND REGULATORY CONSIDERATIONS 50
21.1. Declaration of Helsinki 50
21.2. Guidelines for Good Clinical Practice 50
21.3. Approvals 51
21.4. Other ethical considerations 51
21.4.1. Informed consent in an emergency situation. 51
21.5. Reporting 51
21.6. Transparency in research 51
21.7. Participant confidentiality 52
21.8. Expenses and benefits 52
22. FINANCE AND INSURANCE 52
22.1. Funding 52
22.2. Insurance 52
22.3. Contractual arrangements 52
23. PUBLICATION POLICY 52
23.1. Dissemination 53
24. ARCHIVING 53
24.1. Minimum archiving period 53

24.2. Trial Master File 54
24.3. Investigator Site File and participant medical records 54
25. REFERENCES 54
APPENDICES 57
Appendix 1: Blinded Endpoint Review Committee (BERC) Eligibility Flowchart for Children With Confirmed Viral Meningitis 58
Appendix 2: Blinded Endpoint Review Committee (BERC) Eligibility Flowchart for All Children Except Those With Confirmed Viral Meningitis 59
Appendix 3: Relevant organisms 60
Appendix 4: Participant schedule of procedures 61
Appendix 5: Amendment history 63

1. KEY TRIAL CONTACTS

UK Sponsor	City St George's, University of London City St George's Joint Research & Enterprise Service (JRES) Cranmer Terrace London SW17 0RE On behalf of Sponsor Contact: Mark Cranmer Position: Director, Research and Innovation Services Email: sponsor@sgul.ac.uk
Canada Sponsor	University of British Columbia Innovation UBC, 103-6190 Agronomy Road, Vancouver, BC Canada V6T 1Z3 Tel 604 822 8580
International Coordinating Centre	National Perinatal Epidemiology Unit (NPEU) Clinical Trials Unit National Perinatal Epidemiology Unit Nuffield Department of Women's and Reproductive Health University of Oxford Email: bobbi@npeu.ox.ac.uk
Statistician	Rema Ramakrishnan NPEU Clinical Trials Unit National Perinatal Epidemiology Unit Nuffield Department of Women's and Reproductive Health University of Oxford Email: rema.ramakrishnan@npeu.ox.ac.uk
Committees	**Trial Steering Committee (TSC) Chair** Professor Mark Peters Professor of Paediatric Intensive Care Infection, Immunity & Inflammation Department University College London (UCL) Great Ormond Street Institute of Child Health Gower Street London WC1E 6BT Email: mark.peters@ucl.ac.uk **Data Monitoring Committee (DMC) Chair** Professor John Norrie Professor of Health and Social Sciences Methodology School of Medicine, Dentistry and Biomedical Sciences Queen's University Belfast 97 Lisburn Road, Whitla Medical Building Belfast BT9 7BL Email: j.norrie@qub.ac.uk

2. PROTOCOL STRUCTURE

The BOBBi core trial protocol describes the overarching procedures and information applicable to the international study. Each participating country will have a Country-specific Annex that provides additional details and outlines any local adaptations required to meet national or institutional requirements. These documents should be read together. For the purposes of this study, the term ‘protocol’ refers to the combination of this core trial protocol and the relevant Country-specific Annex.

.

3. LAY SUMMARY

Meningitis is a serious illness that affects the lining around the brain and spinal cord (a column of nerve tissue in the backbone); it is often caused by bacteria, germs that can be killed by antibiotics. Meningitis is more common in babies under 3 months of age. Unfortunately, even with current treatment, around 1 in 20 babies with bacterial meningitis die and 1 in 3 babies who survive have long-term problems like deafness, cerebral palsy (which affects movement and co-ordination) and learning difficulties. This is why we need to find better ways to treat it.

In older children with meningitis, giving steroids (medicines that reduce inflammation and swelling) alongside usual care can reduce serious long-term problems. But we do not know if steroids help babies with meningitis.

The BOBBi trial (**B**etter **O**utcomes in **B**abies with **B**acterial meningitis) will find out if giving steroids to babies with suspected bacterial meningitis means more survive without long term difficulties.

BOBBi will recruit babies up to 3 months of age who doctors think may have bacterial meningitis. This could be based on test results or if the baby has seizures (fits) or is unconscious and their doctors suspect bacterial meningitis. Babies will be randomly placed into one of two groups: one group will get a steroid called dexamethasone along with usual care, and the other group will get usual care without the steroid. Each baby has a 50:50 chance of being in either group.

Because bacterial meningitis is an emergency, doctors will start treatment and randomise babies into BOBBi straight away, without first asking the parents. Within about 48 hours, parents will be given full information about the trial and asked if they agree for their baby to stay in the trial and for information about their baby's health and development to be collected until they are 2 years of age. This is called "deferred consent" and will be approved by a research ethics committee. Parents can say no at any time, and this won't affect the care their babies would normally receive.

Some of the babies in the trial will later be found to have viral meningitis instead of bacterial meningitis. In these babies the steroids will be stopped as they are not expected to help in viral meningitis, but they are also not expected to cause any harm either. We still want to collect information about the health of these babies until they are 2 years old.

To understand how babies in BOBBi are doing, parents will be asked to fill in questionnaires when their baby leaves hospital and until they are 2 years of age. Researchers will also look at the baby's medical notes. They will see if there are any long-term effects on health, learning, or development and compare the outcomes of babies who received steroids with those who did not to see if there is a difference.

The BOBBi trial will recruit 965 babies over 4 and a half years from hospitals in the UK, and also a further 158 babies in hospitals in Canada. We will also ask parents if we can access routinely-collected, linked data about their child up to age 18 to understand whether there are any longer-term impacts.

The results of the BOBBi trial could help improve treatment for future babies with suspected bacterial meningitis, giving them a better chance of surviving and growing up without serious problems with their health or development.

4. TRIAL FLOWCHART

Better Outcomes in Babies with Bacterial meningitis, a randomised controlled trial: BOBBi

Inclusion criteria

- Babies must fulfil one of the following age-based criteria:
  1. Babies born at ≥37^{+0} gestational weeks:
     - Up to and including 3 months from their birth date

  OR
  2. Babies born at 34^{+0} to 36^{+6} gestational weeks:
     - Up to and including 3 months corrected age

  OR
  3. Babies born less than 34^{+0} gestational weeks:
     - Are between 32^{+0} corrected gestational weeks and 3 months corrected age inclusive

  AND
     - Are older than 7 days of age
- Planned or initiated treatment with antibiotics for suspected or confirmed bacterial meningitis based on having one or more of the following three clinical and/or laboratory features:
  1. Seizures or bulging fontanelle or altered consciousness (coma)
  2. Blood C-Reactive Protein (CRP) ≥20 mg/L* AND one or more of:
     a. raised cerebrospinal fluid (CSF) white cell count (>20/mm^3 for neonates ≤28 days post birth; >5/mm^3 for babies >28 days post birth)**
     b. CSF protein ≥0.8 g/L **
     c. CSF/blood glucose ratio <0.5
  3. Positive CSF Gram stain OR positive CSF polymerase chain reaction (PCR) for a relevant bacterium OR CSF culture for a relevant bacterium

**If CRP is not available then an abnormal procalcitonin (PCT) threshold may be used instead (i.e. ≥0.5 mg/dL)*
***When interpreting the results of CSF investigations, take into account red cells in the sample, which may suggest blood contamination or a different diagnosis. In the case of blood contamination if the CSF red blood cell (RBC) count is >=1000 cells/µL then CSF white blood cell (WBC) and CSF protein should be adjusted:*
- *subtract 1 WBC per 500 RBCs*
- *subtract 0.01 g/l protein per 1000 RBCs*

Exclusion criteria

- Where the randomisation cannot occur within 12 hours of the first administration of antibiotics for meningitis, or within 12 hours of the first administration of changed dose/type of antibiotics where antibiotics have been changed in dose or type for newly suspected or confirmed meningitis
- Previous neurosurgical intervention or shunt
- Known hypersensitivity to dexamethasone or any of its excipients
- Previous randomisation into this trial

Randomisation (1:1 allocation ratio)
Secure online randomisation

INTERVENTION
Dexamethasone (0.15 mg/kg intravenously, every 6 hours for 4 days) as therapy in suspected or confirmed bacterial meningitis, alongside treatment-as-usual based on national clinical guidelines

OR

COMPARATOR
Treatment-as-usual based on national clinical guidelines (without dexamethasone)

Primary Outcome

Survival without moderate or severe neurodevelopmental impairment at 24 months corrected for prematurity in preterm babies and at 24 months actual age for term babies, defined as any one or more of the following: cognitive impairment, language impairment, vision impairment, hearing impairment, seizures requiring anticonvulsant medication, gross motor impairment

Secondary outcomes

- **Total number of days spent in critical care; Length of hospital stay in days**: between randomisation and hospital discharge (with an upper limit of 8 weeks from randomisation)
- **Total number of days of antibiotic treatment for this episode of meningitis (including treatment for any relapse if applicable); Relapse of suspected or confirmed bacterial meningitis:** from randomisation to termination of antibiotic treatment for meningitis (with an upper limit of 8 weeks from randomisation)
- **Gastrointestinal haemorrhage; Hypertension requiring drug treatment; Hyperglycaemia receiving insulin treatment; Invasive infection**: between randomisation and hospital discharge or leading to re-admission at hospital up to 8 weeks from randomisation
- **Bacteraemia**: between completion of treatment for this episode of meningitis (including treatment for any relapse if applicable), and hospital discharge or leading to re-admission to hospital up to 8 weeks from randomisation
- **Re-admission after hospital discharge for further treatment for meningitis**: from hospital discharge to 8 weeks from randomisation
- **Individual components of the primary outcome (death; cognitive impairment; language impairment; vision impairment; hearing impaiment; seizures requiring anticonvulsant medication; gross motor impairment)**: at 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies (death up to 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies)
- **Behaviour problems assessed using the Child Behavior Checklist**: at 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies
- **Child-related quality of life; Parental quality of life**: at 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies (child adjusted for 12 month measures; parent adjusted for baseline and 12 month measures)
- **Country-specific outcomes**: as described in the Country-specific Annex (including UK health economic outcomes)

Longer-term follow-up

Parental consent will be sought to access long-term data (up to 18 years of age) to enable comprehensive data-linkage to assess the impact of meningitis on later outcomes (funded separately)

BOBBi trial flow chart 25Mar2026

5. SYNOPSIS

Trial title	Better Outcomes in Babies with Bacterial meningitis (BOBBi) - a multisite, open-label, two-arm, parallel-group, pragmatic, randomised controlled trial to compare dexamethasone versus no dexamethasone as treatment in babies with suspected bacterial meningitis
Short title	BOBBi
Trial registration	Name of registry: ISRCTN Registry ID: ISRCTNXXXXXXXX URL to registry record: tbc Date of Registration: tbc
Overarching Study Sponsor	City St George's, University of London
Sponsor for UK sites	City St George's, University of London
Sponsor for Canadian sites	University of British Columbia
Contact for public queries	bobbi@npeu.ox.ac.uk
Contact for scientific queries	Name: Professor Paul Heath Email: pheath@citystgeorges.ac.uk
Health condition studied	Bacterial meningitis
Clinical phase	Phase III
Trial design	A multisite, open-label, two-arm, parallel-group, pragmatic, randomised controlled trial with an integrated 18-month internal pilot phase. In the UK, the study will include an integrated health economic evaluation.
Trial participants	Babies from 32^{+0} corrected gestational weeks up to and including 3 months' corrected age at randomisation, with suspected or confirmed bacterial meningitis (BM). Babies born at term (37^{+0} or greater), may be enrolled up to 3 months from their birth date.
Eligibility criteria	**Inclusion criteria** • Babies must fulfil one of the following age-based criteria: ○ Babies born at ≥ 37^{+0} gestational weeks: ▪ Up to and including 3 months from their birth date OR ○ Babies born at 34^{+0} to 36^{+6} gestational weeks: ▪ Up to and including 3 months corrected age OR ○ Babies born less than 34^{+0} gestational weeks: ▪ Are between 32^{+0} corrected gestational weeks and 3 months corrected age inclusive AND ▪ Are older than 7 days of age • Planned or initiated treatment with antibiotics for suspected or confirmed bacterial meningitis based on having one or more of the following three clinical and/or laboratory features: 1. Seizures or bulging fontanelle or altered consciousness (coma)

	2. Blood C-Reactive Protein (CRP) ≥20 mg/L* AND one or more of: a. raised cerebrospinal fluid (CSF) white cell count (>20/mm^3 for neonates ≤28 days post birth; >5/mm^3 for babies >28 days post birth)** b. CSF protein ≥0.8 g/L** c. CSF/blood glucose ratio <0.5 3. Positive CSF Gram stain or positive CSF polymerase chain reaction (PCR) or culture for a relevant bacterium (see Appendix 3) **If CRP is not available then an abnormal procalcitonin (PCT) threshold may be used instead (i.e. ≥0.5 mg/dL)* ***When interpreting the results of cerebrospinal fluid (CSF) investigations, take into account red cells in the sample, which may suggest blood contamination or a different diagnosis. In the case of blood contamination:* *If the CSF RBC count is ≥1000 cells/µL then CSF WBC count and CSF protein should be adjusted* *- subtract 1 WBC per 500 RBCs* *- subtract 0.01 g/l protein per 1000 RBCs* **Exclusion criteria** • Where the randomisation cannot occur within 12 hours of the first administration of antibiotics for meningitis, or within 12 hours of the first administration of changed dose/type of antibiotics where antibiotics have been changed in dose or type for newly suspected or confirmed meningitis • Previous neurosurgical intervention or shunt • Known hypersensitivity to dexamethasone or any of its excipients • Previous randomisation into this trial
Sample size	The planned sample size is 965 babies randomised in approximately 60 sites in the UK. We also plan to recruit from international sites to enhance the generalisability of the trial. In Canada we have set a target of 158 babies to be randomised in approximately 14 sites, in addition to the 965 at UK sites.
Countries of recruitment	UK and Canada
Planned trial period	The total planned duration of the trial is 96 months: from 1 September 2025 (grant start) to 31 August 2033 (grant end). The duration of participation will be up to final follow-up assessment at 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies
Planned recruitment period	54-month recruitment period, including an 18-month internal pilot, planned from 1 June 2026 until 30 November 2030.

Objective	Outcome measure	Timepoint(s)
Primary Objective To determine if treating babies with suspected or confirmed bacterial meningitis with dexamethasone alongside treatment-as-usual based on national clinical guidelines, compared to not treating with dexamethasone, improves survival without moderate or severe neurodevelopmental impairment at 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies	Survival without moderate or severe neurodevelopmental impairment, defined as any one or more of the following: 1. Cognitive impairment 2. Language impairment 3. Vision impairment 4. Hearing impairment 5. Seizures requiring anticonvulsant medication 6. Gross motor impairment	24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies
Secondary Objective To evaluate the effect of dexamethasone, alongside treatment-as-usual based on national clinical guidelines, on other outcomes	Total number of days spent in critical care	Between randomisation and hospital discharge (with an upper limit of 8 weeks from randomisation)
	Length of hospital stay in days	Between randomisation and hospital discharge (with an upper limit of 8 weeks from randomisation)
	Total number of days of antibiotic treatment for this episode of meningitis (including treatment for any relapse if applicable)	From randomisation to termination of antibiotic treatment for meningitis (with an upper limit of 8 weeks from randomisation)
	Relapse of suspected or confirmed bacterial meningitis (relapse defined in Section 8)	
	Gastrointestinal haemorrhage	Between randomisation and hospital discharge or leading to re-admission to hospital up to 8 weeks from randomisation
	Hypertension requiring drug treatment	
	Hyperglycaemia receiving insulin treatment	
	Invasive infection	
	Bacteraemia	Between completion of treatment for this

		episode of meningitis (including treatment for any relapse if applicable), and hospital discharge or leading to re-admission to hospital up to 8 weeks from randomisation
	Re-admission after hospital discharge for further treatment for meningitis	From hospital discharge to 8 weeks from randomisation
	Individual components of the primary outcome: 1. Cognitive impairment 2. Language impairment 3. Vision impairment 4. Hearing impairment 5. Seizures requiring anticonvulsant medication 6. Gross motor impairment 7. Death	At 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies Death up to 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies
	Behaviour problems assessed using the Child Behavior Checklist (CBCL) for ages 1½ to 5 years completed by parent/carer	At 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies
	Child-related quality of life (QoL) assessed using the EuroQoL Toddler and Infant Populations Instrument (EQ-TIPS) questionnaire completed by parent/carer	At 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies and adjusted for 12-month measures
	Parental QoL, completed by parent/carer using the EuroQol-5 Dimensions 5 Levels (EQ-5D-5L) questionnaire	At 24 months of age corrected for prematurity in preterm babies; 24 months actual age

		for term babies and adjusted for baseline and 12-month measures
Country-specific outcomes	As described in the Country-specific Annex. In the UK, this includes an integrated cost-effectiveness analysis.	
Intervention	Dexamethasone 0.15 mg/kg intravenously every 6 hours (0.6 mg/kg daily dose) started within 12 hours of first antibiotic dose for suspected or confirmed bacterial meningitis, and administered for 4 days (total = 16 doses) as therapy alongside treatment-as-usual based on national clinical guidelines (indicated in the Country-specific Annex). If a virus is identified as the sole cause of the meningitis, or if antibiotics are stopped, any dexamethasone being administered for the purposes of the trial will be stopped.	
Comparator	Treatment-as-usual based on national clinical guidelines (without dexamethasone).	
Data sharing statement	De-identified participant data will be made available after the publication of the main findings upon reasonable request. Access to the dataset set may be granted for secondary analyses following review. Data access requests to be sent to the Chief Investigator for consideration. If approved, a data sharing agreement will be put in place.	

6. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BERC	Blinded Endpoint Review Committee
BM	Bacterial meningitis
BOBBi	Better Outcomes in Babies with Bacterial meningitis
BPD	Bronchopulmonary dysplasia
CBCL	Child Behavior Checklist
ChiMES	Childhood Meningitis and Encephalitis Study
CI	Chief Investigator
CI	Confidence interval
CIHR	Canadian Institutes of Health Research
CP	Cerebral palsy
CPS	Canadian Paediatric Society
CRF	Case Report Form
CRP	C-Reactive Protein
CS	Corticosteroid
CSF	Cerebrospinal fluid
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EV	Enterovirus
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels
EQ-TIPS	EuroQol Toddler and Infant Populations
GBS	Group B streptococcus
GCP	Good Clinical Practice
GMFCS	Gross Motor Function Classification System
GP	General Practitioner
HES	Hospital Episode Statistics
HRA	Health Research Authority
HRG	Health Resource Group
HSV	Herpes Simplex Virus
HTA	Health Technology Assessment
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IRAS	Integrated Research Application System
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous

LP	Lumbar puncture
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NHSP	Newborn Hearing Screening Programme
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NNTH	Number needed to harm
NPEU	National Perinatal Epidemiology Unit
OUHFT	Oxford University Hospitals NHS Foundation Trust
PARCA-R	Parent Report of Children's Abilities-Revised
PCR	Polymerase chain reaction
PCT	Procalcitonin
PI	Principal Investigator
PIL	Participant/Patient Information Leaflet
PMG	Project Management Group
PPIE	Patient and Public Involvement and Engagement
PV	Pharmacovigilance
QALY	Quality-Adjusted Life Year
QoL	Quality of life
RBC	Red blood cell
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RR	Risk Ratio
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering Committee
USM	Urgent Safety Measure
VM	Viral meningitis
WBC	White blood cell
WCC	White cell count

7. BACKGROUND AND RATIONALE

Bacterial meningitis (BM) is a serious infectious disease that affects adults, children and babies. Worldwide, in 2019, there were 1.2 million disability-adjusted life-years lost due to BM in babies under 28 days of age, with a further 4.4 million up to 1 year of age (1).

7.1. Burden of bacterial meningitis

7.1.1. Burden of bacterial meningitis in babies in the UK

A national UK and Ireland surveillance study conducted in 2010–11 identified 364 cases of BM in babies under 3 months of age over a 13-month period (2). Of these, 30% either died or had a serious central nervous system complication (seizures, motor disorder or abnormal neurology, hydrocephalus, hearing loss or extradural collection requiring intervention) at discharge, emphasising the considerable mortality and morbidity of this condition despite the use of effective antibiotics.

An analysis of the meningitis burden in all age groups in England, based on laboratory surveillance, showed that there was no substantial change in rates of bacterial meningitis in babies under 3 months of age over the period 2012–2019; the rate in babies being by far the highest of any age group in life (3).

Although there is limited evidence on the costs of meningitis care of babies in the UK (4) estimates based on expert opinion have quantified the UK lifetime costs of severe meningitis and septicaemia at £1.4–1.7 million per child (5).

7.1.2. Burden of bacterial meningitis in babies in Canada

The burden of BM in Canada is difficult to accurately estimate, because the predominant pathogens in young infants, group B streptococcus (GBS) and *Escherichia coli*, are not notifiable in most jurisdictions. Using data from studies conducted in single provinces or amongst a few paediatric centres (6-11), an estimated ~150–300 cases of BM occur per year in infants aged <90 days across Canada, with a total annual cost to the healthcare system of ~$4–5M. A recent population-based cohort study in Ontario reported 803 cases of GBS during 2012–2018 (7). A cohort study at 7 paediatric hospitals during 2013–14 identified 113 cases of BM in infants <90 days of age, of whom 74% had clinically significant sequelae (e.g., seizures, deafness, visual loss, motor disorders, developmental delay) and 7% died, despite appropriate antibiotic treatment and critical care support (11).

7.2. Longer term outcomes of bacterial meningitis

7.2.1. Longer term outcomes of bacterial meningitis in babies in the UK

There are only two UK studies reporting long term outcomes after BM in babies under 3 months of age, both of which found very high risk of neurodevelopmental impairment. One compared a national cohort of children who had meningitis born in England and Wales in 1996–7 (12), with children in two matched control groups without meningitis. At 5 years of age, questionnaires completed by general practitioners (GPs) and parents showed that 23% of children who had neonatal meningitis had a serious disability compared to 2% of GP recruited controls and 7% of hospital recruited controls. Notably, the overall incidence of serious disability was little changed over 11 years: 25.5% in 1985 and 23.5% in 1996. Another study included 51 children recruited 2010–2014; follow-up at 2–5 years of age using a developmental test and parent-completed

questionnaire revealed that 37% had moderate or severe neurodevelopmental impairment, including 11.8% with cerebral palsy (13). Notably, both studies demonstrated the validity of parent report questionnaires to identify neurodevelopmental impairment in this population. The paucity of data on long-term outcomes has led the National Institute for Health and Care Excellence (NICE) to make a recommendation for research to investigate long-term outcomes after bacterial meningitis in infancy (14, 15).

7.2.2. Longer term outcomes of bacterial meningitis in babies in Canada

There are limited data on long-term outcomes of BM in Canada, with studies focusing on specific populations and/or pathogens. In a recent Ontario study (7), infants with GBS had a 2-fold increased risk of neurodevelopment impairment by age 5 years, including higher rates of cognitive, motor, social/behavioural, and sensory impairments (16). In a study of preterm infants with meningitis, 32% had significant neurodevelopment impairment during follow-up to age 2 years (17). The paucity of data has led to international recommendations to assess long-term outcomes after infant BM (15).

7.3. Corticosteroids (steroids) as therapy in bacterial meningitis

Dexamethasone is a steroid that is currently recommended in older children with suspected or confirmed BM (NICE Guidance NG240, published 19 March 2024 (14), and Canadian Paediatric Society (CPS) Guidelines (18)). However, at present there is insufficient evidence to support the use of dexamethasone in neonates or babies up to 3 months of age (nor any other trial in progress (19)). We are proposing to address this research uncertainty in the BOBBi trial.

Evidence supports corticosteroids in older children with suspected BM. A systematic review and meta-analysis (20) identified 29 randomised controlled trials and included 3,433 children (under 18 years old); while overall this found no evidence of a difference in mortality for corticosteroids compared to control (risk ratio (RR) = 0.88; 95%CI, 0.74–1.06; 17 trials, 2,408 children), a reduction in neurological sequelae was found in children who received 0.6 mg/kg daily of dexamethasone therapy (RR = 0.60; 95%CI, 0.47–0.77; 11 trials, 1140 children); when the dosage increased to 0.8 mg/kg daily, the advantage was lost. The risk of hearing loss was also reduced when corticosteroids were administered compared with control (RR = 0.62; 95%CI, 0.47–0.81; 17 trials, 2,188 children).

Dexamethasone at a dose of 0.15 mg/kg given 6 hourly (0.6 mg/kg daily) for 4 days was the steroid used in the majority of studies in children and is currently recommended for bacterial meningitis in older children (14, 18); as above, neurological sequelae were significantly reduced in children using this dose but not reduced using a higher dose (20).

The available evidence suggests that steroids should be administered as early as possible in meningitis treatment. NICE guidance recommends "…that if corticosteroids could not be started before or with antibiotics then they should be administered within the 12-hour window" (14). CPS guidance recommends that corticosteroids should be administered "…immediately before, concomitant with, or within 4 hours of administering the first dose of antimicrobials. Clinical benefit is probably greater when steroids are received earlier within this 4-hour window."

7.4. Diagnosing bacterial meningitis in babies

Definitive diagnosis of meningitis requires sampling of the cerebrospinal fluid (CSF) via a lumbar puncture (LP). A small number of babies may not have an LP performed for a variety of reasons and will be treated

empirically for meningitis based on clinical signs alone (e.g. seizures). However, the vast majority of babies under 3 months will have an LP if meningitis is suspected. The first laboratory results available following an LP are microscopic and biochemical analysis of the CSF are generally available within 4 hours of the LP (14). The microbiological culture of the CSF, which will provide a definitive diagnosis of bacterial meningitis and is available in all sites, will usually take 24–48 hours. In some sites a polymerase chain reaction (PCR), which detects fragments of a virus or bacteria, may also be available and may provide a specific aetiology earlier, within 12–24 hours.

A common dilemma faced by clinicians when diagnosing BM is that babies with BM can have similar clinical presentations and laboratory (including CSF) findings, to babies with viral meningitis (VM) and other forms of meningitis. This means that some babies with suspected BM at both their initial assessment and immediately after their LP, will in fact be found to have VM when a definitive diagnosis based on microbiological or PCR results is made several days later. Giving antibiotics early in this situation is straightforward: the adverse consequences of antibiotics are minimal, even though they will be of no benefit to babies with VM, and the benefit of early antibiotics to babies with BM is great.

Because the available evidence suggests that steroids should be administered early in meningitis treatment to maximise potential benefit, in the BOBBi trial we will test giving dexamethasone within 12 hours of antibiotics (and as early as possible). This means that a proportion of babies who go on to be diagnosed with VM (rather than BM) a few days later will also receive steroids, which will be stopped when their diagnosis of VM is confirmed. There is no evidence that steroids would be harmful to babies with VM (21), but there is also no evidence that they will receive any benefit.

7.4.1. Relative incidence of viral and bacterial meningitis in babies

Between 2012 and 2016, children with suspected or confirmed meningitis or encephalitis were recruited from 31 UK hospitals (not including neonatal units) in the ChiMES study (22). There were 1,684 cases of suspected meningitis in babies under 3 months, of which 70 were confirmed BM and 316 were VM. The relative proportion of babies with BM to VM is expected to be higher in neonatal units.

7.4.2. Outcomes of viral meningitis

Outcomes following viral meningitis are much less severe than following BM. A national surveillance study of 703 cases of enteroviral (EV) meningitis (the most common viral cause of meningitis) in babies under 3 months of age (23) found mortality was 0.3% and the prevalence of any complications at 12 months (including seizures) only 0.6%; all had normal hearing at 2-year follow-up, similar to other reports (24).

7.4.3. Differentiating bacterial from viral meningitis

We have re-analysed data from the ChiMES study (22), to optimise our inclusion criteria and maximise the proportion of included cases with BM. The eligibility criteria include babies with clinical signs suggestive of BM but who do not have an LP performed, as well as babies who have an LP performed and have CSF and other laboratory findings that are suggestive of BM. In the ChiMES study, seizures were 4 times as common in BM compared with VM cases, and a bulging fontanelle over 6 times as common, hence these clinical signs form the inclusion criteria for the BOBBi trial. However, as most babies being assessed for suspected meningitis will have an LP performed, a combination of blood test and CSF findings will be used to guide trial inclusion (14). Data from ChiMES suggest that a combination of using the diagnostic thresholds for CSF cell counts and biochemistry recommended by the NICE meningitis guideline (14), together with a raised C-

Reactive Protein (CRP) >20 mg/L, will best predict BM. Procalcitonin (PCT) is often used as a biomarker for infection in place of CRP in Canada and other countries; an abnormal PCT threshold (i.e. ≥0.5 mg/dL) can be used in place of CRP where applicable(25).

7.4.4. Safety of steroids

There are no studies specifically assessing the long-term effects of steroids in babies born at or near term and under 3 months of age, other than the 2 neonatal trials in which they were used in bacterial meningitis (26, 27).

The only substantial evidence on the long-term sequelae of steroids in babies is from antenatal use to prevent complications of prematurity or postnatal use to prevent or treat bronchopulmonary dysplasia (BPD) in preterm babies. A recent Cochrane review comprehensively synthesised the evidence for steroids to prevent or treat BPD in preterm babies (28). This found no increased risk of long-term harm following late (≥7 days after birth) systemic administration of dexamethasone in preterm babies (less than 1,500g birthweight or under 33 gestational weeks) (29). There is however some evidence of long-term harm following early high dose steroids in preterm babies (30). For this reason, we will exclude babies born under 34 gestational weeks from the BOBBi trial if they have meningitis diagnosed in the first week after birth.

The limited data available support the safety of corticosteroids in babies with viral meningitis. One US study of 32 children who had viral or aseptic meningitis but had received a course of dexamethasone for presumed bacterial meningitis found no adverse consequences documented at post-discharge follow-up (21). Enteroviruses (EV) are the most common cause of viral meningitis, and an association has been reported between adverse outcomes and steroid use in children in China and Cambodia with a specific type of EV, called EV71, which causes outbreaks in the Asia-Pacific region. EV71 is very rare in the UK, accounting for only 20 of over 2,000 EV typed strains in 2022 (31).

Another recognised cause of viral meningitis in babies is herpes simplex virus (HSV), accounting for only 4/316 cases in ChiMES (22). Of note, in a non-randomised retrospective study of 45 patients with HSV encephalitis treated with acyclovir, outcomes at three months were better with the additional use of steroids (32).

7.5. Aim

In babies less than 3 months of age with suspected or confirmed bacterial meningitis, to evaluate whether administering dexamethasone, compared to not administering dexamethasone, alongside treatment-as-usual based on national clinical guidelines (indicated in the Country-specific Annex) is clinically effective.

In the UK, an integrated health economic analysis will evaluate whether administering dexamethasone, compared to not administering dexamethasone, alongside treatment-as-usual based on national clinical guidelines is cost-effective (described in the Country-specific Annex).

7.6. Research question

In babies between 32^{+0} corrected gestational weeks and 3 months' corrected age in preterm babies or 3 months of actual age in term babies with suspected or confirmed bacterial meningitis (**P**opulation), does administering dexamethasone alongside treatment-as-usual based on national clinical guidelines

(**I**ntervention), compared to treatment-as-usual without administering dexamethasone (**C**omparator), improve survival without moderate or severe neurodevelopmental impairment at 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies (**O**utcome)?

8. OBJECTIVES AND OUTCOME MEASURES

Primary Objective	**Primary Outcome Measures**	**Time point(s) of evaluation**
To determine if treating babies with suspected or confirmed bacterial meningitis with dexamethasone as an alongside treatment-as-usual based on national clinical guidelines, compared to not treating with dexamethasone, improves survival without moderate or severe neurodevelopmental impairment at 24 months of age corrected for prematurity	Survival without moderate or severe neurodevelopmental impairment, defined as moderate or severe impairment in any one or more of six domains specified below. Neurodevelopmental impairment will be assessed using parent-completed questionnaires, with additional review of routine clinical follow-up information by a Blinded Endpoint Review Committee for all children except those with confirmed viral meningitis, and also for children with confirmed viral meningitis where parent-reported data are missing or were completed outside of required timeframe, or parent-reported data indicate the child may have vision, hearing or gross motor impairment or seizures (see Appendix 1 and Appendix 2). **1. Cognitive impairment** • Moderate impairment defined by standardised developmental test score using -2 standard deviations (SD) to -3SD (PARCA-R non-verbal cognitive scale score 55–69) • Severe impairment defined by standardised developmental test score <-3SD (PARCA-R non-verbal cognitive scale score <55) **2. Language impairment** • Moderate impairment defined by standardised developmental test score -2SD to -3SD (PARCA-R language scale score 55–69) • Severe impairment defined by standardised developmental test score as <-3SD (PARCA-R language scale score <55)	At 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies

Primary Objective	Primary Outcome Measures	Time point(s) of evaluation
	3. Vision impairment • Moderate impairment defined as reduced vision even when wearing glasses, or blind in one eye with good vision in the contralateral eye • Severe impairment defined as blind or can only perceive light or light reflecting objects **4. Hearing impairment** • Moderate impairment defined as moderate sensorineural hearing loss in better hearing ear defined as 40–70 dBHL using at least 3 frequency average between 0.5 and 4 KHz or severe or greater hearing loss in one ear with normal hearing in the contralateral ear. • Where a child has a hearing aid but audiometric data are not available, hearing impairment will be classified as moderate or severe without further disaggregation • Severe impairment defined as severe or greater sensorineural hearing loss in better hearing ear defined as >70 dBHL using at least 3 frequency average between 0.5 and 4 KHz; or child has a cochlear implant (where audiometric data are not available) **5. Seizures requiring anticonvulsant medication** • Moderate impairment defined as seizures requiring anticonvulsant therapy at the time of assessment • Severe impairment defined as seizures requiring anticonvulsant therapy at the time of assessment with more than 1 seizure per month despite treatment **6. Gross motor impairment** • Moderate impairment defined as cerebral palsy (CP) with Gross Motor Function Classification System (GMFCS) Level 2; or unable	

Primary Objective	Primary Outcome Measures	Time point(s) of evaluation
	to walk or sit unaided if GMFCS data not available • Severe impairment defined as CP with GMFCS Level 3, 4 or 5; or unable to walk or sit even with support if GMFCS data not available	

Secondary Objective	Secondary Outcome Measures	Time point(s) of evaluation
To evaluate the effect of dexamethasone, alongside treatment-as-usual based on national clinical guidelines, on other outcomes	Total number of days spent in critical care • Number of days of neonatal intensive care (defined as per national standards, indicated in the Country-specific Annex) • Number of days of paediatric intensive care (defined as per national standards, indicated in the Country-specific Annex)	Between randomisation and hospital discharge (with an upper limit of 8 weeks from randomisation)
	Length of hospital stay in days	
	Total number of days of antibiotic treatment for this episode of meningitis (including treatment for any relapse* if applicable)	From randomisation to termination of antibiotic treatment for meningitis (with an upper limit of 8 weeks from randomisation)
	Relapse* of suspected or confirmed bacterial meningitis **Relapse defined as the reappearance of clinical and/or laboratory features of bacterial meningitis (as described in Section 10.1: Inclusion criteria) within 2 weeks of completing treatment for this episode*	
	Gastrointestinal haemorrhage	Between randomisation and hospital discharge or leading to re-admission to hospital up to 8 weeks from randomisation
	Hypertension requiring drug treatment	
	Hyperglycaemia receiving insulin treatment	
	Invasive infection defined as: • Isolation of a relevant bacterial or fungal organism from a normally sterile body fluid, such as pleural fluid, pericardial fluid, joint fluid, bone aspirate or deep tissue abscess (NOT from urine or CSF or blood) OR	

Secondary Objective	Secondary Outcome Measures	Time point(s) of evaluation
	• No isolation of a relevant organism, but clinician decides to treat as a deep-seated infection, such as empyema, osteomyelitis, septic arthritis, etc.	
	Bacteraemia Isolation of a relevant organism from blood (see Appendix 3)	Between completion of treatment for this episode of meningitis (including treatment for any relapse if applicable), and hospital discharge or leading to re-admission to hospital up to 8 weeks from randomisation
	Re-admission after hospital discharge for further treatment for meningitis	From hospital discharge to 8 weeks from randomisation
	Individual components of the primary outcome 1. Cognitive impairment 2. Language impairment 3. Vision impairment 4. Hearing impairment 5. Seizures requiring anticonvulsant medication 6. Gross motor impairment 7. Death	At 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies Death up to 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies
	Behaviour problems assessed using the Child Behavior Checklist for ages 1½ to 5 years (CBCL 1½–5) completed by parent/carer; defined as T score ≥64 for internalising or externalising problems	At 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies
	Child-related quality of life (QoL) assessed using the EuroQol Toddler and Infant Populations (EQ-TIPS) questionnaire completed by parent/carer	At 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies
	Parental QoL, completed by parent/carer using the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire	At 24 months of age corrected for prematurity in preterm babies; 24 months actual age for term babies
Country-specific objectives	As described in the Country-specific Annex. In the UK, this includes health economic outcomes.	

8.1. Longer-term follow-up

Parental consent will be sought to access long-term data (up to age 18 years of age) to enable comprehensive data-linkage to assess the impact of meningitis on later outcomes (funded separately).

9. TRIAL DESIGN

BOBBi is a multisite, open-label, two-arm, parallel-group, pragmatic, randomised controlled trial of an investigational medicinal product (CTIMP) with an integrated health economic evaluation and an 18-month internal pilot phase.

The trial flowchart and schedule of events are summarised in Section 4 and Appendix 4: Participant schedule of procedures respectively.

9.1. Internal pilot progression criteria

An internal pilot (over 18 months) will review progress across three domains relating to sites opened and participant recruitment using the criteria set out in Table 1. In addition, the proportion of cases that are confirmed as bacterial meningitis (BM) versus non-bacterial meningitis (non-BM) will be monitored.

Table 1: Internal pilot trial progression criteria

Progression criteria	**Red**	**Amber**	**Green**
% Threshold	*<60%*	*60–99%*	*100%*
Recruitment rate/site/6-months	<1.3	1.3–2.0	≥2.1
Number of sites opened	<36	36–59	≥60
Total number of participants recruited	<117	117–194	≥195

Green: continue into the main trial
Amber: mitigation, e.g., open new sites, identify and address site-specific issues through site visits and training, review in 6 months
Red: urgent detailed review of options with the Trial Steering Committee (TSC) and NIHR HTA

10. PARTICIPANT ELIGIBILTY CRITERIA

10.1. Inclusion criteria

- Babies must fulfil one of the following age-based criteria:

    1. Babies born at ≥ 37^{+0} gestational weeks:
        - Up to and including 3 months from their birth date

    OR

    2. Babies born at 34^{+0} to 36^{+6} gestational weeks:
        - Up to and including 3 months corrected age

    OR

    3. Babies born less than 34^{+0} gestational weeks:
        - Are between 32^{+0} corrected gestational weeks and 3 months corrected age inclusive

    AND

        - Are older than 7 days of age

- Planned or initiated treatment with antibiotics for suspected or confirmed bacterial meningitis based on having one or more of the following three clinical and/or laboratory features:
    1. Seizures or bulging fontanelle or altered consciousness (coma)
    2. Blood C-Reactive Protein (CRP) ≥20 mg/L* AND one or more of:
        a. raised cerebrospinal fluid (CSF) white cell count (>20/mm^3 for neonates ≤28 days post birth; >5/mm^3 for babies >28 days post birth)**
        b. CSF protein ≥0.8 g/L**
        c. CSF/blood glucose ratio <0.5
    3. Positive CSF Gram stain OR positive CSF polymerase chain reaction (PCR) for a relevant bacterium OR CSF culture for a relevant bacterium (see Appendix 3)

**If CRP is not available then an abnormal procalcitonin (PCT) threshold may be used instead (i.e. ≥0.5 mg/dL)*
***When interpreting the results of cerebrospinal fluid (CSF) investigations, take into account red cells in the sample, which may suggest blood contamination or a different diagnosis. In the case of blood contamination:*

If the CSF RBC count is ≥1000 cells/µL then CSF WBC count and CSF protein should be adjusted
- subtract 1 WBC per 500 RBCs
- subtract 0.01 g/l protein per 1000 RBCs

10.2. Exclusion criteria

- Where the randomisation cannot occur within 12 hours of the first administration of antibiotics for meningitis, or within 12 hours of the first administration of changed dose/type of antibiotics where antibiotics have been changed in dose or type for newly suspected or confirmed meningitis
- Previous neurosurgical intervention or shunt
- Known hypersensitivity to dexamethasone or any of its excipients
- Previous randomisation into this trial

Where approved, BOBBi will use a deferred consent model whereby babies with a diagnosis of suspected bacterial meningitis will be randomised when they meet the above criteria. Consent will subsequently be sought for ongoing trial participation and data collection (Section 11.2).

10.3. Definitions of meningitis

10.3.1. Bacterial meningitis (BM)

10.3.1.1. Confirmed bacterial meningitis

The definition of confirmed bacterial meningitis for the trial will be the presence of at least one of the following:

- A relevant bacterial pathogen present in CSF on culture or PCR;
- An abnormal CSF WCC, protein or glucose (see Inclusion criteria Section 10.1) and relevant bacterial pathogen present in blood on culture or PCR;
- A positive CSF Gram stain AND corresponding relevant bacterial pathogen present in blood on culture or PCR.

See Appendix 3 for list of relevant pathogens.

10.3.1.2. Possible bacterial meningitis

The definition of possible bacterial meningitis for the trial will be the presence of at least one of the following:

- A relevant bacterial pathogen present in blood on culture or PCR and no evaluable LP result
- A CSF WCC >500 after correction with no relevant viral/bacterial pathogen present on CSF or blood culture or PCR

See Appendix 3 for list of relevant pathogens.

10.3.2. Non-bacterial meningitis (non-BM)

All other situations not covered by Sections 10.3.1.1 and 10.3.1.2, and including confirmed viral meningitis *(Section 10.3.3).*

10.3.3. Confirmed viral meningitis

The definition of confirmed viral meningitis for the trial will be the presence of at least one of the following:

- A relevant virus present in CSF on PCR
- An abnormal CSF WCC (see Inclusion criteria Section 10.1) and relevant virus on blood PCR

See Appendix 3 for list of relevant pathogens including relevant viruses.

11. TRIAL PROCEDURES

See Appendix 4: Participant schedule of procedures.

11.1. Recruitment

11.1.1. Trial setting

Babies will be recruited at selected hospital sites comprising settings where babies with meningitis may present, as indicated in the Country-specific Annex.

11.1.2. Inter-hospital transfers

Participating sites will be either:

1. A recruiting site where babies may be recruited, randomised, commence, continue and complete participation in the trial;

OR

2. A continuing care site where the allocated trial arm will continue to be followed and data collected if a participating baby is transferred in from a recruiting site before cessation of the trial period.

The responsibility for data collection lies with the recruiting site. Networks of potential continuing care sites will be identified during the setup of recruiting sites, so that where possible, regulatory and local approvals to continue trial-related activities can be obtained in advance of any transfers from the original recruiting sites or admission to a continuing care site during the trial phase.

11.1.3. Participant identification

Eligible babies will be identified by the clinical care team and recruited by appropriately trained individuals.

11.1.4. Screening and eligibility assessment

Babies potentially meeting the eligibility criteria will be screened for eligibility by their clinical care team at the recruiting site.

Since the eligibility criteria do not require specific medical evaluation, assessment of eligibility is accepted to be within the scope of competency of appropriately trained and experienced doctors and nurses, as delegated by the Principal Investigator.

11.1.5. Recruitment to other studies

Co-recruitment of participating babies to other non-interventional studies would generally be permitted. Co-recruitment to another CTIMP may be possible following discussion and agreement between Chief Investigators of BOBBi and the other CTIMP, if perceived to not affect the outcome of either trial in any way. The burden to the family and risk to the safety of the patient of involvement in additional research will also be considered when making a decision.

11.2. Informed consent

The consent pathway may vary depending on applicable local regulations and ethical approvals, as detailed in the Country-specific Annex.

A deferred consent model is being used (also known as research without prior consent) where allowable in the trial jurisdiction, in keeping with other trials of interventions in emergency situations in children (33, 34) and adults. The deferred consent approach is supported and justified by the life-threatening and emergency nature of suspected bacterial meningitis in early infancy, and the importance of timely steroid administration to detect any potential benefit of the intervention.

When babies with a diagnosis of suspected bacterial meningitis meet the trial eligibility criteria they will be randomised to receive dexamethasone or no dexamethasone in addition to treatment-as-usual based on national clinical guidelines (indicated in the Country-specific Annex). This will most commonly be after a lumbar puncture has been performed and the CSF examination is strongly suggestive of bacterial meningitis, and when the likely diagnosis of bacterial meningitis has just been explained to the parents or carers.

After randomisation, parents or carers with legal responsibility (hereafter referred to as “parents/carers”) will be approached to discuss the trial as soon as appropriate – ideally within (but not limited to) 48 hours of randomisation and prior to hospital discharge. The site team will make every reasonable and appropriate effort to obtain written consent, taking into account individual circumstances. Where written informed consent is not obtained (see Sections 11.2.2 and 11.2.3), parents/carers will be informed about the trial, and data will be retained for trial use where permitted under applicable regulations and ethical approval, as detailed in the Country-specific Annex.

Parent information materials to explain the trial and the deferred consent approach have been co-designed with parents of babies who have experience of meningitis in early infancy and in collaboration with parent charities Meningitis Research Foundation (MRF) and Group B Strep Support (GBSS). These include an animation. Parent information materials will be translated into the most commonly used languages at trial sites, based on site assessments.

Written informed consent for ongoing trial inclusion and data collection will be sought during trial discussions. A Participant Information Leaflet (PIL) and Informed Consent Form will be presented to the parents/carers. A video may be used to aid understanding. These materials will detail 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 parent/carers may withdraw consent for the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to provide a reason for withdrawal of consent.

Parents/carers will be given the opportunity to consider the information, and to ask questions of the research team or other independent parties to decide whether they would like to consent to ongoing participation in the trial. Where parents do not have a good understanding of English, sites may use the translation and interpreting services which they routinely use in clinical practice for informed consent discussions whilst in hospital.

Parents/carers can decline to give consent (Section 11.2.3). If consent is given, parents/carers will be able to withdraw consent from further data collection and/or discontinue the intervention (if they have been randomised to the intervention arm) at any point. Further details around withdrawal of consent and discontinuation of the intervention are provided in Section 11.3.

If consent is given, a parent/carer must sign and date the latest approved version of the Informed Consent Form. Written informed consent will be obtained by means of parent/carer dated signature, and dated signature of the person who presented and obtained the informed consent.

The person who obtains the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. The original signed Informed Consent Form will be stored in the trial site file, with a copy filed in the baby’s medical notes, a copy provided to the parent/carer and a copy sent via secure document transfer to the National Perinatal Epidemiology Unit Clinical Trials Unit (NPEU CTU), University of Oxford.

11.2.1. Longer-term follow-up beyond 2 years

To enable follow-up of trial babies to assess the impact of meningitis on later outcomes (after 2 years and funded separately), additional, optional, parental consent will be sought to access routinely collected, linked data for up to 18 years of age. This will enable future comprehensive data linkage, as indicated in the Country-specific Annex.

11.2.2. Discharge or death prior to written consent being sought

In accordance with applicable local regulations and approved ethical frameworks, efforts will be made to obtain data for babies where written consent has not been obtained prior to discharge from hospital or death, as specified in the Country-specific Annex. The use of confidential patient information will be guided by the relevant national/local regulations, as indicated in the Country-specific Annex.

11.2.3. Consent declined

If deferred written informed consent is declined by the parent/carer, their baby will no longer participate in the trial. Therefore, if their baby is on the intervention arm (treatment with dexamethasone), this treatment will stop.

If a parent/carer declines consent for continued participation in the trial, and where this approach is approved by relevant regulatory and/or ethics authorities, parents/carers will be informed that a minimum amount of key safety data will be collected for trial purposes. This limited data collection is necessary to allow ongoing safety evaluation by the Data Monitoring Committee (DMC) and to ensure that any genuine safety signals in the trial are identified.

11.3. Discontinuation and withdrawal of participants

11.3.1. Withdrawal of consent

Parents/carers that have given written informed consent can withdraw consent for their baby to be involved in part or all of the trial at any point and for any reason, including no reason given. Changing their level of involvement in the trial will not affect their baby's ongoing clinical care. Withdrawal will be recorded on an eCRF and the reason detailed, if it has been provided.

Parents/carers have the right to withdraw their baby from some or all of the study data collection. Where parents/carers withdraw their baby from some or all of the continued data collection (via any method), and where this approach is approved by relevant regulatory and/or ethics authorities, data collected up to the point of change of consent will be used in the trial.

If parents/carers agree to ongoing data collection but wish to discontinue their baby taking part in the intervention arm (treatment with dexamethasone) this does not constitute a withdrawal, but a discontinuation of the intervention (as detailed below in Section 11.3.2).

11.3.2. Discontinuation of the intervention

Parents/carers will have the right to request to discontinue their baby's participation in the intervention arm (treatment with dexamethasone). The decision to discontinue the intervention will be recorded on an eCRF and data will continue to be collected unless the parent/carer requests to withdraw their baby from some or

all data collection (which would then constitute a withdrawal, as described above in Section 11.3.1). Discontinuation from the intervention will not affect their baby's ongoing clinical care.

In addition, the treating clinician may discontinue the allocated arm at any time, if they consider this to be in the best interests of the baby's health and wellbeing. The decision to discontinue permanently will be recorded on an eCRF and data will continue to be collected.

11.4. Randomisation

Randomisation of babies to either *treatment with dexamethasone* or *no treatment with dexamethasone* will be managed via a secure web-based randomisation facility hosted by the National Perinatal Epidemiology Unit Clinical Trials Unit (University of Oxford) with telephone backup available at all times (365 days per year). A Senior Trials Programmer at the NPEU CTU will write the web-based randomisation program and hold the allocation codes. The Senior Trials Programmer and a Senior Statistician will monitor implementation of the randomisation procedure throughout the trial. Randomisation reports will be provided to the DMC.

Randomisation will occur as soon as possible after a diagnosis of suspected bacterial meningitis, using a 1:1 allocation ratio. Randomisation will use a probabilistic minimisation algorithm. To ensure balance between the randomised groups, minimisation criteria will include: site, unit (neonatal or paediatric), presentation (as defined by inclusion criteria: included based only on clinical criteria [seizures or bulging fontanelle or altered consciousness/coma] or included based on any other criteria), chronological age at randomisation (days 0–3, days 4–7, days 8–28, day 29 and above), gestational age at birth (<28^{+0}, 28 to 31^{+6}, 32^{+0} to 36^{+6} and ≥37^{+0} weeks), and sex (male, female/indeterminate). Multiple birth sets are expected to be rare and will be randomised independently.

11.5. Blinding

BOBBi is an open-label study. It is expected that healthcare professionals and parents will know which arm a baby is allocated to. The DMC will monitor attrition, non-adherence and drop out by allocated arm at interim assessments.

Adjudication of the primary outcome will be performed by a Blinded Endpoint Review Committee (BERC) (described in Section 11.8).

11.6. Baseline data

Baseline data will be collected from the baby's medical notes including demographic data such as ethnicity in order to accurately report on the demographics of the groups allocated to each pathway.

After consent has been obtained the parent/carer will be asked to complete a baseline questionnaire to measure parental/primary carer health-related quality of life, as well as to collect additional demographic and socio-economic data such as parental educational qualification.

11.7. Trial assessments

Data will be collected from medical notes for the trial period by the research team using trial-specific Case Record Forms (CRFs).

After hospital discharge, parents/carers will be contacted at 8 weeks from randomisation to ask if their baby has been re-admitted since discharge. If applicable, details about the hospital re-admission will be collected by the research team from medical notes using trial-specific CRFs.

Parents/carers will be sent two short questionnaires: one when their child is at 12 months of age (corrected for prematurity in preterm babies) and another at 24 months of age (corrected for prematurity in preterm babies). Both will ask about their child's quality of life and parental quality of life. The 24-month questionnaire will also ask about their child's development.

Prior to sending questionnaires, recruiting sites will carry out a wellbeing check via hospital records and relevant registries to check if any babies have died post discharge and obtain updated contact details

Contact and reminders may be made by email, text message, phone call and post.

Parent questionnaires will be completed electronically using a bespoke secure online trial questionnaire, with alternative methods offered for those not wishing to complete online, i.e. on paper via postal questionnaire or over the telephone with a member of the trial team. Parents/carers will also be given an option of completing the questionnaires over the telephone via translation services where they do not read or speak English sufficiently to complete the questionnaire.

Where required, data relating to the child's 24-month clinical follow-up assessment will be requested from sites for review by the BERC (Section 11.8).

11.7.1. Payment

Parents/carers will receive an unconditional voucher at the time that the 24-month questionnaires are sent out as a thank you for the time spent completing the forms (as indicated in the Country-specific Annex).

11.7.2. Feedback of outcomes to families

Parents/carers will be sent their child's results from the Parent Report of Children's Abilities-Revised (PARCA-R) assessment of cognitive and language development, collected from the 24-month questionnaire, via automated letter. Parents will be advised to contact their GP or clinical care team for any concerns in the first instance. Clinical co-investigators will be available to assist with any further clinical queries.

11.8. Blinded Endpoint Review

Blinded Endpoint Review will be used to classify neurodevelopmental outcomes at 24 months of age (corrected for prematurity in preterm babies; 24 months actual age for term babies) for all children except those with confirmed viral meningitis (for definitions of meningitis see Section 10.3), and also for children with confirmed viral meningitis where:

(i) a 24-month questionnaire was not completed OR
(ii) a 24-month questionnaire was completed outside of the timeframe required for deriving PARCA-R standard scores (less than 23.5 months or more than 27.5 months corrected age) OR
(iii) there are missing data on questionnaire items precluding classification of one or more of the individual components of the primary outcome OR
(iv) parent reported data indicate the child may have vision, hearing or gross motor impairment or seizures.
(See Appendix 1 and Appendix 2).

Routine follow-up data for children who meet the above criteria, including clinic letters and the results of vision and hearing tests, will be obtained to supplement information gained from parents. In England, newborn hearing screen results may be obtained via the Newborn Hearing Screening Programme (NHSP).

All clinical data obtained alongside parent reported data will be reviewed by a BERC to classify the primary outcome.

Reviews will be conducted in accordance with a BERC Charter, written and agreed by the Project Management Group (PMG) and TSC (Section 16.3). The BERC reviewers will be professionals who are expert in the fields or conditions for which endpoint data is being collected for analysis.

11.9. Sample handling

No additional blood or tissue samples are required for this trial.

11.10. Definition of End of Trial

The end of trial will be defined as the date when the trial database is locked after completion of follow-up.

12. TRIAL INTERVENTIONS

12.1. Trial arms

The two trial arms to be compared are:

Intervention: Dexamethasone 0.15 mg/kg intravenously every 6 hours (0.6 mg/kg daily dose) for 4 days (total = 16 doses) as therapy in suspected or confirmed bacterial meningitis. This will be administered alongside treatment-as-usual based on national clinical guidelines (as indicated in the Country-specific Annex).

Comparator: Treatment-as-usual based on national clinical guidelines but without dexamethasone.

If a baby is diagnosed after randomisation with confirmed viral meningitis (Section 10.3.3), or if antibiotics are stopped, any dexamethasone being administered for the purposes of the trial will be stopped at the same point.

12.2. Investigational Medicinal Product (IMP)

12.2.1. Name and description of IMP

The experimental IMP (dexamethasone group) is described in Table 2. There is no comparator product in this trial. All babies will receive treatment-as-usual based on national clinical guidelines.

Table 2: IMP description

Drug	Dexamethasone
IMP or Non-IMP	IMP
Description of active substance	Chemical origin
Excipients	As per relevant product information specified in the Country-specific Annex
Pharmaceutical form	Solution for injection/infusion
Concentration	Any concentration of a marketed product in the relevant country.
Brand	Any brand of a marketed product in the relevant country.
Packaging	No modification or re-packaging
Labelling	No clinical trial labelling (see risk assessment)
Regulatory status of the IMP	Off-label use
Sourcing	Provided from local hospital stock

12.2.2. Regulatory status of the IMP

The use of intravenous dexamethasone in this trial is considered off-label use.

12.2.3. Product characteristics

Refer to Table 2.

12.2.4. Dosage

For babies randomised to the dexamethasone group, refer to Table 3.

Table 3: Dosage of IMP for dexamethasone group

Drug	Dexamethasone
Route	Intravenous
Dosage	0.15 mg/kg every 6 hours (**Dose expressed as dexamethasone base**) The first dose should be administered within 12 hours of the first dose of antibiotics (or within 12 hours of the first administration of changed dose/type of antibiotics where antibiotics have been changed in dose or type for newly suspected or confirmed meningitis); and as early as possible after randomisation.
Duration	4 days (Total = 16 doses)

	Stop dexamethasone if a virus is confirmed as the sole cause of meningitis or if antibiotics are stopped.

12.2.5. Blinding of IMP

Blinding is not applicable as this is an open-label trial.

12.2.6. Storage and supply of IMP

IMP will be supplied by each site from local hospital stock. Temperature monitoring should align with local requirements for the storage of medicines used in routine clinical care and must comply with the relevant product information as indicated in the Country-specific Annex.

12.2.6.1. Accountability of the IMP

Trial-specific IMP accountability will not be required, as the IMP will be sourced from each site's local hospital stock. Documentation of IMP administration will be recorded in the individual babies' medical records in accordance with standard clinical practice.

12.2.7. Preparation and labelling of IMP

IMP will be sourced from each site's local hospital stock and therefore under the risk-adapted approach there will be no specific trial labelling (see statement of exemption and risk assessment). Prepared dexamethasone intravenous solutions will be labelled at the time of preparation using the site-approved intravenous additive label. This label will include, but is not limited to, the patient's name, drug name, and time of preparation, in accordance with the policies and procedures of each individual site.

For preparation and administration of intravenous dexamethasone, refer to the relevant IMP product information (indicated in the Country-specific Annex) or local guidance.

12.2.8. Administering and prescribing IMP

Dexamethasone will be prescribed as per local procedures, by appropriately trained and delegated clinical staff whose clinical role includes prescribing.

Dexamethasone will be administered by appropriately qualified and trained clinical staff. Additional trial-specific IMP training and trial delegation will not be required, as this is considered within the remit of their usual clinical roles.

12.2.9. Known drug reactions and interaction with other therapies

Single cases of severe anaphylactic reactions with circulatory collapse, cardiac arrest, arrhythmia, bronchospasm and/or hypotension or hypertension have been observed with the use of intravenous dexamethasone.

12.2.10. Concomitant medication

To ensure that this pragmatic trial is as generalisable as possible, all other aspects of the baby's care will follow usual hospital practice.

The use of other medications deemed clinically necessary by the treating clinician is permitted in this trial. However, the manufacturer of dexamethasone advises caution with certain concomitant medications, as they may alter the metabolism and, consequently, the therapeutic effects of either dexamethasone or the co-administered drug. Treating clinicians should refer to the current product information as specified in the Country-specific Annex for interactions and incompatibilities when determining all other aspects of care. Concomitant use of systemic corticosteroids among babies enrolled in BOBBi will be recorded.

A four-day course of dexamethasone is not considered to be immunosuppressive so there is no need to delay the administration of live vaccines (35).

12.2.11. Compliance with trial treatment

For babies in the intervention arm treatment initiation and total treatment (doses given), including stopping dexamethasone as per Section 12.1, will be monitored. A CRF will be used to capture doses given.

Babies in the comparator arm will not be given dexamethasone as part of the trial. However, the use of dexamethasone for clinical reasons outside of the trial indication is permitted. Reasons for administration of dexamethasone outside of the trial indication will be collected in a CRF.

12.3. Other treatments (non-IMPs)

There are no non-IMPs in the trial. Management of meningitis (treatment-as-usual) is in line with national clinical guidelines.

12.4. Other interventions

There are no additional interventions in the trial.

12.5. Post-trial treatment

Provision of dexamethasone beyond the trial period would only take place as part of ongoing clinical management.

13. SAFETY REPORTING

13.1. Adverse event 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. 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 etiology that would explain the event.
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* * Please note this only relates to a congenital anomaly in the offspring of the randomised baby, and is therefore not expected in this trial. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. 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 to be an untoward and unintended response in a participant, which is related to an IMP.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product

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.

13.2. Assessment of causality

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

- **Unrelated** – where an event is not considered to be related to the IMP

- **Possibly** – although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
- **Probably** – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP
- **Definitely** – the known effects of the IMP, its therapeutic class or based on challenge testing suggest that the IMP is the most likely cause

All AEs (SAEs) labelled possibly, probably or definitely will be considered as related to the IMP.

13.3. Justification of safety reporting requirements

In this population we anticipate day-to-day fluctuations of pre-existing conditions, new conditions, and deaths. The reportable events are considered appropriate due to the well-established safety profile of the IMP, see Section 7.4.4. Relevant outcomes in both trial arms are also being collected and will be assessed by the DMC according to the DMC Charter.

13.4. Procedures for reporting adverse events

Many adverse events are foreseeable due to the nature of the participant population and their routine care/treatment. Consequently, we are not reporting adverse events that do not fulfil SAE criteria as below.

13.5. Requirements for Serious Adverse Event (SAE) reporting

13.5.1. From randomisation to 8 weeks from randomisation, only the following events should be reported as SAEs:

- All instances of death
- SAEs that are causally related to the IMP (Serious Adverse Reactions (SARs))
- Re-admission to hospital for the following:

    - Gastrointestinal haemorrhage
    - Hypertension requiring drug treatment
    - Hyperglycaemia
    - Confirmed invasive infection
    - Further meningitis treatment

13.5.2. Where participation is withdrawn before 8 weeks, or parents/carers do not provide deferred consent

Where local approvals allow, efforts will be made to collect SAEs up to 8 weeks after randomisation to ensure any safety signals are identified. See Sections 11.2.3 and 11.3.1.

13.6. Reporting procedures for Serious Adverse Events

All SAEs that require reporting (as above) must be reported on the SAE Reporting Form to the NPEU CTU immediately or within 24 hours of the site study team becoming aware of the event being defined as a reportable event. See the Country-specific Annex for requirements at participating countries.

13.6.1. Procedure for immediate reporting of Serious Adverse Events

Sites may use one of the following SAE reporting methods:

1. Paper forms, with instructions, will be provided with the trial documentation to enable anyone to report an SAE. The completed SAE form must be uploaded to NPEU CTU via NPEU CTU systems or sent via other equally secure method

2. Staff with access to the trial electronic clinical database should complete the SAE form online. An automatic email notification to the NPEU CTU staff will be triggered for SAEs reported electronically.

3. Where the above routes are not possible, then the SAE may be reported to NPEU CTU by telephone and the SAE form will be completed by NPEU CTU staff in compliance with internal NPEU CTU safety reporting SOPs.

Follow-up SAE information should be reported as necessary by the site staff and sent back to the NPEU CTU using reporting methods above.

13.7. Expectedness

For SAEs that require reporting, the expectedness of SARs will be determined based on the relevant Reference Safety Information (RSI) for the IMP (as specified in the Country-specific Annex). The RSI used for assessment will be the current version approved by the Sponsor and the relevant regulatory authority that was in effect at the time of the event. Details of the country-specific RSI or equivalent reference document are provided in the Country-specific Annex.

The NPEU CTU will forward the SAE form to the Chief Investigator (CI) (or safety delegate) for assessment and to determine expectedness, and will copy the relevant Sponsor to ensure real-time notification of SAEs.

For assessment of expectedness in the Development Safety Update Report (DSUR), see Section 13.11 below.

13.8. SUSAR reporting

All SUSARs will be reported by the Sponsor delegate to the regulatory authority and other parties as applicable (as described in the Country-specific Annex). 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 (PIs) 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. This is undertaken by sending the submitted DSUR to sites annually (Section 13.11).

13.9. Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the Reference Safety Information approved for the trial.
2. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning whether and event/reaction was anticipated or expectedness in line with the Reference Safety Information
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor: (NB where relevant these can be delegated to CI)

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
7. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

13.10. Overdose

For this study, an overdose is defined as any dose exceeding the protocol-specified amount (taking into account appropriate dose rounding for drug preparation). No specific antidote exists. In the case of an overdose, the baby should be treated symptomatically and supportive measures implemented as clinically necessary. The quantity of the excess dose as well as the duration of the overdose will be recorded in the CRF. This will be reported by the site as an incident which will be sent to the Sponsor. If an SAE is associated with the overdose, the overdose will be fully described in the SAE Report Form

13.11. Development Safety Update Reports

The CI will submit (in addition to the expedited reporting above) DSURs once a year throughout the clinical trial, or on request, to the relevant regulatory authorities, ethics committees, and/or other bodies as required in each participating country. A single DSUR will be submitted in all participating countries as per applicable local requirements (detailed in the Country-specific Annex).

For assessment of SARs in the DSUR, the RSI that was approved at **the start of the safety reporting period** will be used. When there has been approved changes to the RSI by substantial amendment during the reporting period, the RSI used for the DSUR will differ to the RSI used to assess expectedness at the time of SAR occurrence for SARs which require expedited reporting.

14. STATISTICS

14.1. Sample size determination

The target sample size is 965 babies randomised in 60 UK sites (note that each site will consist of at least 2 units – e.g., neonatal unit and paediatric ward). This sample size will enable the detection of survival without moderate or severe neurodevelopmental impairment at 24 months of corrected age of 95.2% in the intervention group compared to 88.9% in the control group (risk ratio of 1.07 or 6.3% relative benefit increase), assuming 90% power, 5% alpha and 20% loss to follow-up. The control group event rate of 88.9% combines the assumed event rates for subsequently confirmed diagnoses of BM and non-BM in the enrolled population of 70% (assumes mortality of 5% in babies from 32 weeks gestation (4) and 26% of survivors with moderate/severe neurodevelopmental impairment (14, 15)) and 100% respectively (23), and assuming a BM:non-BM ratio of 37:63 based on analysis conducted using ChiMES data (22). We anticipate that only those with BM will (potentially) benefit from the administration of steroids and thus the 6.3% relative benefit increase takes account of the corresponding dilution of the treatment effect due to the non-BM group. The treatment effect detectable for babies with BM is consistent with that seen in trials in older children with confirmed BM (neurological sequelae in survivors RR 0.60 (95%CI, 0.47–0.77); hearing loss in survivors RR 0.62 (0.47–0.81)) (20).

We also plan to recruit babies from international sites to enhance the generalisability of the findings. In Canada, a target of randomising 158 babies across 14 sites has been set. If the study recruits to target, this will provide a total sample size of 1,123 babies (n=965 UK, n=158 Canada) which will enable the detection

of survival without moderate or severe neurodevelopmental impairment at 24 months of corrected age of 94.8% in the intervention group compared to 88.9% in the control group (risk ratio of 1.07 or 5.9% relative benefit increase), assuming 90% power, 5% alpha and 20% loss to follow-up.

At 18 months when the internal pilot progression criteria are assessed, a formal assessment of the sample size assumption relating to the BM:non-BM ratio will be undertaken, with an assessment of any impact on the sample size calculation guided by the DMC and TSC.

14.2. Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan that will be available prior to the first DMC review of interim data. The SAP will be finalised before final data lock takes place and will be made available on the ISRCTN registry record.

14.3. Description of statistical methods

14.3.1. Descriptive statistics

The CONSORT diagram will be used to illustrate the flow of participants by trial arm at each stage in the trial. Baseline characteristics, demographic and clinical, will be summarised using counts and percentages for categorical variables, mean (standard deviation) for normally distributed continuous variables, and median (interquartile range) for non-normally distributed continuous variables. There will be no tests of statistical significance performed for differences between randomised groups on any baseline variable.

14.3.2. Comparative analysis

An intention-to-treat approach will be used for the primary analysis whereby participants will be analysed based on the treatment arm they were randomised to, irrespective of deviation from the protocol. Treatment-as-usual based on national clinical guidelines but without dexamethasone will be used as the reference group in all analyses.

For binary outcomes including the primary outcome, risk ratios, risk differences and associated 95% confidence intervals (CI) will be calculated using a mixed effects log-binomial or Poisson model (random intercept to account for clustering at site-level and for multiples enrolled). Continuous outcomes will be analysed using mixed effects linear regression with mean differences and 95% CIs presented, where model assumptions are satisfied. If model assumptions are not satisfied, then a mixed effects quantile regression model will be used with median differences and 95% CIs presented. Analyses will be adjusted for the randomisation (minimisation) factors as fixed effects, except site which will be included as a random effect. Quality of life outcomes will also be adjusted for their corresponding baseline and 12-month measures where collected.

Pre-specified subgroup analyses for the primary and secondary outcomes will be conducted to investigate whether the treatment effect differs according to type of meningitis (BM vs non-BM). Additional descriptive subgroup analyses (summary statistics only) will be conducted by type of major pathogen (viral vs bacterial) and timing of receipt of dexamethasone in relation to the first dose of any antibiotic prescribed (≤12 hrs vs >12 hrs and ≤ 4 vs >4 hrs).

14.4. Analysis populations

The intention-to-treat (ITT) approach will be followed for the analysis of primary and secondary outcomes where all participants randomised will be analysed based on the treatment arm they were randomised to, irrespective of deviation from the protocol. The safety population will also follow the ITT approach.

14.5. Data monitoring

Accumulating data from the trial will be reviewed by an independent Data Monitoring Committee (DMC) at least annually during the recruitment period of the trial, or as requested. The DMC will make recommendations to the Trial Steering Committee based on their findings (see Section 14.6 below). There are no planned interim analysis.

14.6. Stopping guidelines

A recommendation may be made by the DMC to the TSC to stop the trial early following review of accumulating data, or evidence from other relevant studies becoming available. In addition to the internal pilot progression criteria (see Section 9.1), guidelines for the early cessation of the trial will be agreed with the DMC and documented in the DMC Charter.

14.7. The level of statistical significance

Two-sided statistical testing will be performed for the primary and key long-term outcomes, adopting a 5% level of statistical significance. Treatment effects for all outcomes will be presented with two-sided 95% confidence intervals.

14.8. Procedure for accounting for missing, unused, and spurious data

Standardised PARCA-R scores can only be calculated for questionnaires completed within 23.5 to 27.5 months of age corrected for prematurity (inclusive). PARCA-R standardised scores will be calculated using multiple imputation where (i) a questionnaire is returned but it is completed out of this time window; (ii) if the non-verbal scale is completed but had more than four items missing; or (iii) if there is no cognitive or language classification from the BERC (in infants with no data for PARCA-R score). This will then be included in the computation of the composite outcome which will be reported as the primary inference. A sensitivity analysis will be conducted, excluding infants whose assessments were completed outside this range.

14.9. Procedures for reporting any deviation(s) from the original Statistical Analysis Plan

Any deviations from the original SAP will be described and justified in the final report, as appropriate.

15. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

15.1. Source data

Source documents are where data are first recorded, and from which babies' CRF data are obtained. CRF entries will be considered source data if the CRF is the site of the original recording (i.e., there is no other written or electronic record of data). Parent-reported data (for example 12- and 24-month study questionnaires) will be considered source data.

15.2. Access to data

Site staff will have authenticated and restricted access to the secure Clinical Database Management System (OpenClinica), ensuring they are only able to see data on participants recruited at their site. Access to the electronic data is strictly controlled using individual passwords for all staff accessing the electronic databases.

15.3. Data recording and record keeping

The majority of trial-specific data will be collected using electronic CRFs and either entered directly into OpenClinica or automatically transferred into it from the bespoke randomisation database.

The 12- and 24-month study questionnaire data will be entered into OpenClinica either directly by parents or by the study team from returned paper questionnaires or parents' responses obtained via a telephone call.

The clinical database will be validated and maintained in accordance with NPEU CTU Standard Operating Procedures (SOPs). Data will be entered and at the point of entry will undergo validation checks to verify the validity and completeness of the data captured. A separate administrative database application will be used to store the participant's identifiable details such as email address. Trial participants will be identified by a unique trial number, which will be used to link the clinical and administrative database applications.

In the UK, consent forms containing the participant's names will be sent securely electronically (using encryption) or in pre-addressed envelopes to the NPEU CTU. All data will be processed in line with the NPEU CTU Data Management SOPs. It is the responsibility of all parties involved (Sponsor, NPEU CTU, UBC, trial sites and the NHS organisations) to ensure confidentiality of participant information is maintained.

Electronic files will be stored on a restricted access (named individuals) server held in a secure location. In line with the NPEU CTU security policy, authorised access to the NPEU CTU is via an electronic tag entry system and individual rooms are kept locked when unoccupied. Authorised staff will process data via a secure network which requires individual login name and password (changed regularly). No data are stored on individual workstations. The data is backed up automatically overnight to an offsite storage area accessed by authorised personnel via electronic tag and key-pad systems.

All paper and electronic data will be stored securely in strict compliance with data protection regulations.

16. QUALITY ASSURANCE PROCEDURES

16.1. Risk assessment

The trial will be conducted in accordance with the current approved protocol, Good Clinical Practice (GCP), relevant regulations and standard operating procedures (SOPs). A risk assessment (RA) and monitoring plan (MP) will be prepared before the trial opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

16.2. Monitoring

The Principal Investigator (PI) will be responsible for the running of the trial at their site. This will include ensuring successful recruitment, staff education and training, and trial data completeness and quality. The NPEU CTU will develop an appropriate central monitoring plan (MP) for the trial, based on the Risk Assessment (RA) for the trial.

Recruitment patterns at sites and within the data will be monitored. Any unexpected patterns, issues, or outlier data will be investigated and may trigger 'for cause' site monitoring. No other routine monitoring will be conducted unless the central monitoring triggers cause to do so.

16.3. Trial committees

16.3.1. Project Management Group (PMG)

The trial will be run on a day-to-day basis by the Project Management Group (PMG), which reports to the Trial Steering Committee (TSC), which in turn is responsible to the Funders. The PMG will comprise the Chief Investigator and country-specific Co-Leads, clinical experts, NPEU CTU Director and representatives from the following: Head of Operations (UK and Canada), Senior Trials Managers, Trial Managers (UK and Canada), Sponsor representatives, Trial Statistician, Trial Health Economist, Trials IT Development and Data Management Team and other project staff.

16.3.2. Co-Investigator Group (CIG)

The Co-Investigator Group (CIG), an extended PMG, will comprise all members of the co-applicant group and the members of the PMG, and will review progress, troubleshoot and plan strategically.

16.3.3. Trial Steering Committee (TSC)

The trial will be overseen by a TSC consisting of an independent Chair and other independent members, to include clinicians, statisticians and PPIE representatives. The TSC will be established in line with the latest NIHR Research Governance Guidelines, which requires that at least 75% of the Committee membership be independent (36).The Chair and members of the TSC will be nominated as per the NIHR guidelines for their approval (36). The TSC will aim to meet at least annually.

The role of the TSC is to provide overall supervision on behalf of the Sponsor and Funder(s) and to ensure that it is conducted to the rigorous standards set out in the UK Policy Framework for Health and Social Care Research (37), the Guidelines for Good Clinical Practice (38), and all relevant national and international regulations.

The TSC will monitor the progress of the trial and its conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the Data Monitoring Committee (DMC) and ultimately carry the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy. Details about the roles, responsibilities and conduct of the committee with be set out in a TSC Charter, which will be agreed at the first meeting.

16.3.4. Data Monitoring Committee (DMC)

The DMC members will be independent from the trial team, the TSC, the Sponsor and the Funder, and will include a Chair, a clinician and a statistician. All members of the DMC will be independent, as defined in the NIHR Research Governance Guidelines (36). The Chair and members of the DMC will be nominated as per the NIHR guidelines for their review and approval. During the recruitment phase, the committee will meet annually or more often as appropriate, review trial conduct, progress, and accumulating data, and make recommendations to the TSC. Details about the roles, responsibilities and conduct of the committee with be set out in a DMC Charter, which will be agreed at the first meeting.

16.3.5. Blinded Endpoint Review Committee (BERC)

The BERC reviewers will be healthcare professionals who are expert in the fields or conditions for which blinded endpoint review data is being collected. The BERC has the role of reviewing and classifying endpoints in a blinded and objective fashion. Please refer to Section 11.8 for more detail.

16.4. Patient and Public Involvement and Engagement (PPIE)

PPIE representatives, including parents of children affected by meningitis and representatives from meningitis charities, are involved in all aspects of the study, including its design, conduct and reporting. PPIE representatives are co-investigators on the trial and members of the Trial Steering Committee (TSC).

Representatives of the Meningitis Research Foundation (MRF) and Group B Strep Support (GBSS) have informed the BOBBi trial from conception. Parents and families of babies who had meningitis within the first three months of life provided input into the research plan, selection of primary and secondary outcomes and development of the approach to informed consent, with the support of MRF and GBSS. Seven mothers, as well as representatives from MRF and GBSS, participated in two focus groups to inform the trial design.

A Parent Advisory Group (PAG) will be established to ensure continued PPIE input throughout the trial. The PAG will comprise up to approximately 10 public members identified through working with charity partners. The group will meet regularly during trial set up and during results dissemination, and at least annually. They will advise on all aspects of the research cycle, including co-production of parent-facing trial information materials, study conduct, promotion and dissemination (Section 23.1).

17. URGENT SAFETY MEASURES

The Sponsor or Investigator may take appropriate urgent safety measures (USMs) to protect trial participants from any immediate hazard to their health or safety. USMs may be taken without prior authorisation but they should be reported immediately to the Sponsor, ethics committee(s) and regulatory authority as described in the Country-specific Annex. This should be followed by submission of a substantial amendment specifically covering the USM related changes.

18. PROTOCOL DEVIATIONS

A trial-related deviation is a departure from the ethically approved trial protocol or other trial document or process (e.g. consent process) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in incident forms and where applicable the relevant corrective and preventative action completed. All incidents will be recorded in an Incident Log database as per country requirements.

19. DATA BREACHES

Suspected personal data breaches must be reported immediately as per country requirements. In the UK this will be reported directly to the University of Oxford's Information Compliance Team (ICT) (data.breach@admin.ox.ac.uk) and in accordance with NPEU CTU's SOP and Sponsor requirements.

Sites may also have reporting obligations within their own organisation.

20. SERIOUS BREACHES

In the event that a serious breach is suspected the Sponsor must be contacted within one working day, so that the Sponsor can report this breach, if necessary, within 7 days as per the relevant regulatory requirements.

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 collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the relevant regulatory authorities within the required reporting timelines as specified in the Country-specific Annex.

21. ETHICAL AND REGULATORY CONSIDERATIONS

21.1. Declaration of Helsinki

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

21.2. Guidelines for Good Clinical Practice

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

21.3. Approvals

Relevant study documentation will be submitted to the national competent authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the trial.

Any substantial amendments to the original approved documents will be submitted to the above parties for review and approval.

21.4. Other ethical considerations

21.4.1. Informed consent in an emergency situation.

The BOBBi trial will be involving babies up to 3 months who cannot consent for themselves, therefore consent will be sought from a parent or carer.

Due to the emergency nature of the condition being examined, bacterial meningitis, the trial can only be conducted in emergency situations, and based upon advice from parents with experience of having a baby with bacterial meningitis, we will be randomising babies and administering the first doses of dexamethasone for babies allocated to the intervention arm prior to obtaining informed consent from parents. This deferred consent approach will be used because parents clearly report that receiving a diagnosis of presumed bacterial meningitis is such a devastating and distressing event that they would be unable to make an informed decision about consent in the first 12 hours following this. Data from mechanistic and physiological studies and previous trials in older children indicate that dexamethasone is more effective the earlier it is administered in bacterial meningitis and is unlikely to be effective if administered more than 12 hours after diagnosis of suspected bacterial meningitis. Thus, prospective consent would not be possible within the therapeutic window.

Consent will be sought from parents/carers for ongoing trial participation and data collection as soon as appropriate and ideally within 48 hours of randomisation (Section 11.2).

21.5. Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the appropriate ethics committee(s), research governance bodies, host organisation, funder (where required) and Sponsor according to local/national requirements. In addition, an End of Trial notification and final report will be submitted to the regulatory authority, the ethics committee(s), host organisation and Sponsor.

21.6. Transparency in research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

Where the trial has been registered on multiple public platforms, the trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial declaration.

21.7. Participant confidentiality

The trial will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018, in addition to any site-specific regulations. All documents will be stored securely and only accessible by trial staff and authorised personnel. The trial staff will safeguard the privacy of participants' personal data.

In the UK, all personal identifiers will be stored in a separate database also held at the NPEU CTU. These databases will only be linked by the baby's trial number. After the trial has been completed and the reports published, the data will be archived in a secure physical or electronic location with controlled access.

21.8. Expenses and benefits

A voucher will be given unconditionally to parents with the 24-month questionnaire as this has been shown to lead to a substantially higher response rate (39).

22. FINANCE AND INSURANCE

22.1. Funding

This trial is funded by project grants from the NIHR Health Technology Assessment (HTA) and the Canadian Institutes of Health Research (CIHR). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

The funders will have no influence on study design, collection, management, analysis and interpretation of data, writing of the report and the decision to submit for publication.

22.2. Insurance

In the UK the study is sponsored by City St George's, University of London. The sponsor is responsible for initiating and managing the study, delegating responsibility for trial management, database and data analysis support to the NPEU Clinical Trials Unit in the UK.

Further details are described in the relevant Country-specific Annex

22.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties before they undertake trial activities.

23. PUBLICATION POLICY

The success of the trial depends on a large number of health professionals and parents. Credit for the trial findings will be given to all who have collaborated and participated in the trial, including all local co-ordinators and collaborators, members of the trial committees, the BOBBi Coordinating Centre and trial staff.

Authorship at the head of the primary results paper will take the form “[name], [name] and [name] on behalf of the BOBBi Collaborative Group”. The drafting of the paper will be the responsibility of a writing committee. All contributors to the trial will be listed at the end of the main paper, with their contribution identified.

It is the intention of the BOBBi Collaborative Group to publish the protocol and peer-reviewed articles including the analysis of key outcomes. All published material will contain an acknowledgement of funding.

The results will be published in an open-access, high-impact peer-reviewed general medical journal. Full details of the trial will be made available through the trial website: https://www.npeu.ox.ac.uk/bobbi.

The trial protocol will be accessible on the trial website and ISRCTN registry record (ISRCTN - ISRCTN17216564: Better outcomes in babies with bacterial meningitis). The final protocol will be published in an open access journal.

Publication authorship will follow the International Committee of Medical Journal Editors’ (ICMJE) recommended criteria (http:// www.icmje.org), as well as that of the final selected journal.

23.1. Dissemination

The trial website and social media channels will provide updates throughout the lifetime of the study. We will co-design information leaflets with our charity partners and the PAG, including an infographic summary and video (in relevant languages), to be distributed via website, email, social media and charity partners websites. Plain English summaries will be available on the study website and HRA website.

The PAG will be involved in interpretation of results, importantly advising on what the results mean for families. Members will co-produce a lay summary of the results and infographics and videos of the trial for dissemination.

Following publication, a full dissemination plan will be developed by the PMG which will include a wide range of routes to disseminate the results of the study. This will include dissemination to parents, clinicians, provider organisations and policy makers through charity partners, social media, professional conferences, and lay and peer review publications.

24. ARCHIVING

24.1. Minimum archiving period

Archiving of research data will follow the completion of the trial and publication of results for an initial period of 25 years in the UK and 15 years in Canada. At this point, the requirements to continue to archive these data will be reviewed in line with the applicable data protection guidelines and NPEU CTU’s Archiving SOP.

Archiving of identifiable data will follow the completion of the trial and publication of results for a maximum of 25 years, to allow for contact in the unlikely event of very long-term treatment effects being discovered. Parents are aware that we will hold identifiable data for long-term use. Long-term follow-up using linked routine data is not within the scope of this protocol.

In the UK a separate funding application will be submitted for linkage to routinely recorded long-term outcome data (including the Department for Education National Pupil Database and Hospital Episode Statistics (HES) and equivalent data from devolved administrations).

24.2. Trial Master File

The Trial Master File and trial database will be retained and archived in accordance with NPEU CTU's Archiving SOP which is compliant with the UK GDPR.

24.3. Investigator Site File and participant medical records

The Investigator Site Files will be archived at the participating sites in accordance with the site agreements, and with site local procedures. Where applicable, the medical records of trial participants will not be archived and must be retained at the site for the minimum archiving period above and in accordance with requirements of the host healthcare provider (where that is the longer retention period).

25. REFERENCES

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22.
2. Okike IO, Johnson AP, Henderson KL, Blackburn RM, Muller-Pebody B, Ladhani SN, et al. Incidence, etiology, and outcome of bacterial meningitis in infants aged <90 days in the United kingdom and Republic of Ireland: prospective, enhanced, national population-based surveillance. Clin Infect Dis. 2014;59(10):e150-7.
3. Subbarao S, Ribeiro S, Campbell H, Okike I, Ramsay ME, Ladhani SN. Trends in laboratory-confirmed bacterial meningitis (2012-2019): national observational study, England. Lancet Reg Health Eur. 2023;32:100692.
4. Salman O, Procter SR, McGregor C, Paul P, Hutubessy R, Lawn JE, et al. Systematic Review on the Acute Cost-of-illness of Sepsis and Meningitis in Neonates and Infants. Pediatr Infect Dis J. 2020;39(1):35-40.
5. Wright C, Wordsworth R, Glennie L. Counting the cost of meningococcal disease : scenarios of severe meningitis and septicemia. Paediatr Drugs. 2013;15(1):49-58.
6. Davies HD, Raj S, Adair C, Robinson J, McGeer A, Alberta GBSSG. Population-based active surveillance for neonatal group B streptococcal infections in Alberta, Canada: implications for vaccine formulation. Pediatr Infect Dis J. 2001;20(9):879-84.
7. Fakhraei R, Fell DB, El-Chaar D, Thampi N, Sander B, Brown KA, et al. Burden of infant group B Streptococcus disease and impact of maternal screening and antibiotic prophylaxis in Ontario, Canada: a population-based cohort study. Lancet Reg Health Am. 2024;39:100914.
8. Hartley J, Li Y, Kunkel L, Crowcroft NS. The burden of infant group B streptococcal infections in Ontario: Analysis of administrative data to estimate the potential benefits of new vaccines. Hum Vaccin Immunother. 2019;15(1):193-202.
9. Ladhani SN, Henderson KL, Muller-Pebody B, Ramsay ME, Riordan A. Risk of invasive bacterial infections by week of age in infants: prospective national surveillance, England, 2010-2017. Arch Dis Child. 2019;104(9):874-8.
10. Madrid L, Seale AC, Kohli-Lynch M, Edmond KM, Lawn JE, Heath PT, et al. Infant Group B Streptococcal Disease Incidence and Serotypes Worldwide: Systematic Review and Meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S160-S72.
11. Ouchenir L, Renaud C, Khan S, Bitnun A, Boisvert AA, McDonald J, et al. The Epidemiology, Management, and Outcomes of Bacterial Meningitis in Infants. Pediatrics. 2017;140(1).
12. de Louvois J, Halket S, Harvey D. Neonatal meningitis in England and Wales: sequelae at 5 years of age. Eur J Pediatr. 2005;164(12):730-4.

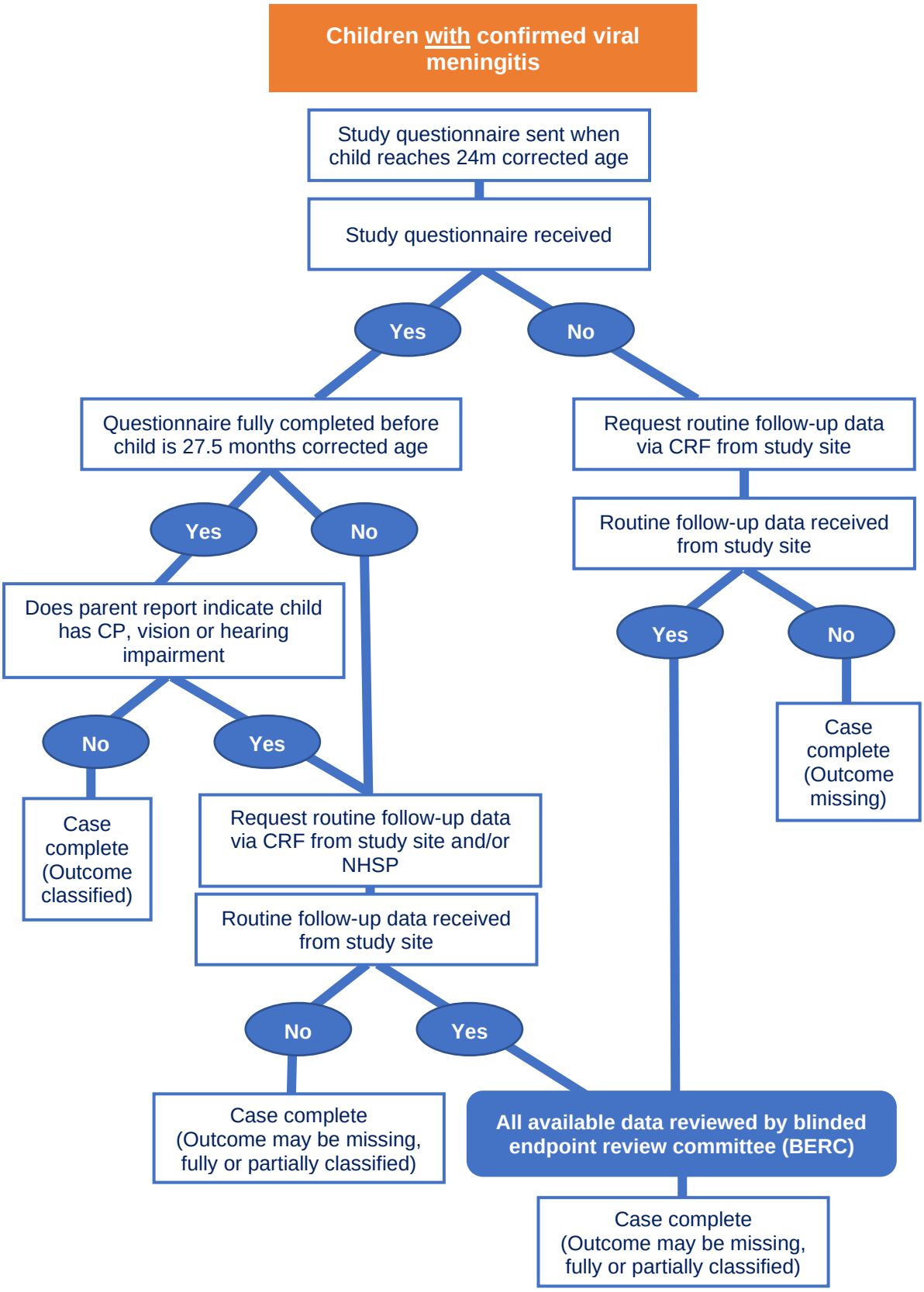
13. Davies HG, O'Sullivan CP, Al Janabi H, Rattue H, Trotter C, Giorgakoudi K, et al. Comparison of Neurodevelopmental Outcomes in Children With Group B Streptococcal Sepsis and Meningitis. Clin Infect Dis. 2022;75(5):922-3.
14. Meningitis (bacterial) and meningococcal disease: recognition, diagnosis and management, (2024).
15. Neonatal infection: antibiotics for prevention and treatment, (2021).
16. Fakhraei R, Fell DB, El-Chaar D, et al. Neurodevelopmental impairments in children following Group B Streptococcal disease: A population based cohort study in Ontario, Canada. European Perinatal and Pediatric Epidemiology Conference 2024.
17. Zhou Q, Ong M, Ye XY, Ting JY, Shah PS, Synnes A, et al. Long-Term Neurodevelopmental Impairment among Very Preterm Infants with Sepsis, Meningitis, and Intraventricular Hemorrhage. Neonatology. 2024;121(1):65-73.
18. Le Saux N. Guidelines for the management of suspected and confirmed bacterial meningitis in Canadian children older than 2 months of age. Canadian Paediatric Society,2020 [cited 2025 22 August]. Available from: https://cps.ca/en/documents/position/management-of-bacterial-meningitis.
19. ICTRP Search Portal [Internet]. [cited 2024 17 July]. Available from: https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal.
20. Tian C, Jin S, Zhao Z, Liu X, Cheng H, Wang X, et al. Association of Corticosteroid Treatment With Outcomes in Pediatric Patients With Bacterial Meningitis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Clin Ther. 2022;44(4):551-64.
21. Waagner DC, Kennedy WA, Hoyt MJ, McCracken GH, Jr. Lack of adverse effects of dexamethasone therapy in aseptic meningitis. Pediatr Infect Dis J. 1990;9(12):922-3.
22. Martin NG, Defres S, Willis L, Beckley R, Hardwick H, Coxon A, et al. Paediatric meningitis in the conjugate vaccine era and a novel clinical decision model to predict bacterial aetiology. J Infect. 2024;88(5):106145.
23. Kadambari S, Braccio S, Ribeiro S, Allen DJ, Pebody R, Brown D, et al. Enterovirus and parechovirus meningitis in infants younger than 90 days old in the UK and Republic of Ireland: a British Paediatric Surveillance Unit study. Arch Dis Child. 2019;104(6):552-7.
24. Choong CT, Lee EY, Tan HKK, Lazaroo D, Tan NWH. Good hearing outcome in children recovering from non-polio enteroviral meningitis. J Paediatr Child Health. 2021;57(9):1438-41.
25. Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L. Validation of the "Step-by-Step" Approach in the Management of Young Febrile Infants. Pediatrics. 2016;138(2).
26. Daoud AS, Batieha A, Al-Sheyyab M, Abuekteish F, Obeidat A, Mahafza T. Lack of effectiveness of dexamethasone in neonatal bacterial meningitis. Eur J Pediatr. 1999;158(3):230-3.
27. Mathur NB, Garg A, Mishra TK. Role of dexamethasone in neonatal meningitis: a randomized controlled trial. Indian J Pediatr. 2013;80(2):102-7.
28. van de Loo M, van Kaam A, Offringa M, Doyle LW, Cooper C, Onland W. Corticosteroids for the prevention and treatment of bronchopulmonary dysplasia: an overview of systematic reviews. Cochrane Database Syst Rev. 2024;4(4):CD013271.
29. Doyle LW, Cheong JL, Hay S, Manley BJ, Halliday HL. Late (>/= 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2021;11(11):CD001145.
30. Doyle LW, Cheong JL, Hay S, Manley BJ, Halliday HL. Early (< 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev. 2021;10(10):CD001146.
31. UK Health Security Agency. Enterovirus: summary of strain characterisation 2019 [updated 7 August 2023; cited 2025 Jun 5]. Available from: https://www.gov.uk/government/publications/enterovirus-strain-characterisation/enterovirus-summary-of-strain-characterisation.
32. Kamei S, Sekizawa T, Shiota H, Mizutani T, Itoyama Y, Takasu T, et al. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. J Neurol Neurosurg Psychiatry. 2005;76(11):1544-9.
33. Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet. 2019;393(10186):2125-34.
34. Woolfall K, Young B, Frith L, Appleton R, Iyer A, Messahel S, et al. Doing challenging research studies in a patient-centred way: a qualitative study to inform a randomised controlled trial in the paediatric emergency care setting. BMJ Open. 2014;4(5):e005045.
35. Chapter 6: Contraindications and special considerations. 2017. Immunisation against infectious disease: the Green Book. Available from: https://www.gov.uk/government/publications/contraindications-and-special-considerations-the-green-book-chapter-6.

36. NIHR. Research Governance Guidelines 2022 [updated January 2023; cited 2025 4 June]. Available from: https://www.nihr.ac.uk/about-us/who-we-are/policies-and-guidelines/research-governance-guidelines.
37. UK Policy Framework for Health and Social Care Research 2025 [updated 10 Jan 2025; cited 2025 28 August]. Available from: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/uk-policy-framework-health-social-care-research/.
38. Good Clinical Practice 2020 [updated 10 Feb 2020; cited 2025 28 August]. Available from: https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/good-clinical-practice/.
39. Juszczak E, Hewer O, Partlett C, Hurd M, Bari V, Bowler U, et al. Evaluation of the effectiveness of an incentive strategy on the questionnaire response rate in parents of premature babies: a randomised controlled Study Within A Trial (SWAT) nested within SIFT. Trials. 2021;22(1):554.

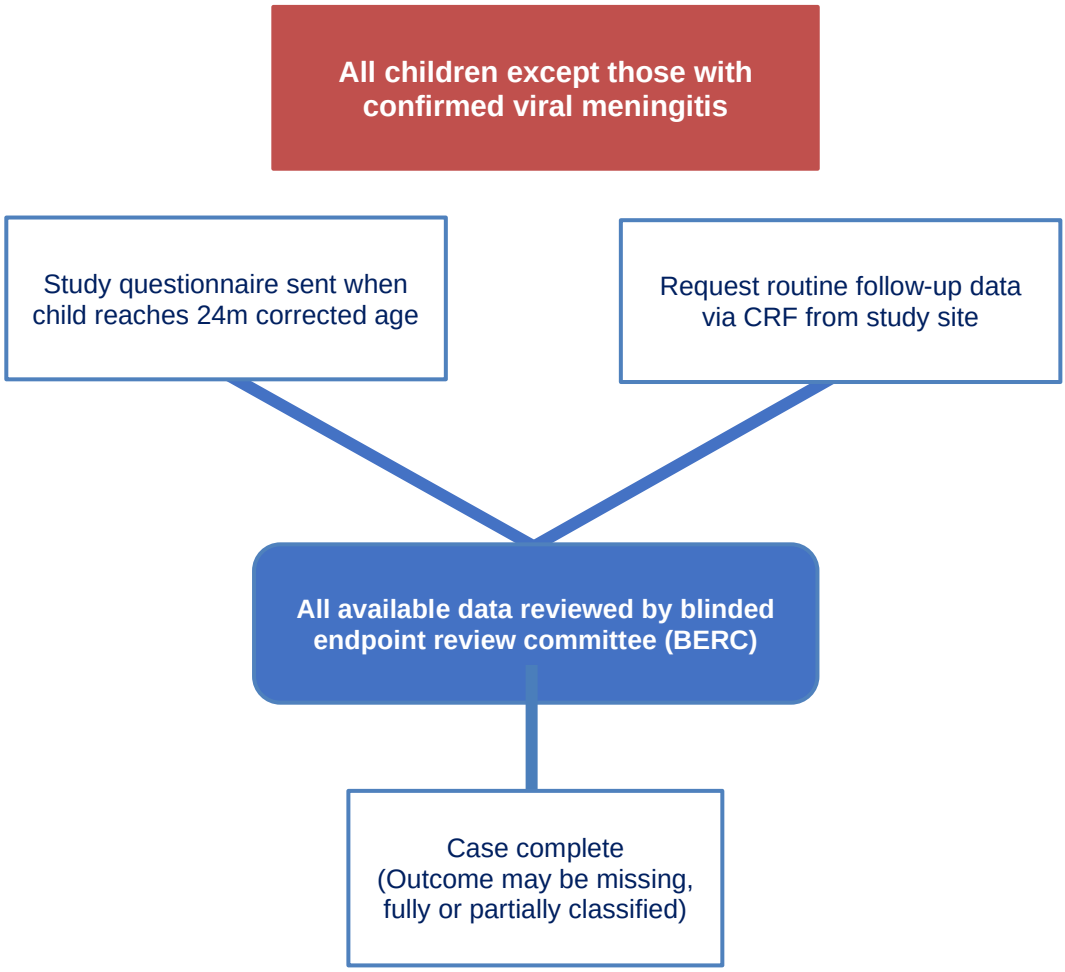
APPENDICES

Appendix 1: Blinded Endpoint Review Committee (BERC) Eligibility Flowchart for Children With Confirmed Viral Meningitis 58
Appendix 2: Blinded Endpoint Review Committee (BERC) Eligibility Flowchart for All Children Except Those With Confirmed Viral Meningitis 59
Appendix 3: Relevant organisms 60
Appendix 4: Participant schedule of procedures 61
Appendix 5: Amendment history 63

Appendix 1: Blinded Endpoint Review Committee (BERC) Eligibility Flowchart for Children With Confirmed Viral Meningitis



Appendix 2: Blinded Endpoint Review Committee (BERC) Eligibility Flowchart for All Children Except Those With Confirmed Viral Meningitis



Appendix 3: Relevant organisms

The following organisms are defined as relevant pathogens when identified in CSF or blood:

- *Acinetobacter species*
- *Citrobacter species*
- *Enterobacter species*
- *Escherichia coli*
- Group A Streptococcus (*Streptococcus pyogenes*)
- Group B Streptococcus (*Streptococcus agalactiae*)
- *Haemophilus influenzae*
- *Klebsiella species*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Pseudomonas aeruginosa*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae* (pneumococcus)

The following organisms are defined as contaminants when identified in CSF or blood **unless treated as a pathogen by the clinical team**:

- Coagulase-negative staphylococci
- *Diphtheroids*
- *Micrococci*
- *Bacillus species*
- *Corynebacterium*
- Alpha haemolytic streptococci
- *Pseudomonas oryzihabitans*
- *Pantoea dispersa*
- *Kocuria species*
- *Moraxella osloensis*
- *Granulicatella elegans*
- *Neisseria elongate*
- *Cutibacterium acnes*

List of relevant viruses:

- Herpes Simplex Virus (HSV)
- Varicella Zoster Virus (VZV)
- Cytomegalovirus (CMV)
- Epstein-Barr Virus (EBV)
- Enterovirus
- Parechovirus
- Mumps
- Measles
- Influenza
- Adenovirus

Appendix 4: Participant schedule of procedures

	ENROLMENT			POST-RANDOMISATION						CLOSE OUT	
Timepoint	Screening	Eligibility Confirmed	Baseline	Day 1	Day 2	Day 3	Day 4	Hospital discharge	8 weeks	Corrected age for preterm babies and actual age for term babies	
										12 months	24 months
Enrolment											
Eligibility assessment	X										
Randomisation		X									
Informed consent		X	X* (deferred consent)	→	→	→	→	→			
Intervention or comparator											
Treatment with dexamethasone** (16 doses over first 4 days)		X		→	→	→	X				
Treatment-as-usual		X		→	→	→	X				
Assessments											
Clinical data collection [CRF]		X		→	→	→	→	→	X		X***
Baseline questionnaire including parental quality of life [parent-reported]			X								
8-week post discharge re-admission status [parent-reported]									X		
Neurodevelopmental outcomes [parent-reported]											X***
Parental carer and infant quality of life [parent-reported]			X							X	X
UK only: Use of NHS secondary care [data linkage (England and Scotland), CRFs and hospital records (for Wales and NI)]										X	X

Adverse Event assessment (SAEs, SUSARs etc)		X →							→ X		

* Deferred consent will be used whereby babies will be randomised when they meet the eligibility criteria. Parents/carers will be approached to discuss the trial as soon as appropriate, ideally within 48 hours of randomisation, and provided with trial information. Written informed consent for ongoing trial inclusion and data collection will be sought during trial discussions. The site team will make every reasonable and appropriate effort to obtain written consent, taking individual circumstances into account.

** If a virus is identified as the cause of the meningitis or if antibiotics are stopped, dexamethasone being administered for the purposes of the trial will be stopped.

*** Data will be requested from sites for participants at 24 months corrected age where either a child has confirmed bacterial meningitis or the parent questionnaire has not been completed, was completed outside of the timeframe required, parent reported data are missing or parent reported data indicate the child may have vision, hearing or gross motor impairment or seizures (Section 11.8 Blinded Endpoint Review). In England, data may also be requested from NHSP (Newborn Hearing Screening Programme)

Appendix 5: Amendment history

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

List details of all protocol amendments here whenever a new version of the protocol is produced. This is not necessary prior to initial REC / MHRA / HRA submission.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee, HRA (where required) or MHRA.