THE CLINICAL AND COST-EFFECTIVENESS OF TESTING FOR GROUP B STREPTOCOCCUS IN PREGNANCY: A CLUSTER RANDOMISED TRIAL WITH ECONOMIC AND ACCEPTABILITY EVALUATIONS (GBS3)

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TRIAL PERSONNEL AND CONTACT DETAILS

Sponsor: University of Nottingham

Contact name Ms Angela Shone

Research and Innovation

University of Nottingham

East Atrium, Jubilee Conference Centre

Triumph Road

Nottingham

NG8 1DH

Email: sponsor@nottingham.ac.uk

Chief Investigator: Professor Jane Daniels (Non-Clinical)

Professor of Clinical Trials, University of Nottingham

Phone: 0115 82 31619

Email: jane.daniels2@nottingham.ac.uk

Deputy Chief Investigator: Dr Kate Walker (Clinical)

Clinical Assistant Professor in Obstetrics and Gynaecology, University of Nottingham

Phone: 0115 82 31581

Email: kate.walker@nottingham.ac.uk

Co-investigators: Dr James Gray

Consultant Microbiologist, Birmingham Women's and Children's NHS Foundation Trust

Professor Stavros Petrou

Professor of Health Economics, University of Oxford

Professor Susan Ayers

Professor of Maternal and Child Health, City University of London

Dr Reuben Ogollah

Associate Professor of Medical Statistics, University of Nottingham

Ms Eleanor Mitchell

Assistant Professor of Clinical Trials, University of Nottingham

Professor Jon Dorling

Professor of Pediatrics, Dalhousie University, Canada

Dr Shalini Ojha

Clinical Associate Professor of Neonatology

University of Nottingham

Professor James Thornton

Professor of Obstetrics and Gynaecology, University of Nottingham

Ms Jane Plumb MBE

Chief Executive, Group B Strep Support

Professor Soo Downe OBE

Professor of Midwifery Studies, University of Central Lancashire

Ms Nicky Grace

Independent Midwife, Grace Academy of Midwifery and Birth

Ms Dot Parry

Midwife/ Antenatal Educator, National Childbirth Trust

Dr Tracey Cooper

Consultant Midwife, Warrington and Halton Hospitals NHS Foundation Trust

Ms Rachel Haines

Senior Trial Manager

Nottingham Clinical Trials Unit, University of Nottingham.

Trial Statistician: Dr Reuben Ogollah

Associate Professor of Medical Statistics

Phone: 0115 823 1583

Email: Reuben.Ogollah@nottingham.ac.uk

Trial Coordinating Centre:

Nottingham Clinical Trials Unit

Building 42

University Park

Nottingham

NG7 2RD

For all public and scientific queries contact:

Email: gbs3@nottingham.ac.uk

Phone: 0115 8231608

SYNOPSIS

Title	The clinical and cost-effectiveness of testing for Group B Streptococcus: a cluster randomised trial with economic and acceptability evaluations (GBS3)
Acronym	GBS3
Short title	Routine testing for Group B Streptococcus (GBS)
Chief Investigator	Professor Jane Daniels
Deputy Chief Investigator	Dr Kate Walker
Objectives	To test whether routine testing of women for GBS colonisation either in late pregnancy or during labour reduces the occurrence of early-onset neonatal sepsis, compared to the current risk factor based strategy.
Trial Configuration	A multi-centre prospective two-arm parallel cluster randomised controlled superiority trial with internal pilot, feasibility evaluation, qualitative study and parallel economic modelling.
Setting	Up to 80 maternity units (obstetric unit or alongside maternity unit) in England, Scotland and Wales.
Sample size estimate	320,000 women will enable detection of a 40% relative reduction in the primary outcome of early-onset neonatal sepsis with 90% power, two-sided significance level of 5% and inflating for clustering due to the cluster randomisation
Number of participants	320,000 women from up to 80 maternity units. Detailed data collection for 100 women per unit. Interviews with up to 80 women and 80 healthcare professionals.
Eligibility criteria	There will be two levels of eligibility, specific for the type of maternity unit, for individual women: • Testing level – eligibility to have a ECM or rapid test, or be reviewed for risk factors • Dataset level – eligibility to be included in the dataset for analysis, regardless of whether test performed. There is no exclusion based on age of women or multiple births. Mothers whose baby (or all babies) has a known congenital anomaly incompatible with survival at birth, or who have experienced an antepartum intrauterine death, with be excluded from testing and the dataset. Women who withdraw consent to use data, through the NHS data-opt out, will not be included in the dataset.

Description of strategies	The routine testing strategies will use antenatal enriched culture medium (ECM) testing or intrapartum rapid testing using the Cepheid GeneXpert system, with Intrapartum Antibiotic Prophylaxis (IAP) offered if the test is positive for GBS presence in the sample taken. The control strategy is to offer IAP if a maternal risk factor for Early-onset Group B Streptococcus (EOGBS) in her baby is identified before or during labour.
Duration of trial	The overall duration of the project is planned for 42 months. This includes a 12 month set-up phase, a 24 month recruitment phase (including a 9 month internal pilot and feasibility evaluation) and 7 months for final retrieval of data, analysis and write-up.
Randomisation and blinding	Eligible maternity units will be randomised on a 1:1 ratio to a routine testing strategy or the risk factor based strategy, using a web-based minimisation algorithm with a probabilistic element. Minimisation will be balanced on overall number of deliveries, neonatal unit level of care tier, and presence of an alongside midwifery unit. There will be a further second-level randomisation of the routine testing units to one of the two testing strategies. Blinding of women and healthcare professionals is not possible due to the nature of the strategies.
Outcome measures	PRIMARY OUTCOME: All-cause early neonatal sepsis: either culture-positive (blood or cerebrospinal fluid) or negative/ unknown culture status with ≥3 agreed clinical signs or symptoms, for which antibiotics are given for ≥5 days, within 7 days of birth. SECONDARY OUTCOMES: Neonatal: Birth weight, perinatal mortality, 5 minute Apgar, gestational age at birth, fetal acidaemia (cord arterial pH <7.05 or first neonatal pH), neonatal specialist care (length of stay, highest level of care), seizures, abnormal neurological signs at >24 hours of age (hypotonia or abnormal level of consciousness). Maternal: Mode of onset of labour, mode of delivery, duration of hospital stay, change of intended location of childbirth, maternal intrapartum anaphylaxis. Process: Maternal risk factors for EOGBS infection developing in baby, testing coverage, testing at appropriate time, test result available at least 4 hours before childbirth, GBS-specific IAP coverage, timing of IAP, number of doses of IAP, proportion of women who tested negative, positive or had no test, identified maternal risk factors at all sites, declines and acceptances of IAP, number of babies of mothers who tested positive for GBS and had IAP commenced, observation time following positive GBS result, maternal intrapartum or postnatal sepsis.

	Economic: Incremental cost per case of early neonatal sepsis avoided as a result of alternative testing strategies for GBS in pregnancy or labour, incremental cost per quality adjusted life year gained associated with each strategy, as a result alternative testing strategies for GBS in pregnancy or labour. Qualitative: Acceptability, barriers and facilitators to implementation, and on the influence of site-specific context and process mechanisms on GBS testing.
Statistical methods	The primary outcome analysis will be on an ITT basis. A mixed effect logistic regression model will be used to compare the risk of early-onset all cause neonatal sepsis in the testing sites relative to the usual practice sites, with the maternity unit as a random effect, adjusting for the minimisation factors. Between-group comparison of the secondary clinical (maternal and neonatal) and process outcomes and between the sub-randomisation of testing strategies and implementation outcomes will also be performed using mixed effect models appropriate for each outcome, adjusting for the minimisation variables and the maternity units as a random effect. P-values and 95% confidence intervals will be provided with point estimates of effect size.

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AMU	Alongside Midwifery-led units
CAG	Confidential Advisory Group
CHI	Community Health Index
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
ECM	Enriched Culture Medium
EOGBS	Early-onset Group B Streptococcus
FMU	Freestanding Midwifery Unit
HCP	Health Care Professionals
HRA	Health Research Authority
GBS	Group B Streptococcus
GBSS	Group B Strep Support
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
IAP	Intrapartum Antibiotic Prophylaxis
ICC	Intracluster correlation coefficient
ICF	Informed Consent Form
ICH-GCP	International Conference on Harmonisation Good Clinical Practice
ITT	Intention-to-Treat
MSDS	The English Maternity Services Dataset
MU	Midwifery Unit
OU	Obstetric Unit
NCT	National Childbirth Trust
NCTU	Nottingham Clinical Trials Unit
NICE	The National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
NNRD	National Neonatal Research Database
NSC	The UK National Screening Committee
PI	Principal Investigator
PHE	Public Health England

PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QALY	Quality-adjusted life year
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development department
SMR02	The Scottish Morbidity Record
SBR	Scottish Birth Record
SOP	Standard Operating Procedure
TMG	Trial Management Group
TSC	Trial Steering Committee
UKNC	United Kingdom Neonatal Collaborative

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BACKGROUND AND RATIONALE

EPIDEMIOLOGY

One in four pregnant women in the UK carry group B Streptococcus (GBS) in the gut and genital tract. Approximately 50% of babies whose mothers are GBS carriers will also be colonised with GBS and of those 1-2% will develop early-onset GBS (EOGBS) disease[1]. EOGBS disease is caused by bacteria ascending from the maternal genital tract during pregnancy (usually in the presence of ruptured membranes, though can occur with intact membranes) or labour. Early-onset GBS infections tend to be associated with pneumonia and sepsis.

Early-onset infection (defined by NICE as 'occurring less than 72 hours after birth' and by the Royal College of Obstetricians and Gynaecologists (RCOG) as 'occurring less than 7 days after birth') affects 1 per 1750 births in the UK (517 babies per year)[2]. GBS is the most common proven cause of early-onset infection (accounting for 40% of all isolates in culture positive cases) in the UK [3]. One study has estimated that in the UK EOGBS infection causes more than 40 neonatal deaths and around 25 cases of long-term disability every year[4]. Mortality is higher among preterm babies (23%)[5].

RISK FACTORS FOR GBS DISEASE

Epidemiological studies have suggested that various factors present at the time of birth are associated with the baby having an increased risk of developing GBS disease, presenting as either an early or late onset infection. A systematic review estimated that 71% of deliveries had no recognised maternal risk factors for GBS disease[6].

The current UK approach of offering intrapartum antibiotic prophylaxis (IAP) to 'high risk' groups has been assessed in a recent cohort of 429 UK and Irish cases with EOGBS infection where only 35% fell into the 'high risk' category, having mothers with one or more risk factors for their baby developing EOGBS infection[7].

Giving IAP to mothers who are known to be colonised with GBS has been shown to reduce the risk of babies developing EOGBS infection[8]. However antibiotics may cause short term complications for the mother (anaphylaxis, medicalisation of labour) or baby (effects on gut microbiome), may have as yet unclear long term complications for the mother or baby[9] and there are concerns about antimicrobial resistance both for the individual and the wider population.

CURRENT PRACTICE

The current strategy recommended by the RCOG and adopted locally across the UK involves identifying maternal risk factors for their baby developing GBS disease, defined as preterm labour, GBS colonisation or bacteriuria in the current pregnancy, a previous baby with GBS infection and maternal fever during labour, and offering those 'higher risk groups' IAP[10]. Additionally women with GBS carriage in a previous pregnancy are offered the option of bacteriological testing for GBS in late pregnancy or IAP.

Universal testing for GBS is undertaken in most developed countries (United States of America, France, Spain, Belgium, Canada, and Australia) and has been attributed to the reduction in EOGBS disease in those countries. In the US, the incidence of EOGBS disease per 1000 live births fell from 0.47 in 1999-2001 to 0.34 in 2003-2005 to 0.25 in 2010[11].The risk of EOGBS disease is significantly lower among infants of mothers undergoing universal testing than those who undergo a risk based approach to prevention, with an adjusted relative risk (RR) of 0.46 (95% CI 0.36-.60) [12]. The corresponding incidence in 2014-5[2] in the UK is 0.57/1000 births, a significant increase since previous surveillance undertaken in

2000 (0.48/1000)[13] despite the introduction of a national risk-based prevention strategy in 2001[14].

THE IMPLICATIONS OF GBS TESTING

The UK National Screening Committee (NSC) recommends "not to screen for maternal GBS carriage in the general population" due to the absence of randomised data on either its effectiveness or cost-effectiveness. It regularly reviews the evidence regarding GBS testing against strict, predefined criteria and makes recommendations to the NHS across all four UK countries. In all of its reviews (latest March 2017), they concluded that none of the five key criteria had been met, and therefore could not recommend universal testing for GBS[15]. The key findings of the review were that introduction of testing would result in tens of thousands of women being offered and taking IAP unnecessarily, whilst the long term effects of this widespread intervention are unknown. The key issue, when considering testing at 35-37 weeks of gestation, was the lack of randomised trial evidence of efficacy, and the accuracy of this antenatal testing as an indication of neonatal risk status at delivery[16]. The review recommended a randomised controlled trial (RCT), noting though that the positive predictive power of an antenatal testing policy for the outcome of a baby with EOGBS disease would be very low.

EOGBS infection is associated with significant morbidity and mortality for the baby. Adopting a universal testing programme for GBS carriage in the UK is likely to result in a reduction in the burden of EOGBS infection. However, universal testing is costly, the mechanism by which maternal colonisation leading to vertical transmission and, in turn, resulting in EOGBS infection is poorly understood and the potential for high levels of overtreatment is of concern.

Both EOGBS sepsis and all-cause early-onset neonatal sepsis rates can be influenced by appropriate IAP. Distinction can only be achieved by culturing neonatal samples taken from sterile sites (blood, cerebrospinal fluid) which will differentiate GBS from other species with high accuracy, and is likely consistent across UK laboratories. However, there may be both false negatives, for example where insufficient blood is obtained, underestimating the true incidence of neonatal sepsis, and false positives arising from contaminating skin and environmental bacteria[39].Targeted IAP could reduce culture positive EOGBS infection, but increase the proportion of culture negative or Gram negative sepsis.

THE CHOICE OF TESTING STRATEGIES

The Enriched Culture Medium (ECM) test, recognised as the international 'gold standard' for detecting GBS, is highly sensitive, although maternal colonisation rates are influenced by the sites sampled and culture methods used. Maternal colonisation can also vary throughout pregnancy, a potential limitation of antenatal culture. A systematic review reported a positive predictive value (PPV) of antenatal culture (mean 69%; range 43-100%) and negative predictive value (NPV) (mean 94%; range 80-100%)[17], meaning 6% of women colonised by GBS at delivery would not be offered IAP, unless other risk factors were apparent. Closer examination of only those studies using samples taken at 35-37 gestational weeks showed mean PPV and NPV values of 93.2% and 97.5%, respectively and included studies not using enriched culture media. Testing at 35-37 weeks misses most preterm births, in which there is greater potential for morbidity and mortality.

Intrapartum rapid tests have the potential for more accurately targeted IAP, provided a result is available in time. The GeneXpert system (Cepheid) produces a result in 35 minutes if positive and 52 minutes if negative, with turnaround time expected to be <30 minutes in the Express version of the cartridge, making it a viable intrapartum test. A meta-analysis of 15 accuracy studies suggests a pooled sensitivity of 94% (95%CI 92-95%) and pooled specificity of 98% (95% CI 97- 98%)[18] . This makes it viable as an intrapartum test, having

both sensitivity and specificity higher than the 90% threshold of the Centre for Disease Control in the USA[19].

TRIAL OBJECTIVES

PRIMARY OBJECTIVE

To conduct a cluster randomised trial to address the research question:

Does routine testing of women for GBS colonisation either in late pregnancy or during labour reduce the occurrence of early-onset neonatal sepsis, compared to the current risk factor based strategy?

SECONDARY OBJECTIVES

The trial will also address secondary questions of effectiveness, cost-effectiveness, acceptability and implementation.

Secondary questions - effectiveness

1. Which routine testing strategy provides a higher rate of women with known colonisation status at four hours prior to delivery?
2. Does the coverage (proportion of women providing a sample for testing) differ between the two routine testing strategies?
3. Does routine testing overall reduce neonatal unit admission, compared to the risk factor based strategy, and if so, is one routine testing approach superior?

Secondary questions – cost-effectiveness

1. Which of the three strategies is most cost-effective?

Secondary questions - acceptability

1. What is the acceptability of the different methods of routine testing?
2. What are the barriers and facilitators to implementation of either routine testing strategy?
3. How do context and process mechanisms influence the acceptability and implementation of testing (e.g. place of birth, preterm birth, age, socioeconomic group and ethnicity)?

Secondary questions - implementation

1. What are the key process parameters predictive of reduced neonatal admission?
2. Do unit level factors influence uptake of testing?
3. How can processes be influenced to maximise impact of intrapartum testing?

STRATEGIES TO BE COMPARED

The routine testing strategies will use antenatal enriched culture medium (ECM) testing or intrapartum rapid testing using the Cepheid GeneXpert system, with IAP offered if the test is positive for GBS presence in the sample taken. The control strategy is to offer IAP if a maternal risk factor for EOGBS in her baby is identified before or during labour.

Further details of the testing methods and criteria are given in the *TRIAL PROCEDURES AND DATA COLLECTION* section.

TRIAL DESIGN

TRIAL CONFIGURATION

A multi-centre prospective two-arm parallel cluster randomised controlled superiority trial with internal pilot, feasibility evaluation, qualitative study and parallel economic modelling.

Primary Outcome

All-cause early neonatal sepsis, identified from local and national data sources, and confirmed by a blinded adjudication panel.

Neonatal sepsis will be defined as:

- A positive-culture of a pathogenic bacteria from blood or cerebrospinal fluid, **or**
- Negative/ unknown culture status with ≥3 agreed clinical signs or symptoms, for which antibiotics are given for ≥5 days, within 7 days of birth. Note: If the infant died, was discharged, or transferred prior to the completion of 5 days of intravenous antibiotics, the infant would still be classed as having sepsis if the intention was to treat for 5 or more days.

  The following acute onset clinical or laboratory features are considered predictive of invasive infection:

  - increase in oxygen requirement or ventilatory support
  - increase in frequency of episodes of bradycardia or apnoea
  - temperature instability
  - ileus or enteral feeds intolerance and/or abdominal distension
  - reduced urine output to <1ml/kg/hr
  - impaired peripheral perfusion (capillary refill time >3 seconds, skin mottling or core-peripheral temperature gap >2°C)
  - hypotension (clinician defined as needing volume or inotrope support)
  - irritability, lethargy or hypotonia (clinician-defined)
  - serum C-reactive protein levels >15 mg/L or procalcitonin ≥2 mg/mL
  - white blood cells count 20×10^9 cells/L or platelet count 180 mg/dL)
  - glucose intolerance (blood glucose <2.2mmol/l or >10mmol/l)
  - metabolic acidosis (base excess <-10 mmol/L or lactate >2 mmol/L)

Blinded adjudication panel

An adjudication panel of neonatologists will be convened to review the individual level data of babies with clinically suspected sepsis. Three experts, masked to the location of birth and of the neonatal unit will review each case, state their individual opinion regarding the diagnosis of sepsis, and reach a consensus if not unanimous.

The adjudication panel will also review the individual level data of babies who die during labour (intrapartum stillbirth) to determine whether sepsis is a primary cause of death.

SECONDARY CLINICAL OUTCOMES

With the exception of maternal intrapartum anaphylaxis, all neonatal and maternal outcomes will be collected from routine data sources as detailed elsewhere. Maternal age, parity, ethnicity and the Index of Social Deprivation for their home at the time of childbirth and neonatal sex will be collected as descriptors.

Neonatal

- Birth Weight
- Perinatal mortality

- 5 minute Apgar
- Fetal acidaemia, defined as cord arterial pH < 7.05, or if no cord blood and admitted to neonatal unit, the first neonatal pH obtained.
- Gestational age at birth
- Neonatal specialist care (length of stay, level of care)
- Seizures
- Abnormal neurological signs (hypotonia or abnormal level of consciousness) at > 24 hours of age

Maternal

- Mode of onset of labour
- Mode of delivery
- Duration of hospital stay
- Change of intended location of childbirth
- Maternal intrapartum anaphylaxis due to IAP

SAFETY ENDPOINTS

The main safety outcome we seek to avoid is neonatal sepsis, which is also the primary outcome that GBS testing aims to reduce. Cases of neonatal sepsis will be collected quarterly from routine data sources and confirmed by an adjudication panel.

Cases of maternal intrapartum anaphylaxis due to IAP will be collected from participating units' Maternity Governance teams.

PROCESS OUTCOMES

It is important to collect and analyse process outcomes for usual practice and both testing strategies, as failure to detect differences in early-onset sepsis may be due to poor compliance with the processes, rather than an intrinsic problem with the tests. It will also be important to measure any change in maternal IAP provision and/or neonatal care arising from the strategy allocated. These outcomes will be collected in a consecutive sample of 100 women per unit. Key parameters that will determine feasibility and overall effectiveness of the risk based strategy and the two testing groups will include:

- Number of women with risk factors for EOGBS infection developing in the baby
- Number of women having a swab taken (of all those eligible for testing)
- Number of women who decline a swab when offered
- Number of women having a swab taken at the appropriate time (of all those swabbed and all those eligible). The target time window is >35 weeks of gestation for those in antenatal ECM units and those planning home or FMU deliveries in the Trusts/ Boards with maternity units allocated intrapartum rapid testing, and on admission in labour for those planning consultant-led unit or eligible AMU deliveries in the intrapartum rapid testing units.
- Number of women with a test result available at least 4 hours before childbirth
- Number of women receiving GBS-specific intrapartum antibiotic prophylaxis
- Number of women with first dose of antibiotics administered at least 4 hours before childbirth
- Number of women with first dose of antibiotics administered at least 2 hours before childbirth
- Total dose of IAP
- The proportion of women who tested positive for GBS, tested negative for GBS or who did not have a test result. For intrapartum rapid testing sites, the number of failed tests will be directly available from the GeneXpert machine

- Number of women with risk factors identified, in all units, of all those eligible for testing (testing units) or attempting a vaginal delivery (usual care units)
- Number of women offered IAP, and number of women who were not offered IAP, of those should have been offered according to a positive test result or risk factors
- Number of women declining IAP when offered.
- Number of women offered, and accepting IAP, of those with a negative test result or no documented risk factors
- Number of babies of mothers who tested positive for GBS whose vital signs and clinical condition were observed for at least 12 hours
- Number of babies of mothers who tested positive for GBS who were investigated for infection and had intravenous antibiotics commenced
- Number of women with intrapartum or postnatal sepsis

QUALITATIVE OUTCOMES

- Acceptability, barriers and facilitators to implementation
- The influence of site-specific context and process mechanisms on GBS testing

Qualitative outcomes are further described in *QUALITATIVE STUDY* section

ECONOMIC OUTCOMES

- Incremental cost per case of early-onset neonatal infection avoided as a result of alternative testing strategies for GBS in pregnancy or labour
- Incremental cost per QALY gained associated as a result of alternative testing strategies for GBS in pregnancy or labour

RANDOMISATION

Randomisation will be at the maternity unit level to avoid any risk of contamination. Eligible maternity units will be randomised on a 1:1 ratio to a routine testing strategy or to the risk factor based strategy, using a minimisation algorithm.

Minimisation variables will be:

- Overall number of deliveries per year (<4000, 4000– <5000 and ≥5000), according to national data for preceding year
- Neonatal unit level of care tier associated with maternity unit (Special Care Unit, Local Neonatal Unit or Neonatal Intensive Care Unit)
- Presence of alongside midwifery unit, at the time of randomisation

The allocation algorithm will be created by the Nottingham Clinical Trials Unit (NCTU) in accordance with their Standard Operating Procedure (SOP) and held on a secure server.

The Chief Investigator or authorised designee will use the remote, internet-based randomisation system to obtain the treatment allocation for each unit after clarification of site level eligibility. Eligible women will be offered the care pathways to which their maternity unit is randomised.

There will be a further second-level randomisation of the routine testing units to one of the two testing strategies. This will be restricted to achieve balance between the antenatal ECM and intrapartum rapid test strategies.

Blinding of women and healthcare professionals is not possible due to the nature of the strategies.

TRIAL MANAGEMENT

The University of Nottingham will be the sponsor and the host organisation, with Professor Jane Daniels as the Chief Investigator, lead grant holder and data custodian and Dr Kate Walker as the Deputy Chief Investigator and clinical lead. The Nottingham Clinical Trials Unit (NCTU) will be the trial coordinating centre.

Subcontracts will be put in place between the University of Nottingham, Nottingham Clinical Trials Unit, and other partner organisations, detailing the budget resources, allocating the responsibilities and the expected contributions of each party.

Susan Ayers will be the lead investigator for the qualitative study, which will be undertaken at City, University of London, with liaison with the NCTU and the University of Central Lancaster.

Stavros Petrou will be lead investigator for the economic evaluation, which will be undertaken at Oxford University, with liaison with NCTU and Warwick University.

The Trial Steering Committee (TSC) will meet (in person ideally) prior to commencement of the accrual and then at a minimum of once yearly (in person or remotely) and will provide independent oversight of the trial and associated studies on behalf of the trial sponsor.

The Data Monitoring Committee (DMC) will meet (in person) prior to commencement of the accrual and then at a minimum of once yearly (in person or remotely) to independently assess safety, effectiveness and futility of the trial and will report to the TSC. Full details of both the TSC and DMC will be outlined in a charter.

The Trial Management Group (TMG) will meet at least every two months, and will be responsible for the day-to-day management of the trial, and the linkage with the qualitative and economic studies. The TMG will report to the TSC at their meetings.

All maternity units will nominate a local Principal Investigator (PI) who will be responsible for the implementation of the trial in their unit. The PI does not have to be an obstetrician though must liaise with all services (Obstetrics, Midwifery, Microbiology, Neonatology, Risk Management). Responsibilities and targets will be detailed in a non-commercial site agreement between the NHS Trust/ Board and sponsor.

The Chief Investigator and Deputy Chief Investigator (clinical and non-clinical) have overall responsibility for the trial and shall oversee all trial management. The Deputy Chief Investigator will be responsible for the monitoring of safety outcomes and reporting arrangements. A Senior Trial Manager will provide oversight of the Trial Manager who is responsible for the day-to-day running of the trial.

DURATION OF THE TRIAL

The funding award is for 42 months. This includes a 12 month set-up phase, a 24 month recruitment phase (including a 9 month internal pilot and feasibility evaluation) and 7 months for final retrieval of data, analysis and write-up.

Duration of participation and definition of end of the trial

The overall trial duration is not defined in relation to the accrual of women but relative to data collection. Each individual maternity unit will participate for 12 months and women giving birth during their unit's study period will be included. There is a time lag between this and the data becoming available in routine datasets of about 4 months. The trial will end when the final dataset is retrieved from the last centre to finish accrual.

MATERNITY UNIT AND WOMEN ELIGIBILITY

SETTING

Up to 80 maternity units (obstetric unit or alongside maternity unit) in England, Scotland and Wales are required. There are four locations for maternity care in the UK: birth in a maternity hospital (obstetric unit or OU); birth in two types of midwifery unit (MU), either alongside (AMU) or freestanding (FMU); or birth at home. Women who have their care in a freestanding maternity unit or at home cannot be given IAP.

RECRUITMENT

For the cluster randomised trial with a no consent model, participants will not be approached to join the trial, making the traditional concept of recruitment redundant. Information about the trial will be on display in the relevant clinical areas. Information will also be provided to women (on request) on how to withdraw their data via the national data opt-out process if they wish to. Women will provide clinical verbal consent for vaginal-rectal swabs, in accordance with local guidelines.

Individual data regarding process outcomes will also be collected for 100 women from 2 months after the start of the study period for each unit.

A small sub-set of maternity units will be involved in the qualitative aspect of the study. Women who are eligible and interested in being involved in the qualitative aspect of the study, will be approached prior to discharge but after delivery by a member of their local usual care team (including local Research Team if local operating policies permit this) and asked to provide written consent and contact details which will be provided to the research team. The research team will contact these women 4-6 weeks after birth to reconfirm consent and arrange a convenient time to interview them. Hospital records will be checked prior to contacting women to identify any participants who have experienced perinatal events such as stillbirth. Clinicians who are eligible for the qualitative aspect of the study will be identified and approached by research midwives at each maternity unit (or will contact the research midwifes directly if interested). Those who agree will be given further information and asked to provide consent.

ELIGIBILITY CRITERIA

Site level

Consultant-led maternity units, and alongside midwifery-led units (AMUs) if able to accept women requiring IAP, will be eligible to participate if they are capable of implementing either the antenatal enriched culture or intrapartum rapid testing strategies with training and support.

Up to 80 units will be identified though expression of interest requests via the NIHR Clinical Research Network, maternity research networks and personal contacts. A site selection questionnaire will be completed by a unit and returned to the NCTU. If any service indicates that the unit cannot participate as either a routine testing or usual risk factor based unit, if so allocated, the unit will not be randomised. Withdrawal of units after randomisation must be avoided if at all possible.

One Trust/ Board may contain several maternity units. Each unit can be considered as an individual cluster if the routine data sources can discriminate between the maternity units within the Trust/ Board.

All consultant-led maternity units are capable of providing IAP to women with GBS risk factors. Some AMUs are also able to provide IAP, and these would be eligible for participation if they were able to implement antenatal ECM test and rapid intrapartum testing.

Some Trusts/ Boards will run AMUs that are not able to provide IAP, have freestanding midwifery units or provide homebirth services, in addition to a consultant-led unit or AMU. These units/ services themselves will not be able to offer intrapartum testing and so will not be able to act as an individual cluster and will not be randomised. Women using these services should be informed that the Trust/ Board is participating in the GBS3 trial and be offered the opportunity to consider their intended place of birth within that Trust/ Board. A Trust/ Board randomised to antenatal ECM testing should offer the test to all women, regardless of their intended place of birth, where feasible.

The contracted microbiology laboratories providing services to the maternity units must be prepared to use Public Health England Standard for Microbiological Investigations (PHE SMI) B58 for the ECM testing for GBS for the duration of the trial. The PHE SMI B58 is the Public Health England guidance on the UK Standards for Microbiology Investigations for detection of carriage of group B streptococci.

The maternity unit must be prepared to host a Cepheid GeneXpert machine in a location convenient to the delivery suite

Maternity units are permitted be involved in other clinical trials, with the exception of trials studying intrapartum or neonatal antibiotics. These type of trials would need to be discussed and agreement obtained from the Chief Investigator and Deputy Chief Investigator prior to sites agreeing to participate.

Individual level

There will be two levels of eligibility for individual women:

- Testing level – eligibility to have a ECM or rapid test, or be reviewed for risk factors
- Dataset level – eligibility to be included in the dataset for analysis, regardless of whether test performed.

There is no exclusion based on age of women or multiple births.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria – testing level

- In ECM units, all women attending an antenatal clinic after 35 weeks' gestation
- In rapid test units, all women who experience labour or prelabour rupture of membranes at ≥37 weeks' gestation
- In risk factor units, all women who experience labour or prelabour rupture of membranes at ≥24 weeks' gestation

Exclusion criteria – testing level

- Women who decline clinical consent to provide a swab
- Women who have had a previous baby with GBS disease (early or late onset) and who want IAP
- In rapid test units, women who on arrival at the maternity unit are considered likely to deliver they baby within the next hour
- In rapid test units, women in preterm labour (suspected, diagnosed, established), who should be offered IAP routinely
- Known congenital anomaly incompatible with survival at birth, of a singleton or all multiple fetuses
- Known prelabour intrauterine death, of a singleton or all multiple fetuses

Inclusion criteria – dataset level

In all units, all women giving birth ≥24 weeks' gestation within their unit's study period, regardless of mode of delivery, and all her live born babies.

Women who experience an intrapartum stillbirth will be included as they may have had testing for GBS and GBS may be implicated in the aetiology of their stillbirth. Given that it will not be possible to obtain the primary outcome of neonatal sepsis for those babies, all cases of babies who have died during labour or birth will be reviewed by the adjudication panel. Where the adjudication committee deem the primary cause of death is attributable to sepsis (either from post-mortem findings or positive microbiological results) they will be counted as cases within the primary outcome.

Exclusion criteria – dataset level

- Known congenital anomaly incompatible with survival at birth, of singleton or all multiple fetuses
- Known prelabour intrauterine death, of singleton or all multiple fetuses.
- Withdrawal of consent to use data, through the NHS data-opt out

WITHDRAWAL OF CONSENT

For the cluster trial, there is no individual consent to participation. However, individual women may review the trial information (e.g. posters, videos) and decide that their data is not used. As the trial will use routine data, obtained for all women delivering during the study period, the only route to remove their data is via the national data opt-out. Women in England will need to register on https://www.nhs.uk/your-nhs-data-matters/, by phone or by printing and completing a paper form. If they use the national data opt-out, women will be made aware that this will not affect their future care but that it will be applicable for all research and planning purposes and not solely for GBS3 trial. National Services Scotland and Wales do not have a specific opt-out form.

The withdrawal request would be applicable if the request is received before the routine data for that individual woman has been transferred to the NCTU from the national routine data sources. Once the routine data has been received and processed at NCTU, data will be anonymised and therefore it will not be possible to withdraw the data from the analysis.

Women will be able to decline the opportunity to be interviewed for the qualitative study after providing consent to be contacted and can withdraw consent for the recording and transcribed information from their interview to be used within 14 days of interview recording. Once the analysis has been completed, the interview transcript cannot be removed from the dataset. However, quotes from the interview will not be used in any future report.

Participants cannot be withdrawn from the trial at the request of the Investigator or clinical care team.

TRIAL PROCEDURES AND DATA COLLECTION

TESTING STRATEGY PROCEDURES

Brief details of testing strategies are given here. Working practice templates and flowcharts will be provided to units, which can be adapted to reflect local policies and circumstances, provided the principles described here are followed.

Vaginal-rectal swab for antenatal or intrapartum testing

Depending on the stage of pregnancy or labour, the test is discussed with and offered to the woman. If she consents to testing, swabs will be obtained by either the woman herself, or a suitably trained member of the woman's care team. This could be on admission to the labour or induction ward, before a vaginal examination is performed in the intrapartum testing units,

or at antenatal clinics or visits in hospital or the community for women intending to give birth at antenatal testing units.

A swab will be taken from the lower vagina first and then from the rectum, using the same swab for each orifice. Vaginal specimens for testing will be obtained by gently rotating the swab across the mucosa of the lower vagina. A rectal sample will be obtained by inserting the swab through the anal sphincter and then gently rotating. After withdrawal, the swab should be immediately placed in the transport tube.

Should a woman agree to a vaginal swab but decline the rectal swab, this will be permitted, after it has been explained to the woman that improved detection of GBS colonisation is by taking a swab from the rectum as well as the vagina.

Should lubrication be required to minimise participant discomfort whilst the swabs are taken, use of lubricating gels such as KY should be avoided. These gels contain antimicrobial preservatives which may also interfere with the rapid or ECM test. If lubrication is required the swab should be moistened with sterile non-bacteriostatic fluid (e.g. sterile water or saline) only.

A vaginal examination is usually undertaken to establish labour, which may require the use of a lubricant gel. Furthermore, women who are being induced may have had a pessary inserted distally to the cervix, and placement of this pessary may be assisted by the application of a lubricant gel. The antibacterial chlorhexidine is sometimes used as a vaginal cleanser, although there is no strong evidence for its efficacy in reducing neonatal infection[20] and NICE guidelines recommend using water only for hygienic cleaning[21] Women who have experienced recent internal examinations which have required the use of lubricant gels, or have used chlorhexidine, cetrimide or any other similar antibacterial solutions or creams, are eligible for intrapartum testing and swabbed as described above.

Antenatal enriched culture medium testing

Maternity units randomised to ECM testing will collect vaginal-rectal swabs from women at 35-37 weeks gestation or for women with a planned elective induction of labour prior to 38 weeks, 3-5 weeks before the anticipated delivery date.

Samples from the swabs must be cultured according to Public Health England's Standard for Microbiology Investigation B58 of 2018 or subsequent revision(22). The maternity unit's contracted laboratory will incubate cells from the swab in Lim enriched culture broth. After 18-24 hours incubation at 35-37°C in 5% CO_2, the specimen is sub-cultured onto a selective, blood or chromogenic agar plate. The plates are then cultured again for 18-24 hours at 35-37°C before being read by a microbiologist. Presumptive colonies of GBS are confirmed by a specific antigenic detection test or the Matrix Assisted Laser Desorption Ionisation Time-of-Flight (MALDI-TOF) method.

Intrapartum rapid testing

Maternity units randomised to rapid testing will collect vaginal-rectal swabs from women at ≥37 weeks gestation if they are in labour (latent or established) or about to be induced, and are not perceived to be likely to deliver imminently, by the clinical team. The sample collected on the swab will be tested using the Cepheid GeneXpert GBS test system using the Xpert GBS test cartridges.

The GeneXpert system and the Xpert GBS cartridges are CE marked in the UK for the rapid identification of GBS from vaginal-rectal swabs and will be used in GBS3 in accordance with its marketing licence and will not be modified in any way. Training, cartridges and swabs will be arranged by the GBS3 Coordinating Centre, according to local requirements.

Risk-factor Based Strategy (Usual Care)

Maternity units randomised to the risk factor based screening and treatment approach must continue to use their current local policy. This should be based on the RCOG Greentop

Guideline 36[10], which states women with the following risk factors for their baby developing EOGBS infection should be offered IAP:

- Having a previous baby with GBS disease
- Discovery of maternal GBS carriage during pregnancy
- Preterm labour
- Suspected maternal intrapartum infection, including suspected chorioamnionitis
- Intrapartum pyrexia

Women who are known to have been colonised with GBS in a previous pregnancy should be offered the options of IAP, or ECM testing in late pregnancy with the offer of IAP if GBS is detected.

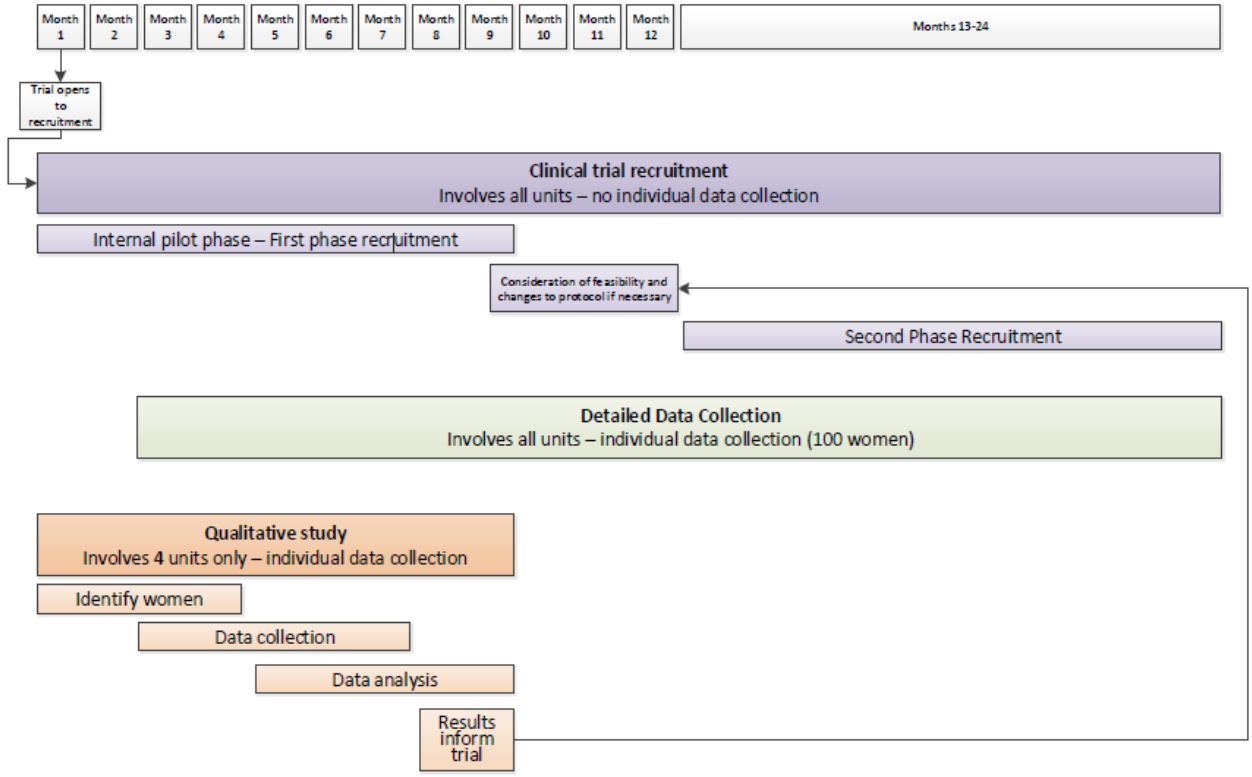
SITE TRAINING AND IMPLEMENTATION ASSESSMENT

The testing strategies will be implemented for a period of time before the start of the study period for which routine data will be collected. During the implementation period, the maternity units assigned ECM or rapid testing will be visited by the trial team, including a trial midwife. The trial team will deliver training on the taking of swabs and use of the GeneXpert machine, or the process by which the ECM test is requested and the results fed-back. When local approvals are in place, the testing will start and the unit deemed to have been initiated.

Each week after the initiation, the number of tests performed as a percentage of those eligible for testing (from the unit's reported birth records) will be determined. The target is 80% coverage: cascaded training must ensure all midwifery teams and shifts are trained promptly and efficiently. After 12 weeks, the Trial Manager will notify the unit that the study period has started. If 80% coverage is not met after the first 4 weeks (acknowledging in ECM units the lag between the swab being taken around 36 weeks' gestation and the average expected delivery date of 40 weeks), the unit will need to extend and intensify the training and implementation of the testing process. Units will not be withdrawn if they fail to achieve the 80% test uptake rate by 12 weeks, but there may be consequences regarding support for excess treatment costs. At 12 weeks, the unit will be deemed to be open and routine data will be used from that point onwards.

If a testing maternity unit fails to achieve 80% test uptake by three months after initiation, it will be included in the primary analysis, but a sensitivity analysis will be conducted excluding units which failed to reach 80% uptake.

RECRUITMENT PHASE OF TRIAL



DETAILED DATA COLLECTION OF TESTING STRATEGIES

For determining the process outcomes described in the Process outcomes section, individual level data, not reported in the National Maternity Data Set, is required. To collect data on all women would negate the advantages of routine data use, so detailed data collection of the testing process in ECM and rapid test units, and of the provision of IAP in all maternity units, will be undertaken. This will be source data collection using an online proforma designed for each testing strategy. At each unit, individual data for 100 women will be gathered. This will commence 2 months after the trial start date.

This will provide individual level data associated with the testing coverage, IAP and resource use for approximately 4000 women in the risk-factor based usual care units, 2000 women in ECM units and 2000 women in rapid testing units.

This data will be extracted from the women's health care records, and transcribed by the research midwife at each unit onto the GBS3 specific online database, using the NHS number as the identifier.

INTERNAL PILOT

An internal pilot will end 9 months after the first maternity units starts their accrual period, to explore aspects of deliverability (e.g. enrolment of units, acceptability and uptake of testing and intrapartum antibiotic prophylaxis (IAP), fidelity in both trial groups). The below stop/ go criteria will be used to assess continuation of trial:

	Adherence to strategy

Sites Opening	Site Level	Trial Level (all sites)
30-45 units open *Continue*	**<10% missed opportunities for testing** *Continue*	**<10% missed opportunities for testing** *Continue*
15-30 units open *Identify problems, implement strategies to address*	**10-30% missed for testing** *Repeat and improve training*	**10-30% missed for testing** *Identify problems, implement strategies to address*
<15 units open *Terminate trial unless barriers are promptly resolved.*	**>30% missed opportunities for testing** *Review, retrain*	**>30% missed opportunities for testing** *Terminate trial unless barriers are promptly resolved.*

TRANSPORT AND STORAGE OF THE VAGINAL-RECTAL SWAB

The vaginal-rectal swab will be used only for clinical purposes and the swab and test consumables (culture plates, test cartridge etc.) disposed of after use, according to local hospital policies.

Antenatal enriched culture test

Vaginal-rectal swabs will be collected, stored and transported in accordance with PHE SMI B58 SMI B 58 (detection of carriage of group B streptococci)[22].

Intrapartum rapid test

Vaginal-rectal swabs will be taken and analysed immediately using the Cepheid GeneXpert GBS rapid testing system which will be located on or near the maternity unit.

STATISTICS

METHODS

The analysis and reporting of the trial will follow the CONSORT extension for cluster trials guidelines. Detailed statistical analyses will be documented in a Statistical Analysis Plan which will be finalised prior to database lock. All data will be analysed using Stata version 15 or later. No interim analyses are planned.

SAMPLE SIZE AND JUSTIFICATION

Main comparison

The sample size is based on the rate of all-cause early-onset neonatal sepsis between the routine testing and the risk factor based randomised strategies. The National Screening Committee model[23] considered a cohort of 711,999 live births, excluding elective Caesarean deliveries and estimated 351 cases of EOGBS infection across all gestation age deliveries under a risk factor based IAP strategy, giving rise to a rate of 0.0493%. Adding antenatal

testing to the risk factor strategy was estimated to result in 294-299 EOGBS infections, a relative risk ratio of 0.84. This control rate is also between other estimates.[24, 25]

Assuming GBS contributes 50% of all early-onset neonatal infection (the remainder *E. coli* (18%), other gram positives (23%),[26]) then the all-cause rate would be 0.98/1000 live births. Benzylpenicillin will have a significant effect on 73% of cases caused by GBS and other Gram-positive yet have no impact on *E. coli* and other Gram-negative infections. A Cochrane review reported a risk ratio for IAP for EOGBS infection of 0.17 (95% CI 0.04-0.74),[27] albeit from three small trials with high risk of bias; this effect should be assumed to be optimal IAP, with perfect compliance, and is based on culture confirmed GBS infection or colonisation. To achieve a reduction in all-cause neonatal infection rate through testing of 40%, the treatment effect achieved on the Gram-positive bacteria needs to be 0.44, which is consistent with the Cochrane data and in line with the trends seen in the USA following introduction of testing.[28] The effect of routine testing will be derived only from term babies, as all pre-term babies will be offered IAP according to the RCOG guidelines.

To detect a 40% reduction (a reduction in event rate from 0.000986 to 0.0005916), with a 90% power and two-sided significance level of 5%, a total sample size of 212,960 women would be required without inflation for clustering effect. There are no published estimates for the hospital-level intracluster correlation coefficient (ICC) for early-onset neonatal infection, but we would expect any variations in the infection rates across clusters to be a result of individuals' clinical or demographic risk factors, biochemical or molecular markers, or bacterial load rather than hospital-level factors, hence we have chosen a small ICC of 0.0001. Assuming this ICC, an average cluster size of 4,500 (calculated using published NHS Maternity statistics for deliveries in consultant-led or AMUs with a minimum of 3000 deliveries per annum), and allowing for a coefficient of variation in cluster size of 0.31, the design effect for the sample size would be around 1.5. Adjusting for the design effect would lead to a total sample size of 320,000 women. These could be recruited from a minimum of 72 maternity units, but we aim to recruit from 80 sites to improve our power should infection rates be lower, and also reduce the trial duration.

Sub-randomisation comparing antenatal enriched culture medium testing versus intrapartum rapid testing

A second level randomisation of maternity units will be performed so that 20 units undertake each testing strategy. The incidence rate of neonatal sepsis is low, so we will have insufficient power (63%) to use the same primary outcome as the principal comparison. Comparisons for this sub-randomisation will focus on rates of uptake, accuracy in relation to maternal colonisation in labour and abilities to deliver a test in time for adequate IAP that cumulatively influence effectiveness.

Data on the proportion of women providing a swab, and of those how many test results were available at least four hours before delivery will not be available from routine data sources. Site level individual-level data collection will be required, but is not feasible on the total trial population. We therefore propose a 2.5% sample, or data from an average of 100 participants from each of the 20 antenatal ECM and 20 intrapartum rapid testing maternity units (total of 4000 datasets). Accounting for clustering and assuming an ICC of 0.005 with cluster size of 100, this gives us an effective sample size of 1350 per test strategy. With this number we will be able to detect difference in "missed testing opportunity" of approximately 4% (e.g. 10% in antenatal ECM testing maternity units to 14% in intrapartum rapid testing units) and a difference in ">4 hours IAP" of 6% (e.g. 65% from intrapartum rapid testing to 71% from antenatal ECM testing) both at 90% power and p=0.05.

Definition of populations analysed

Analysis of primary outcome will be according to intention-to-treat (ITT). The definition of the populations to be analysed will be clarified in the statistical analysis plan prior to database lock.

ASSESSMENT OF EFFICACY

A mixed effect logistic regression model will be used to compare the risk of early-onset all cause neonatal sepsis in the testing maternity units relative to the usual practice units, with the maternity unit as a random effect to take into account the clustering effect, adjusting for the minimisation factors. Further analyses will be performed to check the conclusions are robust using aggregate cluster-level infection rate summaries using a two-stage procedure of first fitting a regression model adjusting for the minimisation factors (but not the testing strategy) to obtain the covariate-adjusted residuals which will then be analysed in the second stage using t-test to test the between group differences in the risk. Should there be any non-compliance with some hospitals refusing to implement the new intervention then a sensitivity analysis will be performed using complier average causal effect (CACE) analysis to account for any non-compliance.

Between-group comparison of the secondary clinical (maternal and neonatal) and process outcomes and between the sub-randomisation of testing strategies and implementation outcomes will also be performed using mixed effect models appropriate for each outcome (linear for continuous outcome and logistic for binary outcomes), adjusting for the minimisation variables and the maternity units as a random effect. P-values and 95% confidence intervals will be provided with point estimates of effect size.

ASSESSMENT OF SAFETY

Analysis of safety data relating to maternal intrapartum anaphylaxis due to IAP will be presented descriptively using frequency counts and percentages in each allocated group.

PROCEDURES FOR MISSING, UNUSED AND SPURIOUS DATA

We will attempt to follow up on all randomised maternity units and retrieve data from all the individuals within the units in order to limit the extent of missing data. However, missing data is inevitable and in this trial will take the form of the whole maternity unit dropping out of the trial or failure to obtain outcome data for some participants within participating units from the routine data sources. Primary analysis will be performed based on complete case analysis, utilising all the received data, with the assumption that missingness is independent of the outcome, given the covariates. Sensitivity analysis will be performed on the primary outcome to explore the impact of departures from this assumption using multiple imputation, taking into account the multilevel structure of the data, on an assumption that missingness depends only on the observed values.

QUALITATIVE STUDY

RATIONALE

For routine GBS testing to be successful it needs to be acceptable to women and health professionals, as well as feasible to implement in different healthcare contexts. This qualitative research study will address these issues and will provide rapid feedback into the cluster randomised trial so procedures can be considered and amended if necessary.

RESEARCH QUESTIONS

The aims of this research are to determine:

1. What is the acceptability of the different methods of routine testing for GBS colonisation to pregnant women and healthcare professionals?
2. What are the barriers and facilitators to implementation of either routine testing strategy?

3. How do individual and site-level context and process mechanisms influence the acceptability of testing?

OBJECTIVES

The objectives of this research are to:

1. Conduct in-depth interviews with women to determine the acceptability of different methods of/timing for routine GBS testing, and contextual barriers and facilitators to implementing these different methods.
2. Conduct in-depth interviews with health professionals to determine the acceptability of different methods of/timing for routine GBS testing, and site-specific contextual barriers and facilitators to implementing these different methods.

THEORETICAL FRAMEWORK

The theoretical framework of acceptability provides a detailed outline of different aspects of acceptability[29] including affective attitudes, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs and self-efficacy. Site-specific contextual factors will be examined using the NICE guidelines on identifying barriers to changing practice which outline the practical, environmental and organisational barriers and facilitators to implementing changes in clinical practice [30].

STUDY SETTING

Women and clinicians will be recruited from 4 NHS sites participating in the pilot phase of the RCT. Sites will be chosen to ensure successful sampling of different groups, and to include sites with high and low uptake of GBS testing. A research midwife at each site will be the nominated lead for that maternity unit to oversee set up and recruitment procedures at that site. There are no other site-specific requirements. All research will be conducted according to the principles of Good Clinical Practice.

IDENTIFICATION OF PARTICIPANTS – WOMEN AND CLINICIANS

Inclusion criteria

- Women will be eligible if they are up to 12 weeks postpartum, 16 years of age or older, and reasonably fluent in English.
- Women giving birth in a maternity unit allocated a testing strategy, and not a usual care unit.
- Clinicians will be eligible if they are a registered health professional working in an NHS maternity or neonatal service in one of the 4 NHS recruitment sites.

Exclusion criteria

- Women will be excluded if their baby died prior to birth or if they lack capacity to give informed consent.
- Clinicians will be excluded if they are not currently practicing and/or working in an NHS maternity or neonatal service.
- Women and clinicians not receiving care or working in the NHS sites taking part in this study will not be eligible.

SAMPLING

Purposive sampling will be used to ensure women from specific groups are represented where there is evidence the characteristics of these groups might influence the acceptability and implementation of either GBS testing strategy. These groups are:

a. Place of birth: routine testing may be more challenging to implement in births at home or in a freestanding or alongside midwifery unit. Women who give birth at home, in hospital and at FMU/AMUs will therefore be recruited.
b. Preterm birth: Testing is more challenging to implement with women who give birth preterm and at present women in confirmed preterm labour are automatically offered IAP, although they may prefer testing and selective IAP for those who test positive. Women who had preterm and term deliveries will therefore be recruited.
c. Age and ethnicity: A study of intrapartum testing for GBS suggested it may be less acceptable to young women and those from specific ethnic groups[31].Women from a range of ethnicities and ages will be recruited.

Purposive sampling will be used to ensure clinicians from different groups are represented (midwifery, obstetric, neonatal, microbiology) with a spread of clinical experience who work in hospital (teaching and general), FMU/AMU and community settings.

SIZE OF SAMPLE

The sample size of women and clinicians will be determined by saturation within subgroups. It is anticipated that to ensure adequate representation of different groups and saturation of themes specific to these groups, we will interview a minimum of 50 women so that a minimum of six women will be included with each characteristic. For clinicians we anticipate a minimum of 30 interviews will be needed to ensure adequate representation of different clinical disciplines and NHS services. More may be recruited depending on saturation.

PARTICIPANT IDENTIFICATION - WOMEN

Clinical midwives at each site will identify postpartum women who meet eligibility criteria, outline the objectives of the study and provide a detailed participant information sheet (PIS). Posters in clinic will display study details and contact details of who to contact if a woman is interested in taking part. Potential participants will have the opportunity to ask any questions from the research midwife or directly from the research team. The research midwife will obtain written consent and their contact details, which will be sent to the research team. The research team will contact the participants at least 48 hours later to reconfirm consent and arrange a convenient time for interview. To ensure diversity amongst the women who participate purposive sampling will be used (see *Sampling* section). Women who decline GBS testing and those who agree will be invited to participate to gain greater understanding of reasons why women decline testing.

PARTICIPANT IDENTIFICATION - CLINICIANS

Research midwives at each site will identify clinicians involved in maternity care and GBS testing and approach them to invite them to take part, provide information about the study and ask for consent to participate. Clinicians can also contact research midwifes to express interest and will be provided with information on study. To ensure diversity purposive sampling will be used to include clinicians from different disciplines and those with different levels of experience (see *Sampling* section).

Clinicians who are interested in participating will be asked to provide written consent and their contact details which will then be sent to the research team. The research team will contact clinicians at least 48 hours later to re-confirm consent and arrange a convenient time to interview them.

DATA COLLECTION

A semi-structured interview schedule will be developed to examine aspects of acceptability, and individual and site-specific contexts that might impact on the acceptability of routine GBS testing. Acceptability will be examined using the theoretical framework of acceptability[17] as a

guide, which includes affective attitudes, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs and self-efficacy. Site-specific contextual factors will be examined, including practical, environmental and organisational barriers and facilitators to implementing routine GBS testing[18]. The draft interview schedule will be reviewed by the project research team, PPI leads and the Research Advisory Group at City, University of London, and revised as necessary.

Telephone interviews will be conducted by an experienced qualitative research fellow using the semi-structured interview schedule. Interviews will be audio-recorded. If, after their interview, a participant no longer wants their interview transcript to be used, it will be withdrawn. Withdrawal requests should be received within 14 days of interview as, once the analysis has been completed, the interview transcript cannot be removed. However, quotes from the interview will not be used in any future report. To protect participants' personal information, audio recordings will be identified by participant number. Transcription will be done by a transcription service under a data-sharing agreement which is GDPR compliant. Audio recordings, interview transcripts and data analysis files will be encrypted and stored on a password-protected, encrypted computer at City, University of London. Audio recordings will be deleted after analysis of the data has been completed.

ANALYSIS

Transcripts will be fully de-identified before analysis by the research fellow. Systematic thematic analysis will be conducted. The Framework Method will be used to provide a structured summary of the data. This type of thematic analysis is suitable for work with multidisciplinary teams and studies where data are compared within and between different subgroups[32]. A combined inductive-deductive approach will be used which enables specific research questions to be addressed as well as identifying unexpected or new themes related to acceptability and implementation of routine GBS testing. Specifically, framework analysis allows us to identify and compare key barriers and facilitators to implementing testing at the four units.

Analysis will be conducted in six steps:

a. transcripts will be re-read for familiarisation with the data
b. data will be coded line by line for meaning by the research fellow
c. the research fellow and project leads will meet to develop a working analytical framework of agreed codes to apply to subsequent transcripts
d. the analytical framework will be applied to remaining data
e. the data from each transcript will summarised, by importing data for each category, into a matrix
f. data will be analysed for characteristics and differences, and connections between categories and relationships will be mapped.

To establish credibility, members of the research team will keep a research diary in which they record reflection and impressions of the data and thoughts about analysis throughout the process; analytical findings will be shared with stakeholders at regular meetings and feedback incorporated into the analysis; and the systematic framework approach will be adhered to. Data will be analysed using NVivo software. Reliability will be ensured by a proportion of codes being redone by a second researcher. Any disagreements will be discussed and agreed with the research team. Credibility will be ensured through regular meetings of the research team where problematic issues are discussed and resolved.

OUTCOME

The main outcome will be summaries of qualitative results on the acceptability, barriers and facilitators to implementation, and on the influence of site-specific context and process mechanisms on GBS testing. These will be provided for rapid feedback into the main trial.

ECONOMIC EVALUATION

RATIONALE

In order to provide decision-makers with the best available evidence on whether or not to recommend a specific form of GBS testing for routine clinical practice, it is important that evidence around its cost-effectiveness is also provided. This economic evaluation will aim to identify, measure and value the costs and consequences of alternative testing strategies for GBS in pregnancy or labour, and to synthesise the evidence using metrics amenable to cost-effectiveness based decision-making.

DESIGN

We will conduct a decision-analytic modelling-based economic evaluation with the view to estimating the cost-effectiveness of alternative testing strategies for GBS in pregnancy or labour, including intrapartum rapid testing, antenatal ECM testing and the current risk factor based strategy. For alternative testing comparators, cost-effectiveness will initially be expressed in terms of incremental cost per episode of early-onset all-cause neonatal sepsis avoided. A decision-analytic framework provides a rigorous methodology for synthesizing information from a variety of sources, including the planned cluster trial. Accepted guidelines for good practice in decision-analytic modelling and the general principles outlined in the NICE 'reference case' will be followed.

DATA SOURCES

The GBS3 trial will provide estimates of the incidence of early-onset all-cause neonatal sepsis as well as mortality and other morbidity outcomes. We will seek to match trial participant records to Hospital Episode Statistics (or devolved nation equivalent) and National Neonatal Research Database data in order to profile each trial participant's duration and intensity of antenatal, intrapartum, postnatal and neonatal care, based on standard criteria for level of care, as well as maternal and neonatal surgical procedures and complications(33). In addition, targeted economic studies will be integrated into the GBS3 trial in order to generate key resource use and economic cost parameter estimates for the model. Specifically, the detailed data collection for 100 women within each trial centre, described above, will provide a vehicle for estimating resource use and cost profiles associated with antenatal ECM and intrapartum rapid testing, and IAP, as well as test and IAP uptake rates. Unit costs for each resource input will largely be derived from national secondary sources, for example the Department of Health's National Schedule of Reference Costs, but supplemented where necessary using primary research methods and discussions with suppliers e.g. Cepheid.

ANALYSIS

The decision-analytic model will allow us to extrapolate the cost-effectiveness of alternative testing strategies for GBS colonisation in pregnancy beyond the parameters of the GBS3 trial. The model will consider the progression of early-onset neonatal sepsis over time, and the model structure will capture disease progression using health states that represent the important natural history and clinical- and event-related activity for early neonatal sepsis, the appropriate model type (e.g. Markov or discrete-event simulation approach) and the appropriate analytical framework (e.g. cohort analysis versus individual-level simulation). Furthermore, the decision-analytic model will provide a framework for integrating data from external studies, for example, GBS1 and GBS2 [34]. A key methodological challenge will involve generating expressions of cost-effectiveness amenable to broader cost-effectiveness comparisons by decision makers. Translating the potential benefits of alternative testing programmes in terms of episodes of early-onset neonatal sepsis avoided into quality-

adjusted life year (QALY) metrics is constrained by the paucity of validated utility measures in the perinatal and early childhood contexts[35]. The utility values placed on health states within the model will be informed by our recent research in this area which includes a systematic review of all published utility values for childhood health state[36]. Model health states for which published utility values are not available will be valued by a representative sample of the general population using the hybrid time trade-off and discrete choice valuation protocol recently applied for the derivation of the EQ-5D-5L value set [35, 37, 38] Multi-parameter uncertainty in the model will be addressed using probabilistic sensitivity analysis [39]. Cost-effectiveness acceptability curves will be used to show the probability of cost-effectiveness of each of the evaluated strategies at alternative cost-effectiveness thresholds held by decision-makers [40]. Any costs occurring beyond the first year after birth will be discounted using nationally recommended discount rates [41].

OUTCOMES

Economic outcomes will be expressed in terms of incremental cost per case of EOGBS avoided and incremental cost per QALY gained associated with alternative testing strategies for GBS in pregnancy or labour.

ADVERSE EVENTS

ADVERSE EVENTS ARISING FROM TESTING

The occurrence of an adverse event as a result of participation within this trial is not expected and no adverse event data will be collected.

ADVERSE EVENTS ARISING FROM ANTIBIOTIC ADMINISTRATION

Maternal intrapartum anaphylaxis is a trial outcome and therefore will be collected as such, rather than reported as an adverse event.

Maternity governance teams at each of the individual participating maternity units will inform the NCTU of any cases of maternal anaphylaxis from 36 weeks gestation onwards occurring on the obstetric unit or AMU during the Trust's recruitment period. Local maternity governance teams will be asked to send a copy of the corresponding incident forms for any cases of maternal anaphylaxis once every three months. The only personal identifiable information required will be the woman's NHS number and date of birth.

If a women receiving IAP has an adverse drug reaction (ADR) that is serious or unlisted in the product information, the MHRA will be informed using the Yellow Card scheme as per usual clinical practice but not reported for the GBS3 trial.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol and all relevant documents have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, the Confidential Advisory Group (CAG) and the Health Research Authority (HRA). Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised documents (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate

hazard to participants (urgent safety measure) may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested retrospectively. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health UK Policy Framework for Health and Social Care Research, 2017.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The principal difference to an individually randomised trial is that individual written consent for participation in the GBS3 cluster trial will not be sought.

Within cluster trials, it is important that all eligible participants are identified before the unit is randomised. As intrapartum risk factors can only be identified, or swabs taken for intrapartum testing, at the time when the testing strategy needs to be applied, we need to include all women birthing in each unit over the period of the trial. If consent was sought for inclusion in the trial there would be selection by midwife (overtly or unintentionally, due to time pressures), and as a result of women declining to provide swabs or data for research. The same principal applies for antenatal testing. The selection bias caused by the need to approach and individually consent participants within a cluster leads to unreliable estimates of testing effectiveness[42]. However, if the testing strategy is adopted as standard practice by the maternity unit, and routinely collected data is retrieved, consent for research is unnecessary. As for all clinical procedures, consent is an important principle, and vaginal-rectal swabs will only be obtained following a discussion with each woman and verbal consent has been obtained.

In the maternity units allocated to the risk based testing strategy, usual practice is being followed and all women would be reviewed and treated in the same manner had the trial not existed. In the maternity units allocated to rapid or antenatal ECM testing, these tests will be considered standard practice for the duration of that unit's trial participation and offered to all women intending vaginal delivery (or in labour in intrapartum testing units). In this situation, participation in the cluster trial is not something that they can choose.

The relevant RCOG/ Group B Strep Support (GBSS) leaflet should be available in all maternity units. Specific trial information will be provided to maternity units randomised to either testing strategy to provide to women. This brief information will follow the principles of provision of information for proportionate informed consent published by the Health Research Authority (https://www.hra.nhs.uk/planning-and-improving-research/best-practice/informing-participants-and-seeking-consent/) . These will be given to all women in maternity units randomised as testing sites. Posters in waiting rooms will signpost women to their local care team and the GBS3 trial website if they want further information. Links to quality information about GBS provided by GBSS and the RCOG will be available on the trial website. Information about use of their data will be provided, and the website will provide a link to the NHS data opt-out registration page. Video clips and cartoons will replicate the written information and will be available on the website and in antenatal clinic waiting rooms, where feasible. All information has been developed in partnership with GBSS, the National Childbirth Trust and the GBS3 parent and panel involvement (PPI) panel.

The Health Research Authority Confidentiality Advisory Group

We will seek approval to use identifiable data in maternal and baby medical records held by the participating NHS Trusts/ Boards and the routine data providers described in *Records*, to form a linked anonymous research database, held by the University of Nottingham. This will require submission to the Health Research Authority's Confidentiality Advisory Group (CAG) in England and Wales. The CAG is the independent statutory body established to monitor information governance in health and adult social care. The CAG reviews and advises the

Secretary of State and HRA on requests to access confidential patient data under section 251 of the NHS Act 2006 (which allows identifiable patient information to be used without consent in specific circumstances). In Scotland, guidance will be provided by the Public Benefit and Privacy Panel for Health (PBPP) and approval obtained from their Caldicott Guardian.

Approval for non-consented access to medical records of mothers and infants, held at NHS sites and by the routine data providers will be required. Use of identifiable data for data matching without consent is justified by several considerations:

- It is regarded as impractical to obtain individual level consent from the complete cohort of 320,000 women on whom data is required.
- The NHS support costs cannot be justified when the trial can be designed so that the data held at University of Nottingham will be anonymous. .
- Obtaining individual consent from women would result in some inevitable distraction to them either during labour or the late antenatal period.
- In usual care maternity units, clinical practice may be altered by the introduction of consent, leading to a different degree of risk factor identification or IAP provision and consequently a treatment effect estimate of routine testing that does not reflect the prevailing neonatal sepsis rate.
- The requirement for individual consent to trial participation would inevitably lead to an incomplete sample within each unit and a potentially biased sample due to selection bias (overt or unintentional selection for approach for consent by clinical midwives).

Section 251 approval from the Confidentiality Advisory Group will be sought to use routinely collected data without individual consent. With this approval, the mothers NHS number, date of birth and postcode, will be obtained from participating sites on a monthly basis. This will locate the randomised site and strategy for each woman and baby, regardless of transfers.

Qualitative Study

The arrangements for provision of information and consent are described in the *Sampling* section.

RECORDS

Routine Data Collection

The routine data sources which will be used for this trial are:

Public Health England, Health Protection Scotland, Health Protection Wales

Data on culture-confirmed EOGBS is voluntarily reported by microbiology laboratories all to their respective health protection agencies by automatically sending files from their laboratory information management systems.

National Neonatal Research Database

All 200 neonatal units in England, Wales and Scotland form the United Kingdom Neonatal Collaborative (UKNC) and contribute electronic health record data to the National Neonatal Research Database (NNRD). The NNRD holds individual patient level data on all infants admitted for National Health Service neonatal care in England, Scotland and Wales from 2014 to present. The NNRD is a national resource formed of the Neonatal Data-Set (an NHS Information Standard), comprising of 450 clearly defined variables, http://www.imperial.ac.uk/neonatal-data-analysis-unit/ extracted at patient level from the commercial Electronic Health Record used by all UK neonatal units.

Information on clinically suspected (negative or unknown culture status with ≥3 agreed clinical signs/symptoms, treated with antibiotics ≥5 days, within 7 days of birth) all-cause early neonatal sepsis will be obtained from this database on a quarterly basis.

Maternity Data

The English Maternity Services Dataset (MSDS) is a patient-level dataset that captures key information at each stage of the maternity care pathway including the mother's demographics, booking appointments, admissions and re-admissions, screening tests, labour and delivery along with the baby's demographics, admissions, diagnoses and screening tests. By the start of accrual to GBS3, Version 2.0 of the MSDS (Amendment 10/2018), which has been accepted as an Information Standard, will be mandated. The MSDS is accessible via NHS Digital.

In Scotland, the Scottish Birth Record (SBR) records details on a baby's care on an individual basis, for all Scottish births. It uses the baby's Community Health Index (CHI) record, generated soon after birth, as the key identifier. The Scottish Morbidity Record (SMR02) captures episode level data for all obstetric appointments and day cases in all Scottish hospitals. Both datasets are managed by the Information Services Division of NHS National Services Scotland.

In Wales, the NHS Wales Informatics Service holds the Maternity Indicators and admitted patient care dataset.

Hospital Episode Statistics

Hospital Episode Statistics (HES) is a NHS Digital database containing details of all admissions, outpatient appointments and accident and emergency attendances at NHS hospitals in England. Regional equivalents will be obtained from the Information Services Division of NHS Scotland and NHS Wales Informatics Service.

DETAILED DATA COLLECTION

One hundred consecutive women at each site identified for the targeted retrospective source data collection will be assigned a trial identity code number, on creation of the record in the trial database. Access to the online trial database will be limited to named research midwives and NCTU staff via personal usernames and passwords. Access will be granted and managed by the NCTU trial management team. Although the database will also collect women's NHS numbers, to enable linkage to outcomes obtained from the routine data sources, the routine data will not be visible within the trial database[26].

QUALITATIVE STUDY

Interviews will be audio recorded, with the interviewee's consent. The audio file will be saved using the study number assigned by the qualitative study tracking system and will not contain the name of the interviewee. These will be transcribed verbatim and the document stored using the study number, on a secure server at City, University of London.

SOURCE DOCUMENTS

Cluster RCT

Data obtained from NHS Digital, PHE or NNRD, and the devolved nation equivalents are obtained directly from electronic health records and as such, are the source data.

There are no informed consent forms for the cluster trial.

Qualitative study

The qualitative study team at City, University of London, will receive informed consent forms from women invited to participate at specific centres. They will also hold audio files and transcripts of the interviews. These will be kept securely at City, University of London.

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and data opt-out, and will adhere to the Data Protection Act, 2018. The routine data requested will only contain the minimum required information for the purposes of the trial and for accurate data linkage. Primary (NHS number) and secondary (date of birth, and full postcode) linkage variables will be obtained from sites. Any patient identifiable data received (e.g. NHS number) will be deleted once the patient data has been linked between the data sets and received from the applicable database. Patient identifiable information will not be used in the datasets analysis.

Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities. Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one-way encryption method).

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE AND AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct may be subject to a systems audit of trial management activities and the Trial Master File for inclusion of essential documents; permissions to conduct the trial; local document control procedures training logs, adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, test equipment and consumable expiry date logs).

The Chief Investigator and Deputy Chief Investigator or where required, a nominated designee of the Sponsor, shall instigate a systems audit at least yearly and an audit report shall be made to the Trial Steering Committee.

TRIAL AND STUDY DATA

Monitoring of trial data will be outlined in the trial monitoring plan. Monitoring of trial data shall include confirmation of informed consent for the qualitative study; routine data import; data linkage; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Chief Investigator and Deputy Chief Investigator, or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the trial. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no longer able to maintain the trial records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator and Deputy Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

The City, University of London, team shall securely store the consent forms for the qualitative study.

This requirement shall not include data that is required to be destroyed as part of the conditions of its receipt from central data suppliers, such as NHS Digital or counterparts in the devolved nations.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Section 251 approval will be obtained from the Confidentiality Advisory Group to use routinely collected data without individual consent for the cluster randomised trial. The NHS number, postcode and date of birth, will be used to identify each woman and her baby in the received datasets and to link datasets.

An online tracking system will be designed by the Nottingham Clinical Trials Unit to enable research midwives at sites participating in the qualitative study to register women and clinicians names and contact details for contact by the City, University of London team. This will be hosted by NCTU with controlled access by the City, University of London team, the trial manager (and/or designee) and research midwives and will enable tracking of women and HCP who consent and those who participate in the interviews, and will generate code numbers for use in identifying interview transcripts.

Individual participant clinical data obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above.

Due to the use of anonymised record identifiers, in the unlikely event that information is disclosed during the study, it highly unlikely that it could pose a risk of harm to the participant or others. Any data breaches from the NCTU or City, University of London will be discussed with the CI, the sponsor and where appropriate, reported accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating investigators, the University of Nottingham sponsors representatives, the REC and local R&D Departments.

PUBLICATION AND DATA SHARING POLICY

PUBLICATIONS

The comprehensive project results will be reported in the journal Health Technology Assessment. The individual component studies will be published together or individually in high-impact peer reviewed journals and by presentation at medical and midwifery conferences locally, nationally and internationally.

Manuscripts will be prepared by the Chief Investigator and Deputy Chief Investigator and TMG and authorship will be determined by mutual agreement. The TSC and DMC will be given opportunity to comment on the manuscripts prior to submission.

Secondary publications, addressing additional objectives or questions beyond those described in this protocol which uses GBS3 data and is intended for publication before the main results will be considered by the TMG. Publication of such secondary data will only be permitted before the main results if they will not jeopardise the integrity and interpretation of the main results.

Presentations prepared by maternity units and local investigators to publicise GBS3 must be reviewed by the Chief Investigator and Deputy Chief Investigator. A slide set will be provided to assist with local publicity.

We will be unable to contact individual women to provide summaries of the research findings. Plain English summaries will be made available by our PPI groups via websites and social media.

DATA SHARING AFTER THE END OF THE PROJECT

Requests for data collected for GBS3 from parties outside the Trial Management Group will be considered by the NCTU Data Sharing review panel. For approved requests, the dataset will be prepared by the NCTU and will be provided as a summary at a maternity unit and trial level only. A data sharing agreement will be required between the sponsor and the external party. Participant level data will not be available, as it is not permitted by the NHS Digital, NNRD or PHE (and devolved nation equivalents) under the terms and conditions under which NCTU receives the data.

PARENT AND PUBLIC INVOLVEMENT

There has been detailed, sustained, and invaluable input into all aspects of the project and this protocol from the two supporting charities. Their respective representatives are co-investigators, who will lead the Parent and Public Involvement (PPI) group and be members of the TMG.

- Group B Strep Support (www.gbss.org.uk), the UK's leading charity working to stop GBS infections in babies represented by Jane Plumb, their Chief Executive. Jane was a member of the Department of Health research prioritisation panel and is the co-vice-chair of the RCOG's Women's Network
- National Childbirth Trust (www.nct.org.uk), the UK's leading charity for parents, represented by Dot Parry, Midwife and Parent Educator.

Both charities will aid in the publicity of the trial throughout its duration, via their respective websites, social media channels and newsletters. They will be instrumental in the dissemination of the trial results, and will update their own information resources with the results and the implications of GBS3.

The helpline of both charities will be provided with structured advice regarding the trial and testing strategies, so that they can directly respond to women's queries.

A PPI group will be convened to provide ongoing advice and support to the trial. There will be group local to Nottingham, who can meet periodically in person with the CI, Deputy CI and Trial Manager, and a dispersed group that will be linked via a closed Facebook group. The Facebook page will be used as a forum and document-sharing repository. The PPI group's tasks will include:

- Review and provide feedback on all public facing information, both for the cluster randomised trial and the qualitative study
- Review and provide feedback on all information provided to healthcare practitioners.
- Help the qualitative researchers develop the interview schedules
- Engage in workshops to develop training packages for midwives in the testing hospitals
- Develop and potentially participate in video clips, for posting online or showing in antenatal clinic waiting rooms, that supplement written information
- Help the co-investigators respond to queries about testing policies
- Advise the co-investigators on the interpretation of the results of the qualitative study
- Create plain language summaries of the results of the project
- Help with the dissemination of the results

All PPI group members will be reimbursed for the time and out of pocket expenses according to INVOLVE guidelines.

TRIAL FINANCES

Funding source

This trial is funded by the NIHR Health Technology Assessment (HTA) Programme grant reference 17/86/06.

Participant stipends and payments

Participants will not be paid to participate in the trial and no travel expenses will be provided. No hospital visits in excess of usual care will be required.

Women who participate in the qualitative study will be given small value shopping vouchers in recognition of their time commitment to the interviews.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name) JANE DANIELS

Signature:

Date: 25OCT2019

Deputy Chief Investigator: (name) K WALKER

Signature:

Date: 04-11-19

Trial Statistician: (name) REUBEN OGOLLAH

Signature:

Date: 04-11-19

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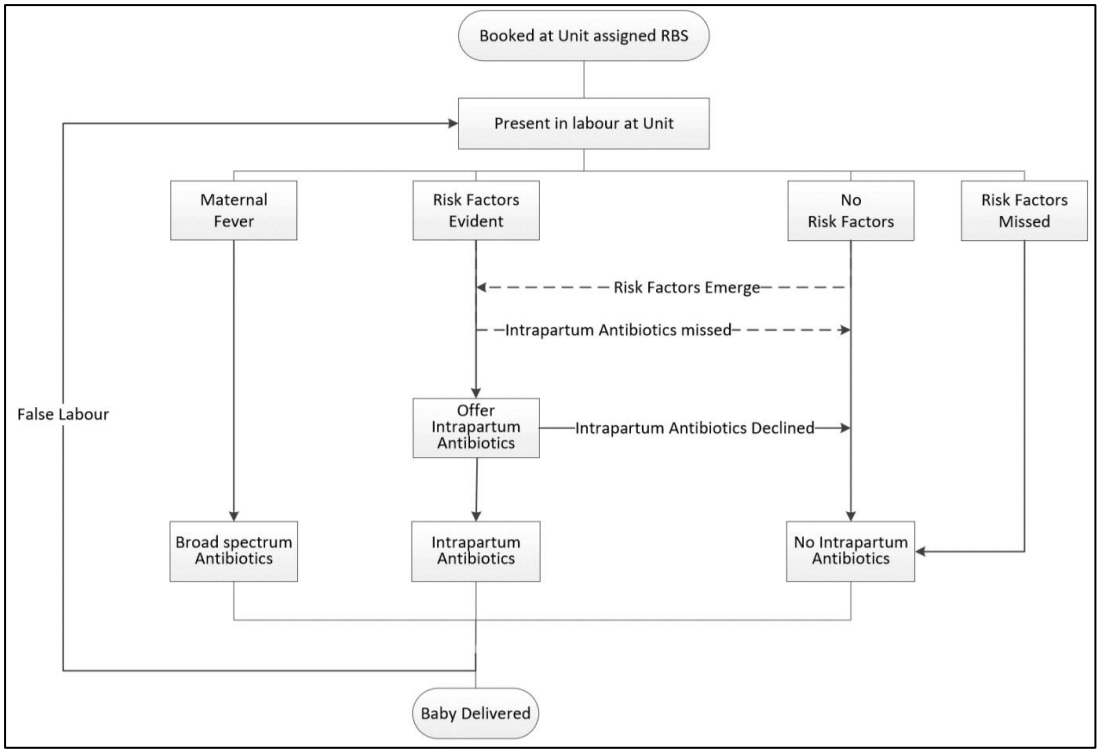
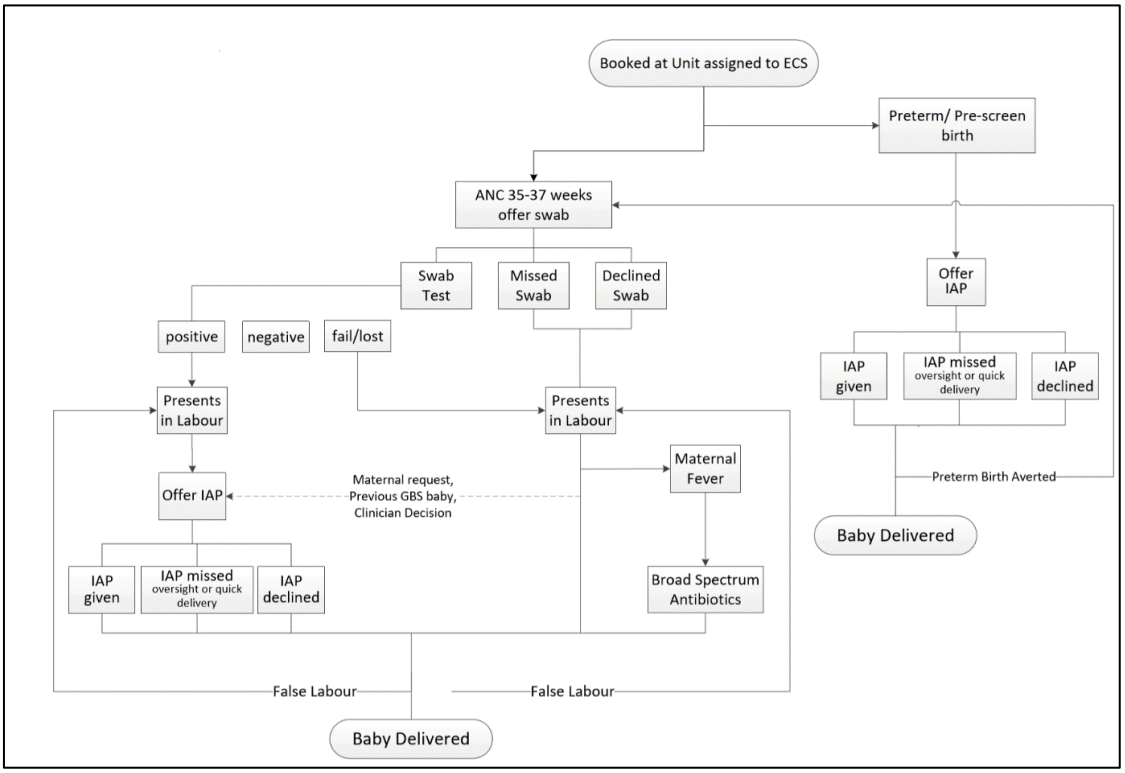
Appendices

Risk Based Strategy Care Pathway



Antenatal Enriched Culture Medium Testing Pathway



Intrapartum Rapid Testing Pathway