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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Short title:	Routine Testing for Group B Streptococcus
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2. 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-group parallel cluster randomised controlled superiority trial with internal pilot, feasibility evaluation, qualitative study and parallel economic modelling.
Setting	Up to 80 sites (obstetric unit with or without an alongside midwifery 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%, inflating for clustering due to the cluster randomisation
Number of participants	320,000 women from up to 80 sites. Detailed data collection for 100 women at each site. Interviews with up to 50 women and 30 health care 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 an Enriched Culture Medium (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 the woman or multiple births. Women whose baby (or all babies) has (or have) a known congenital anomaly incompatible with survival at birth will be excluded from testing and the dataset, Women who have experienced a known prelabour intrauterine death of all her babies within the current pregnancy will not be tested. Women who withdraw consent to use data, through the National Health

	Service (NHS) national data-opt out (or devolved nation equivalent), will not be included in the dataset.
Description of strategies	The routine testing strategies will use either antenatal ECM testing or intrapartum rapid testing using the Cepheid GeneXpert system (according to site randomisation), 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 earlye-onset group B Streptococcus (EOGBS) infection 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 6 months for final retrieval of data, analysis and write-up.
Randomisation and blinding	Eligible sites 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 random 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 sites to one of the two testing strategies. Blinding of women and health care 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 taken, at <7 days of birth) or negative/unknown culture status with ≥3 agreed clinical signs or symptoms, for which intravenous antibiotics are given for ≥5 days, starting < 7 days of birth. SECONDARY OUTCOMES: Neonatal: Birth weight, perinatal mortality, baby death before discharge, 5 minute Apgar, gestational age at birth, fetal acidaemia (cord arterial pH <7.05), 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), late onset (≥7 days – 28 days) culture-positive neonatal sepsis Maternal: Mode of onset of labour, mode of delivery, duration of hospital stay, change of intended location of birth, maternal intrapartum anaphylaxis, intrapartum or postnatal sepsis, duration from ruptured membranes to delivery 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, IV antibiotic use in labour for any other reason

	(except elective caesarean birth), timing of IAP, number of doses of IAP, proportion of women who tested negative, positive, had a failed test or had no test, declines and acceptances of IAP, number of babies of mothers who tested positive for GBS and had IAP commenced, observation time for the baby following positive GBS result. 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 of 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 intention to treat (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 treatment effect.
Informed Consent	The allocated testing strategy will be adopted as standard clinical practice by the site. Mothers in the relevant sites will therefore give standard verbal consent for the test. The data used in the trial will be routinely collected data retrieved from NHS databases. Individual written consent for participation in the trial will therefore not be sought. Written informed consent will be obtained for the qualitative study interviews.

3. ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AMU	Alongside Midwifery-led units
CACE	Complier Average Causal Effect
CAG	Confidential Advisory Group
CONSORT	Consolidated Standards of Reporting Trials
DMC	Data Monitoring Committee
ECM	Enriched Culture Medium
EOGBS	Early-onset group B Streptococcus
FMU	Freestanding Midwifery Unit
HES	Hospital Episode Statistics
HRA	Health Research Authority
GBS	Group B Streptococcus
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
MALDI-TOF	Matrix Assisted Laser Desorption Ionisation Time-of-Flight
MESH	Message Exchange for Social Care and Health
MSDS	The English Maternity Services Dataset
MU	Midwifery Unit
OU	Obstetric Unit
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
NPV	Negative Predictive Value
NSC	The UK National Screening Committee
PI	Principal Investigator
PICANet	Paediatric Intensive Care Audit Network

PHE	Public Health England
PHE SMI	Public Health England Standard for Microbiological Investigations
PIS	Participant Information Sheet
PPI	Parent and Public Involvement
PPV	Positive Predictive Value
QALY	Quality-adjusted life year
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomised Controlled Trial
RA	Research Assistant
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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4. BACKGROUND AND RATIONALE

4.1 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 3% will develop early-onset GBS (EOGBS) infection[1]. EOGBS infection is caused by group B Streptococcus bacteria ascending from the maternal genital tract during pregnancy (usually in the presence of ruptured membranes, although can occur with intact membranes) or labour. EOGBS infections tend to manifest as pneumonia and sepsis.

Early-onset infection is defined by the National Institute for Health and Care Excellence (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'. Early onset sepsis (using the RCOG definition) 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 around 5-10% but higher among preterm babies (23%)[5, 6] .

4.2 RISK FACTORS FOR GBS INFECTION

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 infection (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 infection[7].

The current UK approach of offering intrapartum antibiotic prophylaxis (IAP) to 'higher risk' groups has been assessed in a recent cohort of 429 UK and Irish cases of EOGBS infection within which only 35% fell into the 'higher risk' category of mothers having one or more risk factor for their baby developing EOGBS infection[8].

Giving IAP to mothers who are known to be colonised with GBS has been shown to reduce the risk of babies developing EOGBS infection[9]. 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[10] and may add to existing concerns about antimicrobial resistance both for the individual and the wider population.

4.3 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 infection (defined as: preterm labour, GBS colonisation or bacteriuria in the current pregnancy, a previous baby with GBS infection ,maternal fever during labour) and then offering these 'higher risk groups' IAP[11]. 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 infection in those countries. In the US, the incidence of EOGBS infection per 1000 live births fell from 0.47 in 1999-2001 to 0.34 in 2003-2005 to 0.25 in 2010[12].The risk of EOGBS infection 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) [13]. The corresponding incidence in 2014-2015[2] in the UK is 0.57/1000 births, a significant increase since previous surveillance undertaken in 2000 (0.48/1000)[14] despite the introduction of RCOG Greentop Guideline in 2003 [11]

4.4 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 trial 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), the NSC 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 having IAP administered unnecessarily, whilst the long term effects of this widespread intervention remain unknown. The key issue, when considering testing at 35-37 weeks of gestation, was the lack of randomised trial data, 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, however, that the positive predictive power of an antenatal testing policy for the outcome of a baby with EOGBS infection 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 to be consistent across UK laboratories. However, there may be both false negatives, for example where insufficient blood is obtained, which leads to an underestimation of the true incidence of neonatal sepsis, and false positives arising from contaminated skin and environmental bacteria[2].Targeted IAP could reduce culture positive EOGBS infection but increase the proportion of culture negative or Gram negative sepsis.

4.5 THE CHOICE OF TESTING STRATEGIES

The ECM test, a process which requires the swab to be placed into Lim broth and the broth to be sub-cultured onto solid medium after overnight incubation is recognised as the international 'gold standard' for detecting GBS. The test is highly sensitive, although maternal colonisation rates are influenced by the sites sampled and culture methods used. A UK study found that using ECM before plating onto selective agar identified 97% of the total positive rectovaginal swabs, whereas direct plating onto selective agar identified 75%[17].

Maternal colonisation can also alter throughout pregnancy, creating a potential limitation to 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%)[18], 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 also misses most preterm births, which have a greater potential for morbidity and mortality.

Intrapartum rapid tests have the potential for more accurately targeted IAP, provided the 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%)[19]. 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[20].

5. TRIAL OBJECTIVES

5.1 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?

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

5.2 SECONDARY OBJECTIVES

5.2.1 Secondary questions - effectiveness

1. Does routine testing for GBS colonisation have an impact on secondary neonatal andmaternal outcomes (defined in sections 6.4 and 6.5)?
2. Which routine testing strategy identifies a higher rate of women with known colonisation status at four hours prior to delivery?
3. Does the coverage (proportion of women providing a sample for testing) differ between the two routine testing strategies?
4. Does routine testing reduce neonatal unit admission overall, compared to the risk factor based strategy, and if so, is one routine testing approach superior?

5.2.2 Secondary questions – cost-effectiveness

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

5.2.3 Secondary questions - acceptability

1. What is the acceptability of the two methods of routine testing?
2. What are the barriers and facilitators to implementation of ach of the routine testing strategies?
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)?

5.2.4 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 routine testing?

6. TRIAL DESIGN

6.1 TRIAL CONFIGURATION

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

6.2 PRIMARY OUTCOME

All-cause early neonatal sepsis defined as starting at < 7 days of birth[21].Cases will be identified from national data sources, of which a sample will be reviewed by a blinded adjudication panel.

Early neonatal sepsis will be defined as:

- A positive culture of a pathogenic bacteria from blood or cerebrospinal fluid taken at <7 days of birth, **or**
- Negative/ unknown culture status with ≥3 agreed clinical signs or symptoms (see list below), for which intravenous antibiotics are given for ≥5 days, starting within 7 days of birth[11].

  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)

6.2.1 Blinded adjudication panel

An adjudication panel of UK consultant neonatologists will be convened to review the individual level data of a sample of babies with clinically suspected sepsis. Two experts, masked to the location of birth and the neonatal unit, will review each case, state their individual opinion regarding the diagnosis of sepsis, and if not unanimous, a third expert will be involved to help reach a consensus. The adjudication panel will also review the individual level data of babies who die during the intrapartum period to determine whether sepsis was the primary cause of death. Full details of the adjudication panel process will be included in a separatea Neonatal Adjudication Committee Protocol.

6.3 SECONDARY CLINICAL OUTCOMES

With the exception of maternal intrapartum anaphylaxis, all neonatal and maternal outcomes will be collected from routine data sources as detailed in section 19.1.

6.4 NEONATAL

- Birth Weight
- Perinatal mortality
- Baby death before discharge
- 5 minute Apgar
- Fetal acidaemia, defined as cord arterial pH < 7.05
- Gestational age at birth
- Admission for neonatal specialist care (length of stay, level of care)
- Seizures
- Abnormal neurological signs (hypotonia or abnormal level of consciousness) at > 24 hours of age

- Late onset culture-positive (blood or cerebrospinal fluid taken from 7 days to ≤ 28 days of birth) neonatal sepsis including clearly pathogenic organisms and excluding skin organisms (e.g. coagulase-negative staphylococci).

6.5 MATERNAL

- Mode of onset of labour
- Mode of delivery
- Duration from ruptured membranes to delivery
- Duration of hospital stay
- Change of intended location of childbirth
- Maternal intrapartum anaphylaxis due to IAP
- Intrapartum or postnatal sepsis, within 42 days

6.6 SAFETY OUTCOME

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 regularly from routine data sources and a neonatal adjudication panel will confirm the diagnosis in a sample of cases, outlined in section 6.2.1.

Cases of maternal intrapartum anaphylaxis due to IAP will be regularly collected from the Maternity Governance teams of participating sites.

6.7 PROCESS OUTCOMES

It is important to collect and analyse process outcomes for usual practice and for 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 site, who have delivered at gestational age ≥32 weeks, excluding women admitted for elective Caesarean births. 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 (and reasons why)
- Number of women having a swab taken at the appropriate time (of all those swabbed and all those eligible)
    - For women in antenatal ECM sites: The target time window is
        - > 35 weeks gestation for women without a planned delivery date OR
        - 3-5 weeks prior to the planned delivery date for those women with a planned induction of labour prior to 40 weeks' gestation.
    - For women in intrapartum rapid test sites who are planning to deliver in an obstetric unit (OU) or eligible alongside midwifery-led unit (AMU), the target time window is upon admission, in labour or for induction
- For women planning home or freestanding midwifery unit (FMU) deliveries in sites that are allocated to intrapartum rapid testing the target time window is > 35 weeks. See section 11.4 for further details.
- Number of women with a test result available ≥ 4 hours before time of birth
- Number of women with a test result available ≥ 2 hours before time of birth
- Number of women receiving GBS-specific IAP
- Number of women receiving antibiotics for prophylaxis before operative (Caesarean or instrumental) birth
- Number of women receiving antibiotics for any other reason

- Number of women with first dose of GBS-specific IAP administered at least 4 hours before childbirth
- Number of women with first dose of GBS-specific IAP administered at least 2 hours before childbirth
- Total dose of administered IAP per woman
- The proportion of women who tested positive for GBS, tested negative for GBS or who did not have an available test result.
- The proportion of failed tests. (For intrapartum rapid testing sites, the number of failed tests will be available from the GeneXpert machine)
- Of those who should have been offered IAP according to a positive test result or risk factors, the number of women offered IAP, and the number of women who were not offered IAP
- Number of women declining IAP when offered and reason why.
- 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
    - A) tested positive for GBS (testing sites)
    - or B) with documented risk factors (risk factor sites)
    - whose vital signs and clinical condition were observed for at least 12 hours
- Number of babies of mothers who
    - A) tested positive for GBS (testing sites)
    - or B) with documented risk factors (risk factor sites)
    - who were investigated for infection and/or had intravenous antibiotics commenced

6.8 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 Section 15.3

6.9 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 quality-adjusted life year (QALY) gained associated as a result of alternative testing strategies for GBS in pregnancy or labour

6.10 ADDITIONAL DESCRIPTORS

Descriptors of the dataset population as listed below will be collected and compared:

- Maternal age at booking
- Parity at booking
- Ethnicity
- Smoking at booking
- Index of Multiple Deprivation for maternal home at the time of childbirth
- Number of fetuses (seen at dating ultrasound scan)
- Birth order
- Neonatal sex

6.11 LONG TERM OUTCOMES

The babies born to women in the GBS3 trial create a unique population with detailed perinatal data. Long-term follow-up of this population can explore the association between perinatal factors, for example, intrapartum and postnatal exposure to antibiotics, the neonatal

microbiome and childhood conditions such as asthma and inflammatory bowel disease. It will also be valuable to record the long-term sequelae of babies who have suspected or culture-confirmed early and late neonatal sepsis, including educational attainment.

The understanding of the associations between perinatal exposures and childhood diseases and development is evolving and further factors and outcomes will likely emerge. .The exact nature and source of the long-term outcomes will be defined in light of current knowledge at the point where further analysis is considered. This would not be before the last baby born within the GBS3 trial has reached 2 years of age and could continue throughout childhood.. The end of GBS3 is defined in Section 7.1.1. Any analysis after this point would not be according to randomised strategy group. Approval will be sought to retain all data received from routine data providers, as stated in Section19.7.

7. 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, NCTU 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, in 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, in 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 ideally) 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 sites will assign a local Principal Investigator (PI) who will be responsible for the implementation of the trial at their site. If there are multiple units under one site, a co-PI will be assigned at each unit to oversee the individual unit implementation. The PI does not have to be an obstetrician though must liaise with all relevant services (e.g. 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 (non-clinical and 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.

7.1 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 6 months for final retrieval of data, analysis and write-up. The duration of any phase of the project may be amended following consultation with the Trial Steering and/or Data Monitoring Committees and the funder, and following an amendment to the Research Ethics Committee if the overall length of the project is changed.

7.1.1 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 site will participate for approximately 12 months (including an implementation period) and all eligible women giving birth during their site's study period will be included.

The trial will end when the final dataset has been retrieved from the last site/ routine data source and the overall trial database is locked.

8. RANDOMISATION

Randomisation will be at the site level to avoid any risk of contamination. Eligible sites will be randomised on a 1:1 ratio to a routine testing strategy or to the risk factor based strategy, using a minimisation algorithm with a random element.

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 the participating 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 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 site after confirmation of site participation.

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

Eligible women will be offered the care pathway to which their maternity unit is randomised.

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

9. STRATEGIES TO BE COMPARED

The routine testing strategies will use antenatal 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 infection in her baby is identified before or during labour.

Further details of the testing methods and criteria are given in Section 11.

10. SITE AND WOMEN ELIGIBILITY

10.1 SETTING

Up to 80 maternity sites in England, Scotland and Wales are required.

Where there are multiple maternity units within a Trust/ Board, these units can be considered as separate sites provided each maternity unit is disparate and able to maintain its allocated group.

If there are multiple maternity units under one research site, there will need to be a delegated deputy PI at each unit to oversee the trial and implementation at their respective units.

Where units form consortia for research purposes, these units can be considered as one site.

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):
    - alongside (AMU
    - freestanding (FMU)
- Birth at home.

It is not anticipated that women who have their care in an FMU or at home will be able to have IAP.

10.2 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 and written information will be provided on request (e.g. a participant information sheet). Information will also be provided to women (on request) on how to withdraw their data via the national data opt-out process (or devolved nation equivalent) if they wish to.

Although individual consent will not be obtained for involvement in the trial, women will provide verbal consent for vaginal-rectal swabs, in accordance with local clinical guidelines.

A small sub-set of sites will be involved in the qualitative aspect of the trial. Further information on the recruitment for the qualitative sub study is provided in section 15.

10.3 ELIGIBILITY CRITERIA

10.3.1 Site level Eligibility

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

to 80 sites will be identified through expression of interests, requests via the National Institute for Health Research (NIHR) Clinical Research Network, maternity research networks and personal contacts. A site selection questionnaire will be completed by a site and returned to the NCTU. If any service indicates that the site cannot participate as either a routine testing or usual risk factor based site, that site will not be randomised. Withdrawal of sites after randomisation must be avoided if at all possible, in order to reduce bias.

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

All obstetric-led maternity units are capable of providing IAP to women.

Some Trusts/Boards, in addition to their OU will run AMUs that are not able to provide IAP, and some will have FMU and/or provide homebirth services that are also unable to provide IAP. Those units/ services which cannot offer IAP are unlikely to be able to offer intrapartum testing and will therefore not be able to act as an individual cluster site without the OU or AMU (which offers IAP) 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. See section 11.4 for further information on women planning to give birth at home or at a FMU if their Trust/ Board has been randomised to the rapid test strategy.

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

Participating sites must be prepared to host a Cepheid GeneXpert machine in a location convenient to the delivery suite.

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

10.3.2 Individual level Eligibility

There will be two levels of eligibility for individual women:

- Testing level – eligibility to have an 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.

10.3.3 Inclusion and Exclusion Criteria

10.3.3.1 Inclusion criteria – testing level

- In ECM sites:
  - All women attending an antenatal clinic at ≥35 weeks of gestation without a planned delivery date OR
  - 3-5 weeks prior to the planned induction date for those women with a scheduled induction of labour prior to 40 weeks' gestation
- In rapid test sites, all women who experience labour or prelabour rupture of membranes at ≥37 weeks' gestation.

    - Women planning a home birth or in an FMU (which is not able to offer IAP) can be offered an antenatal rapid test which will be processed on the maternity unit/ labour suite at ≥35 weeks gestation.
- In risk factor sites, women who experience labour or prelabour rupture of membranes at ≥24 weeks' gestation.

10.3.3.2 Exclusion criteria – testing level

- Women who do not provide verbal consent to have a swab.
- Women who have had a previous baby with GBS infection (early or late onset) and who want IAP.
    - These women can still be offered a test and be given IAP regardless of the result (if requested by the woman).
- Women in preterm labour (suspected, diagnosed, established), at ≤37 weeks gestation should be offered IAP routinely.
- Women who have been admitted for a planned elective caesarean birth.
    - Women who have a planned caesarean birth, but labour spontaneously should still be offered a test
- Known congenital anomaly incompatible with survival at birth, of a singleton or all multiple foetuses.
- Known prelabour intrauterine death in the current pregnancy, of a singleton or all multiple foetuses.
- Women who require an emergency caesarean birth but who have intact membranes and are not in labour.

10.3.3.3 Inclusion criteria – dataset level

In all units, all women giving birth ≥24 weeks' gestation within their site's study period, regardless of mode of delivery, and all her babies will be included in the dataset.

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.

Women who experience an antepartum stillbirth will be included as they may have had antenatal testing for GBS prior to in utero death.

10.3.3.4 Exclusion criteria – dataset level

- Known congenital anomaly incompatible with survival at birth, of singleton or all multiple foetuses.
- Withdrawal of consent to use data, through the NHS data-opt out (or devolved nation equivalent)

10.4 WITHDRAWAL OF CONSENT

For the cluster trial, there is no individual consent to participate. However, individual women may review the trial information (e.g. posters, videos) and decide that their data is not to be 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.

Individuals with parental responsibility are able to set a national data opt out on behalf of their child via the non-digital channel only and will need to complete a specific form. For instances when an individual's record contains confidential patient information about another person (such as a mother and baby in the same record), the national data opt-opt applies to the entire record irrespective of whether an opt-out is identified for the individual who is the subject of the record (i.e. whom the record primarily relates to) or for a third party whose confidential patient information is contained within the record. However, it is recognised that the national data opt-out can only be applied in these circumstances where the NHS number is present for the third party. If the record only includes name or another identifier, then it is not possible to apply the national data opt-out.

NHS Scotland and Wales do not have a specific data opt-out forms.

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.

For the qualitative study, women will be able to decline the opportunity to be interviewed after providing consent to be contacted and can withdraw consent, within 14 days of interview, for the recording and transcribed information from their interview to be used. Once the analysis has been completed, the interview transcript cannot be removed from the dataset. However, quotes from the interview with women who wish to withdraw consent 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.

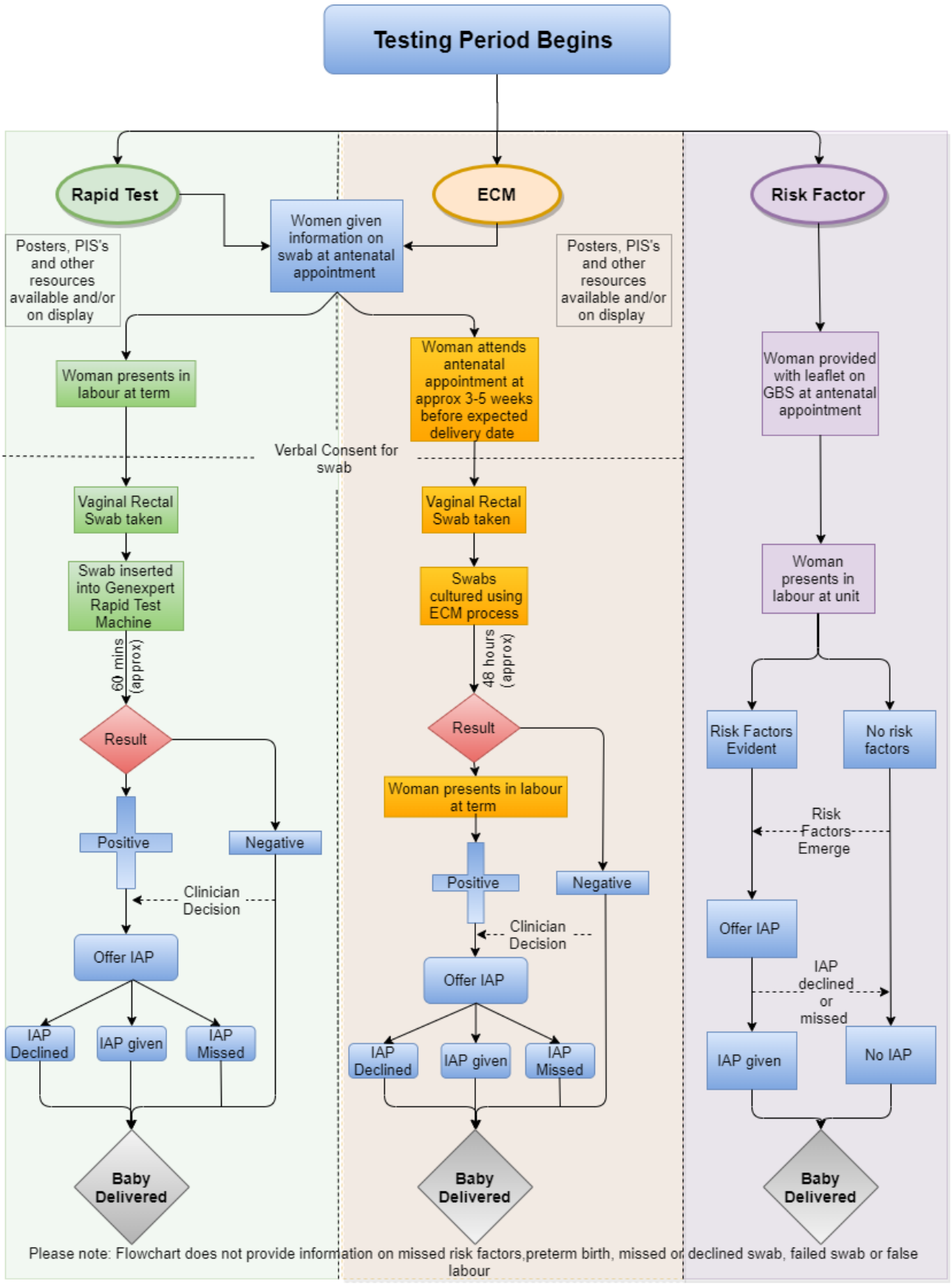
11. TRIAL PROCEDURES AND DATA COLLECTION

11.1 TESTING STRATEGY PROCEDURES

Brief details of testing strategies are given in

Figure 1. Working practice documents and flowcharts will be provided to sites. They can be adapted to reflect local policies and circumstances, provided the principles described here are followed.

Figure 1 Overview Flowchart of Testing Groups and Risk Factor Group



11.2 INFORMING WOMEN OF THE TRIAL AND TEST

Women at all sites will be provided with information on GBS during the antenatal period.

For sites randomised to the Risk-factor Based Strategy, the RCOG/ Group B Strep Support "Group B Streptococcus (GBS) in pregnancy & newborn babies" leaflet should be given to all women.

For sites randomised to either testing strategy (Antenatal ECM or Intrapartum Rapid Test), an adapted version of the RCOG/ Group B Strep Support "Group B Streptococcus (GBS) in pregnancy & new born babies" leaflet should be given to all women. This leaflet includes information on the trial and the vaginal-rectal swab.

Sites will also be provided with a GBS3 trial specific participant information sheet to provide to women upon request, and with posters to display at the sites.

11.3 ANTENATAL ECM TESTING GROUP

Sites randomised to ECM testing will collect vaginal-rectal swabs from women at ≥ 35 weeks of gestation for those women without a planned delivery date (or 3-5 weeks prior to the planned induction date for those women with a planned induction of labour prior to 40 weeks' gestation)

If a vaginal-rectal swab is not collected at 35-37 weeks' gestation, ECM testing should still be offered providing a result can practically be achieved and communicated back to the clinical team and/or the woman in advance of the onset of labour.

The test is discussed with and offered to the woman. If she consents to testing, swabs will be obtained by a suitably trained member of the woman's care team (or the woman may also obtain the swab samples herself). The swab can be obtained at antenatal clinics, visits to hospital or in the community.

A single swab will be used and 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 beyond the anal sphincter and then gently rotating. After withdrawal, the swab will immediately be 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 interfere with the ECM test. If lubrication is required, the swab should be moistened with sterile non-bacteriostatic fluid (e.g. sterile water or saline) only. The vaginal-rectal swab will be placed in the transport tube with a GBS3 trial specific sticker on both the tube and the request form and sent to the applicable microbiology unit for processing.

Samples from the swabs must be cultured according to PHE SMI 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 or appropriate

designee. 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.

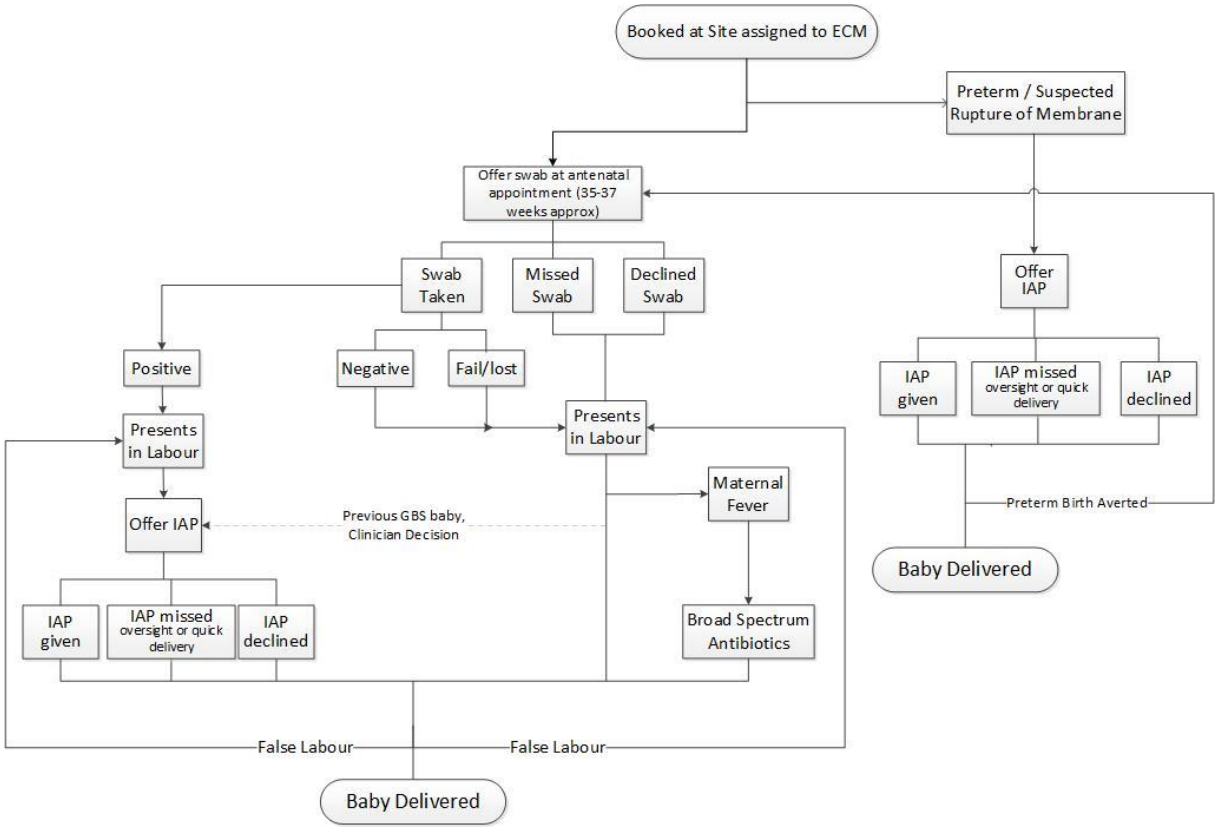
The vaginal-rectal swab will be used only for clinical purposes and the swab and test consumables (culture plates, test cartridge etc.) disposed of after use, according to local hospital policies.

All positive and negative results should be recorded and communicated to the women and clinical staff as per normal local procedures.

If the GBS test is positive, the woman should be informed and offered IAP when she is in labour. If the results are not available when the woman goes into labour, previous risk factor based guidance should be undertaken.

If the result is positive for GBS but the baby has already been born, neonatal management should be in line with NICE CG149 and the RCOG guidelines, covering both all cause and GBS specific infection. Monitoring of infant and decision whether to give neonatal antibiotics will be down to clinical judgement and the NICE guidelines.

11.3.1 ECM Group Pathway Flowchart



11.4 INTRAPARTUM RAPID TEST GROUP

Sites 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.

The test is discussed with and offered to the woman. If she consents to testing, swabs will be obtained by a suitably trained member of the woman's care team.

The test will be on admission to the labour or induction ward, ideally before any vaginal examination (if one is to be performed).

A double headed swab will be used for women in rapid testing sites to comply with the product licence for the Xpert GBS test.

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 beyond the anal sphincter and then gently rotating. After withdrawal, the swab will immediately be 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 test. If lubrication is required, the swab should be moistened with sterile non-bacteriostatic fluid (e.g. sterile water or saline) only.

Vaginal examination and pessary insertion may require the use of 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[23] and NICE guidelines recommend using water only for hygienic cleaning[24] . 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 still eligible for intrapartum testing and swabbed as described above.

The sample collected on the swab will be tested using the Cepheid GeneXpert GBS test system using the Xpert GBS test cartridges. 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.

The double headed swab will be split, with one swab used for the Xpert GBS test and the other placed into the swab transit tube. Should a test fail and there is sufficient time, the second swab can then be used to repeat the test (if the test succeeds, the second swab can be discarded unless the second swab is being used for internal quality control. See section 11.4.1 for more information).

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 will be arranged by the GBS3 Coordinating Centre, according to local requirements.

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.

All positive and negative results should be recorded and communicated to women and clinical staff as per normal local procedures.

If the GBS test is positive, the woman should be informed and offered IAP.

The swab should be offered up to the point of delivery. If the test is positive and baby is delivered prior to the woman receiving IAP, neonatal management should be in line with NICE CG149 and the RCOG guidelines, covering both all cause and GBS specific infection. Monitoring of the infant and decision whether to give neonatal antibiotics will be down to clinical judgement and the NICE guidelines. Women planning to give birth at home or in an FMU who are booked in a Trust randomised to the intrapartum rapid test can be offered the option of a rapid test antenatally after the 35th week of gestation in order to allow them time to consider their birthing location based on the result.

11.4.1 Quality Assurance for the Intrapartum Rapid Test Machine

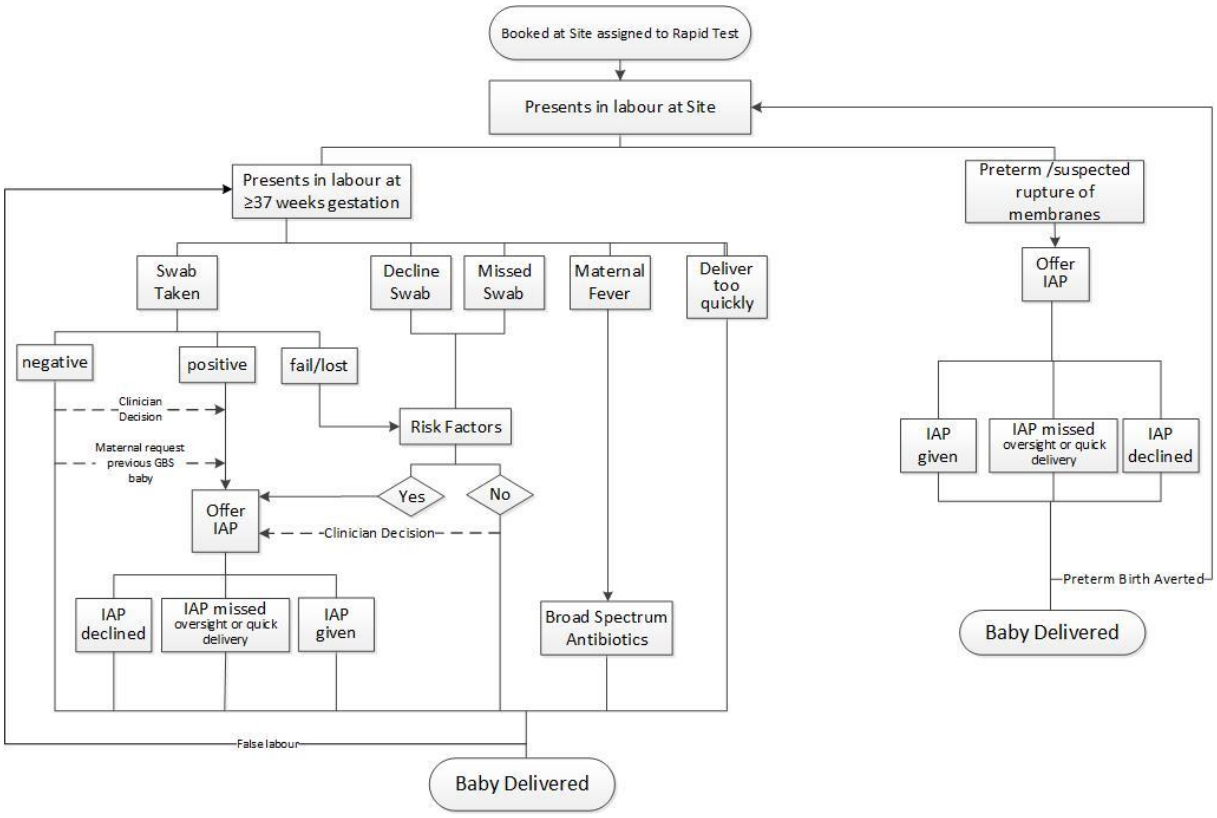
Each site randomised to rapid test group should perform regular internal and external quality assurance tests on the Rapid Test Machine.

Site-level internal quality control tests should be performed on a small percentage of swabs analysed each month.

An external quality assurance test should be performed at regular intervals throughout the testing period using externally purchased positive and negative test samples. The test samples will be transferred onto clean swabs by an unblinded member of staff and analysed by a blinded operator.

Further details will be provided to sites during the set up phase of the study.

11.4.2 Rapid Test Group Pathway



11.5 RISK-FACTOR BASED GROUP (USUAL CARE)

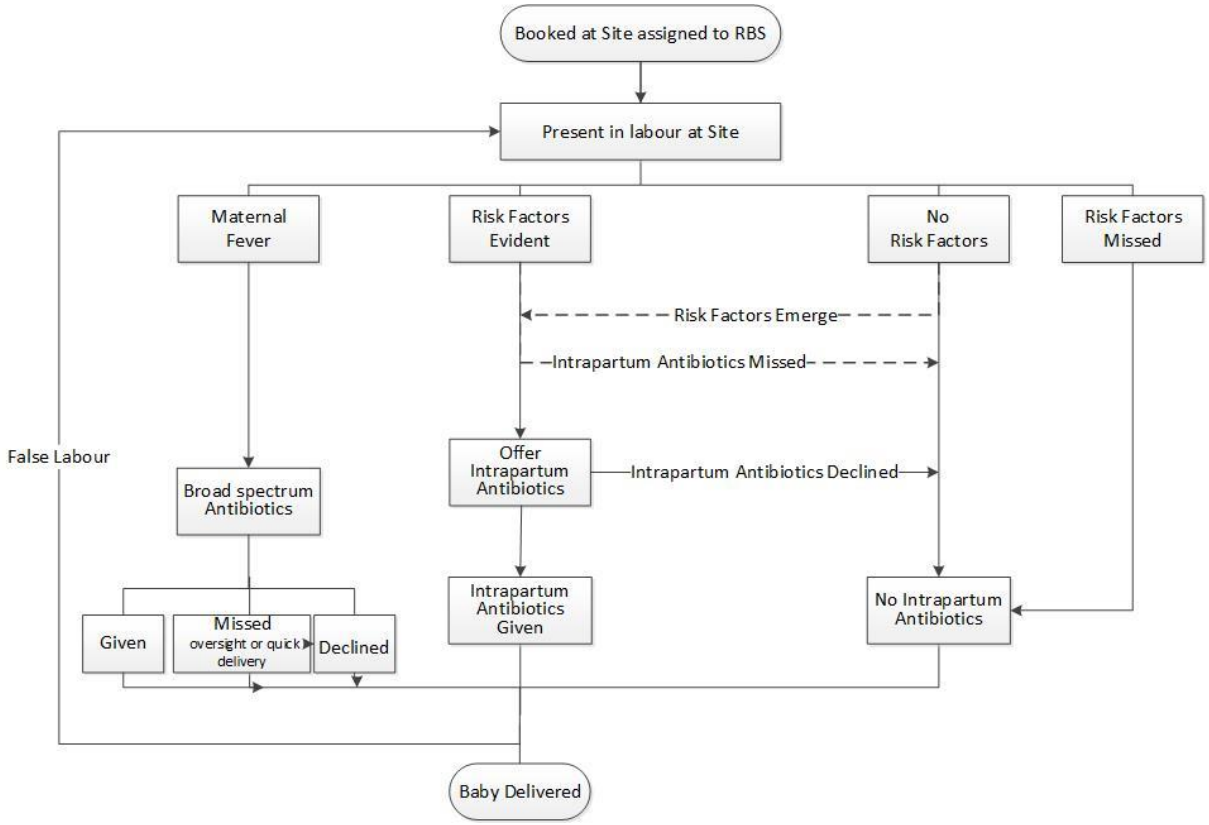
Sites randomised to the risk factor based screening and treatment approach must continue to use their current local guidelines. This should be based on the RCOG Greentop Guideline 36[11], which states women with the following risk factors for their baby developing EOGBS infection should be offered IAP:

- Having a previous baby with GBS infection
- 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. The risk of colonisation in subsequent pregnancies described in the RCOG guidelines should be discussed with the woman.

11.5.1 Risk Factor Based Group (Usual Care Group) Pathway



11.6 SITE TRAINING AND IMPLEMENTATION ASSESSMENT

The testing strategies will be implemented at sites for a period of time before the start of the study period..

Prior to the implementation period, the sites assigned ECM or rapid testing will be visited by the trial team, including a trial midwife (and the team from Cepheid if the site is randomised to Rapid Test Group).

The trial team will deliver training on the trial, 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 and authorisation provided by the GBS3 coordinating centre, the implementation period will begin.

During the implementation period, the number of tests performed as a percentage of those eligible for testing (from the site's reported birth records) will be monitored by the GBS3 coordinating centre. The target is at least 80% coverage (If actual birth rates unavailable, estimation is based on previous years birth rate at site). Cascadedtraining by sitestaff trained on GBS3 during this implementation period must ensure all midwifery teams and shifts are trained promptly andappropriately Once the 80% testing coverage is met, the Trial Manager (or delegate) will notify the site that the study data collection period has started.

If 80% coverage is not met after the first 4 weeks (acknowledging the lag in ECM sites between the swab being taken around 36 weeks' gestation and the average expected delivery date of 40 weeks), the site will need to extend and intensify the training and implementation of the testing process. Support and additional training will be provided by the GBS3 coordinating team.

Sites will not be withdrawn if they fail to achieve the 80% test uptake rate by 12 weeks. At 12 weeks, the site will be deemed to be open to data collectionregardless of testing coverage and it will be included in the primary analysis, but a sensitivity analysis will be conducted excluding sites which failed to reach 80% uptake.

11.7 DATA COLLECTION PHASE OF TRIAL

Once the implementation period has begun, the routine data from NHS databases will be requested on a regular basis. The data will only be used for analysis from the start of the data collection phase, with data from the implementation phase used to retrospectively assess implementation. The routine data will be obtained directly from these databases by the GBS3 coordinating centre. Sites will continue to undertake the testing or risk factor based strategy for at least 10 months from the start of the data collection period.

Further information on which routine data sources are used for this trial are detailed in Section 19 of the protocol.

11.8 DETAILED DATA COLLECTION OF TESTING GROUPS

For determining the process outcomes described in section 6.7, individual level data, not reported in the routine data sources, is required.

To collect data on all women would negate the advantages of routine data use, so detailed data collection will be undertaken for a small subset of women at each site.

This will be retrospective source data collection using an online proforma designed for each testing strategy. At each site, individual data for a consecutive sample of 100 women per site, at gestational age ≥32 weeks, excluding women admitted for elective Caesarean births will be gathered. This will commence approximately halfway through the site's data collection period.

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

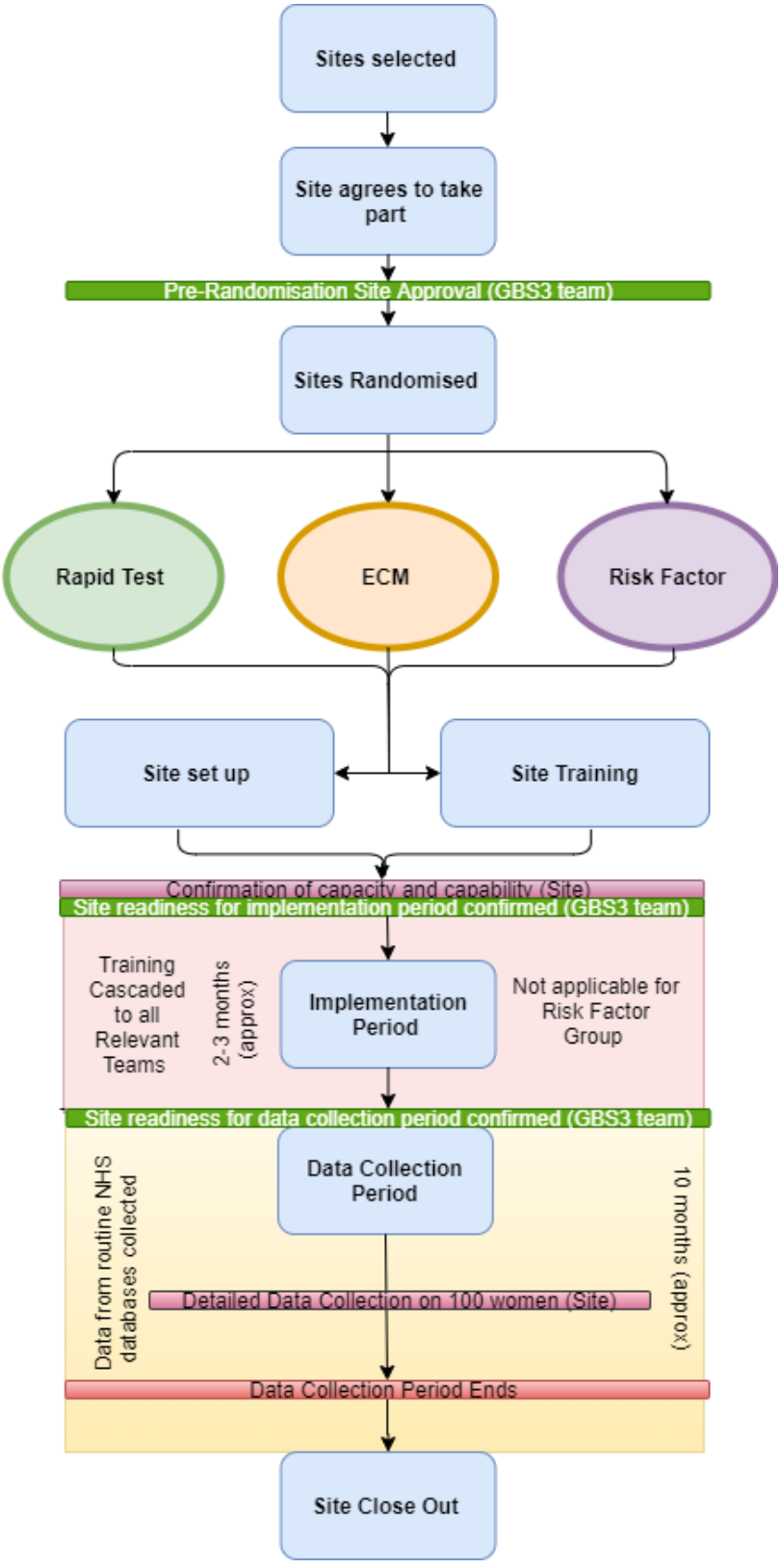
The detailed data collection will provide individual level data associated with the testing coverage, IAP and resource use for approximately 4000 women in the risk-factor based usual care sites, 2000 women in ECM sites and 2000 women in the rapid testing sites.

In order to avoid including women who have opted out of data collection through the national data opt service, sites will use the NHS MESH (Message Exchange for Social Care and Health) service to provide a list of the relevant NHS numbers to be checked against the national data opt-out repository on the Spine system. The MESH service will remove the information of those with opt-outs. The site will receive a list of NHS numbers for the records that can be disclosed for the detailed data collection. If any women have opted out in the first 100, additional NHS numbers will be provided until 100 records are reached.

11.9 END OF DATA COLLECTION PERIOD

The GBS3 coordinating centre will inform the site that the standard data collection period at the site has ended and the site will revert back to the strategy undertaken prior to involvement in GBS3 trial (e.g. risk factor based strategy). The site will be closed after completing all necessary close-out procedures, coordinated by the GBS3 coordinating centre.

11.10 OVERVIEW OF TRIAL



12. INTERNAL PILOT

An internal pilot phase will end 9 months after the first sites start their data collection period, to explore aspects of deliverability (e.g. enrolment of units, acceptability and uptake of testing and 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 sites open *Continue*	**<10% missed opportunities for testing** *Continue*	**<10% missed opportunities for testing** *Continue*
15-30 sites 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 sites 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.*

The duration of the internal pilot and criteria for continuation may be amended following consultation with the Trial Steering and/or Data Monitoring Committees and the funder.

13. OVERALL TRIAL RECRUITMENT TIMELINES

The overall recruitment phase of the project is planned for 24 months (this includes a 9 month internal pilot and feasibility evaluation).

Individuals sites will be opened in waves and will be open for approximately 12 months. This will include both the implementation period and data collection period.

The duration of any phase of the project may be amended following consultation with the Trial Steering and/or Data Monitoring Committees and the funder. and following an amendment to the Research Ethics Committee if the overall length of the project is changed.

14. STATISTICS

14.1 METHODS

The analysis and reporting of the trial will follow the Consolidated Standards of Reporting Trials (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 16 or later. No interim analyses of clinical outcomes are planned.

14.2 SAMPLE SIZE AND JUSTIFICATION

14.2.1 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[25] 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%. This control rate is also between other estimates.[26, 27]Adding antenatal testing to the risk factor strategy was estimated to result in 294-299 EOGBS infections, a relative risk ratio of 0.84.

Assuming GBS contributes 50% of all early-onset neonatal infection (the remainder *E. coli* (18%), other gram positives (23%),[28]) 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 infections 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),[29] 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.[30] 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. This infection rate estimate is conservative as it is based on culture confirmed cases only so the inclusion of clinically suspected cases will likely increase the power. 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 sites, but we aim to recruit from 80 sites to improve our power should infection rates be lower, and also reduce the trial duration. Any possible loss in precision due to uncertainties in the hospital-level ICC and not accounting for multiple births will be offset by the expected increase in infection rate.

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

A second level randomisation for sites randomised to routine testing will be performed so that approximately half 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 from100 participants from each of the antenatal ECM and intrapartum rapid testing sites (total of 4000 datasets). Accounting for clustering and assuming an ICC of 0.005 with cluster size of 100 participants and 20 sites per strategy, 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 sites to 14% in intrapartum rapid testing sites) 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 alpha=0.05.

14.3 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.

14.4 ASSESSMENT OF EFFECTIVENESS

A full statistical analysis plan will be developed and approved prior to the final database lock. 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 site as a random effect to take into account the clustering effect, adjusting for the minimisation factors. The effect of accounting for multiple births will be explored as a sensitivity analysis in the mixed effect model. 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 sites 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 sites as a random effect. P-values and 95% confidence intervals will be provided with point estimates of treatment effect.

14.5 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.

14.6 PROCEDURES FOR MISSING, UNUSED AND SPURIOUS DATA

We will attempt to follow up on all randomised sites and retrieve data from all the individuals within the sites 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 site dropping out of the trial or failure to obtain outcome data for some participants within participating sites 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.

15. QUALITATIVE STUDY

15.1 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 health care contexts. This qualitative sub-study will address these issues and will provide rapid feedback into the cluster randomised trial so procedures can be considered and amended if necessary. It will only recruit women and health care professionals in sites randomised to either of the two routine testing groups.

15.2 RESEARCH QUESTIONS

The aims of this sub-study are to determine:

1. What is the acceptability of the different methods of routine testing for GBS colonisation to pregnant women and Health Care 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?

15.3 OBJECTIVES

The objectives 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.

15.4 THEORETICAL FRAMEWORK

The theoretical framework of acceptability provides a detailed outline of different aspects of acceptability[31] 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 [32].

15.5 STUDY SETTING

Women and clinicians will be recruited from four NHS sites participating in the internal pilot phase of the RCT. Sites will be selected to ensure successful sampling of different groups, and to include sites with high and low uptake of GBS testing.

A research midwife (or appropriate designee) at each site will be the nominated lead for that site 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 (GCP) and the UK Policy Framework for Health and Social Care Research 2018.

15.6 INCLUSION AND EXCLUSION CRITERIA (QUALITATIVE)

15.6.1 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 at:
    - a maternity unit allocated to a testing strategy, and not a usual care site.
    - An FMU/AMU
    - Home
- Health Care Professionals will be eligible if they are a registered health professional working in an NHS maternity or neonatal service in one of the four selected NHS recruitment sites.

15.6.2 Exclusion criteria

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

15.7 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 an FMU/AMU. To examine this possibility, women who give birth at home, in hospital and at FMU/AMUs will be included.
b. Preterm birth: Testing is more challenging to implement with women who give birth preterm. In addition, at present women in confirmed preterm labour are automatically offered IAP, although they may prefer the offer of selective IAP based on testing. Women who had preterm and term births will therefore be included, to enable examination of these issues.
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[33]. Women from a range of ethnicities and ages will therefore be included.

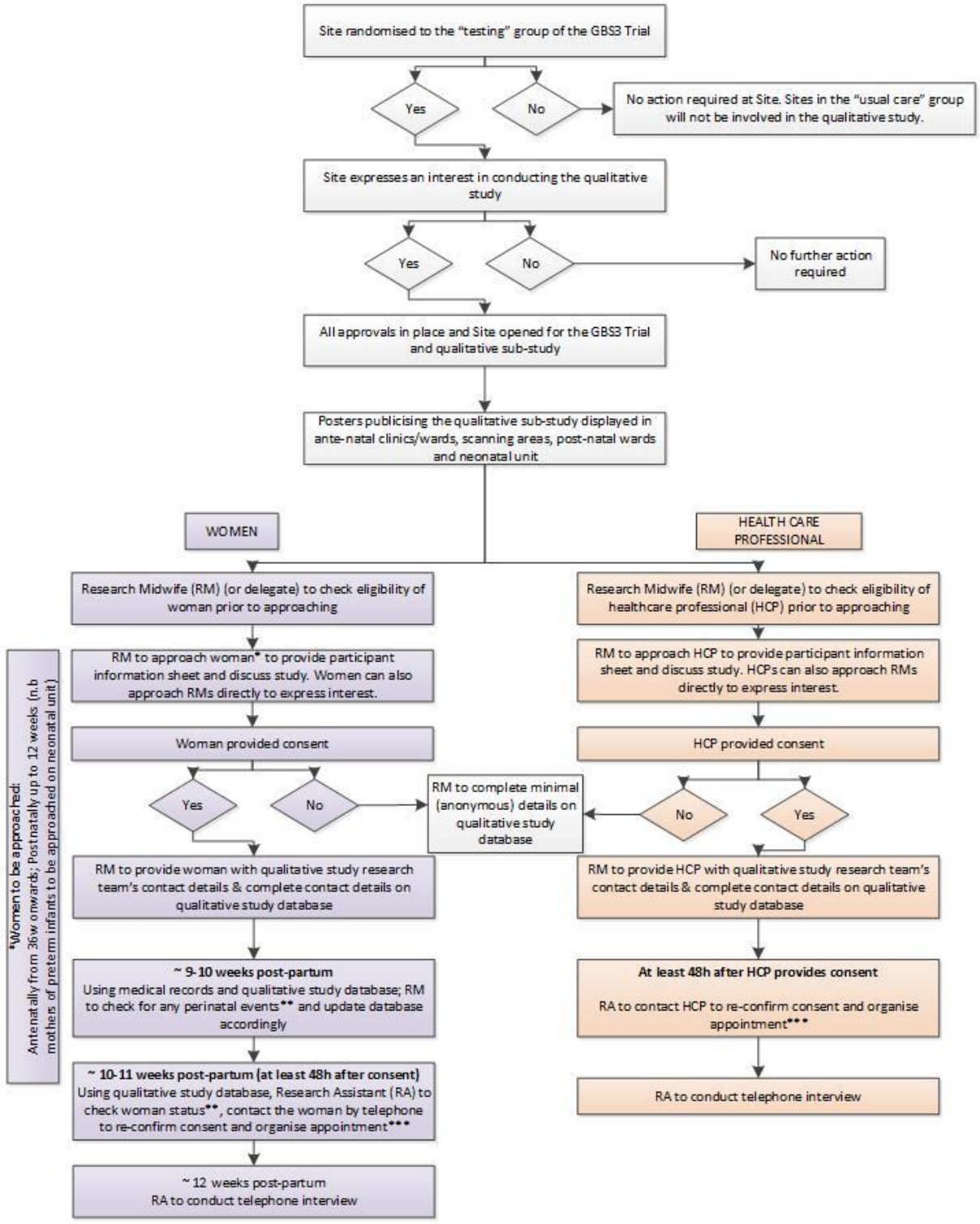
Purposive sampling will be used to ensure Health Care Professionals from different groups are represented (midwifery, obstetric, neonatal, microbiology) with a spread of clinical experience across those who work in hospital (teaching and general), FMU/AMU and community settings.

15.8 SIZE OF SAMPLE

The final sample size for women and Health Care Professionals 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. For Health Care Professionals, 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 if the data cannot yet be fully explained by the analysis after 30 interviews.

15.9 QUALITATIVE SUB STUDY OVERVIEW

GBS3 Qualitative Sub-study Flowchart



***If woman has experienced a perinatal event, the woman will not be telephoned. Instead they will be sent a letter asking them if they would still be willing to participate in the interview. If they **do not** respond, no further contact will be made.*

**** All reasonable efforts will be made to make contact with the woman/HCP and will include leaving voicemail messages, sending reminder letters and calling on different times/days of the week. If consent is not re-confirmed at this time, interview will not take place and qualitative study database will be updated accordingly.*

15.10 PARTICIPANT IDENTIFICATION

15.10.1 Participant identification - women

Clinical midwives at each site will identify women who meet eligibility criteria, outline the objectives of the study and provide a detailed participant information sheet (PIS). Posters in relevant areas at site will display study details and contact details of who to contact if a woman is interested in taking part.

To identify women who give birth at home or at an FMU/AMU, the research midwife will contact community midwives and a range of materials will be used to publicise the qualitative study.

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 added to a secure web-based tracking database for the qualitative study. Women who provide consent will be given information with study team contact details on, should they have further questions. The research team will contact the participants at least 48 hours later, when the woman is approximately 10-11 weeks post-partum, to confirm consent and arrange a convenient time for interview.

Hospital records will be checked prior to contacting women after birth to identify any women who may have experienced an adverse perinatal event. Women who experience an adverse perinatal event, such as perinatal death, can be included in the trial but a specially adapted letter (co-developed with PPI partners) will be sent to the women to check if they are still interested in taking part in the trial. If no response is received, the women will not be followed up.

Interviews will be conducted when the woman is 12 weeks or more postpartum to ensure she has had adequate time to recover from the birth.

If the research team conducting the interviews is unable to contact a woman who has consented to take part in the qualitative sub study (and she has not experienced an adverse perinatal event), a follow up letter will be sent by the research team. If no response is received after this, the woman will not be followed up again.

To ensure diversity amongst the women who participate, purposive sampling will be used (see section 15.7*)* Both women who decline GBS testing and those who agree will be invited to participate to gain greater understanding of reasons why women decline testing.

15.10.2 Participant identification – Health Care Professionals

Research midwives (or their delegate) at each site will identify Health Care Professionals 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. Health Care Professionals can also contact the research midwives to express interest and will be provided with information on the study. To ensure diversity, purposive sampling will be used to include Health Care Professionals from different disciplines and those with different levels of experience (see *Sampling* section 15.7).

Health Care Professionals who are interested in participating will be asked to provide written consent and their contact details which will be added to a secure web-based tracking database for the qualitative study. The health care professionals will be given information with study team contact details on, should they have further questions. The research team will contact Health Care Professionals at least 48 hours later to confirm consent and arrange a convenient time to interview them.

15.11 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 as a guide, [31] 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 [32]. The draft interview schedule will be reviewed by the project research team, Parent and Public Involvement (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 General Data Protection Regulation (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 at the end of the study & the anonymous interview transcripts will be kept for at least 7 years.

15.12 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[34]. 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 sites.

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.

15.13 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.

15.14 PRE- TRIAL QUALITATIVE INTERVIEWS

A separate qualitative study will be performed exploring women's knowledge, attitudes and acceptability of GBS testing including self-swabbing procedures.

In-depth interviews will be conducted with pregnant and postpartum women who are not GBS3 trial participants. Video and telephone interviews will be conducted by an experienced qualitative research fellow using a semi-structured interview schedule. Interviews will be audio-recorded.

Participants will be recruited via advertisements distributed on social media sites, shared by the Group B Strep Support UK (GBSS) organisation and pre-established PPI groups. Recruitment will not involve GBS3 sites.. This pre-trial qualitative study has a separate protocol and has received ethical approval from City, University of London (Ref: ETH2021-0149). Findings from this study will inform the approach to testing in the GBS3 trial and information provided to women when asked to provide swabs for testing.

16. ECONOMIC EVALUATION

16.1 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 testing strategies for GBS in pregnancy or labour, and to synthesise the evidence using metrics amenable to cost-effectiveness based decision-making.

16.2 DESIGN

We will conduct a decision-analytic modelling-based economic evaluation with the view to estimating the cost-effectiveness of alternative prevention strategies for GBS in pregnancy or labour, including intrapartum rapid testing, antenatal ECM testing and the current risk factor based strategy. For 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.

16.3 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 HES (or devolved nation equivalent) and National Neonatal Research Database (NNRD) 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[35]. 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 & Social Care's NHS Reference Costs, but supplemented where necessary using primary research methods and discussions with suppliers e.g. Cepheid.

16.4 ANALYSIS

The decision-analytic model will allow us to extrapolate the cost-effectiveness of alternative testing strategies for GBS colonisation and the usual risk factor approach 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 [36]. 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 QALY metrics is constrained by the paucity of validated utility measures in the perinatal and early childhood contexts[37]. 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[38]. 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 [37, 39, 40]. Multi-parameter uncertainty in the model will be addressed using probabilistic sensitivity analysis [41]. 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 [42]. Any costs occurring beyond the first year after birth will be discounted using nationally recommended discount rates [43].

16.5 OUTCOMES

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

17. ADVERSE EVENTS

17.1 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.

17.2 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 sites will inform the NCTU of any cases of maternal anaphylaxis from 32 weeks' gestation onwards occurring

on the obstetric unit or AMU during the site's recruitment period (this time window from 32 weeks' gestation has been chosen in order to take in to account the process of testing 3-5 weeks prior to any planned induction or delivery date that is before 40 weeks' gestation). 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, date of birth and postcode.

If a woman 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 these will not be reported as adverse events for the GBS3 trial.

18. ETHICAL AND REGULATORY ASPECTS

18.1 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 health care provider's Research & Development (R&D) department, the Confidential Advisory Group (CAG), the Health Research Authority (HRA) and devolved nation equivalents. 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, HRA, and CAG (where required). 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. Non-substantial 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.

18.2 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 site 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 at each site over the period of the trial. If consent were sought for inclusion in the trial there could be biased selection by midwives (overtly or unintentionally, due to time pressures), or 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[44]. However, if the testing strategy is adopted as standard practice by the site, and routinely collected data is retrieved, consent for research is unnecessary. As for all clinical procedures, consent is important, and vaginal-rectal swabs will only be obtained following a discussion with each woman and after verbal consent has been obtained.

In the sites allocated to the risk factor group, usual practice is being followed and all women will be reviewed and treated in the same manner as they would have been had the trial not existed. In the sites allocated to rapid or antenatal ECM testing, these tests will be considered standard practice for the duration of that site's trial participation and offered to all

women intending vaginal delivery (or in labour in intrapartum testing sites). In this situation, participation in the cluster trial is not something that they can choose.

The relevant RCOG/ Group B Strep Support leaflet should be provided to all women at their antenatal appointment and made available in all sites. Specific trial information will also be provided to sites randomised to either testing group to then be provided 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/). Participant information sheets will be available to all women at 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 further information about GBS provided by Group B Strep Support and the RCOG will be available on the trial website. Information about use of data collected during the study period 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 Group B Strep Support, the parents' charity NCT and the GBS3 PPI panel.

18.3 THE HEALTH RESEARCH AUTHORITY CONFIDENTIALITY ADVISORY GROUP

We have obtained section 251 approval from the Health Research Authority CAG to use, without consent, identifiable data in maternal and baby medical records that is held by the participating NHS Trusts/ Boards and by the routine data providers described in section 19**,**. These records will form a linked anonymous research database, held by the University of Nottingham (CAG Reference: 19/CAG/0139) 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.

For the routinely collected data, identifiable information such as the mothers' and babies' NHS numbers, dates of birth and postcodes, will be obtained from NHS databases on a regular basis. This will locate the randomised site and group for each woman and baby, regardless of transfers and allow linkage of the data sources.

Use of identifiable data for data linking purposes 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 necessary NHS support costs to obtain written informed consent cannot be justified when the trial can be designed so that the data held at University of Nottingham will be anonymous.
- Obtaining individual written consent from women would result in some inevitable distraction to them either during labour or the late antenatal period.
- In usual care sites, 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 site and a potentially biased sample due to selection bias (overt or unintentional selection for approach for consent by clinical midwives).

18.4 QUALITATIVE STUDY

The arrangements for provision of information and consent are described in section 15.

19. RECORDS

19.1 ROUTINE DATA SOURCES

A flowchart detailing the below information can be found in the appendices in section 26. Routine Data Collection.

Data sharing agreements between the sponsor and data provider will enable the University of Nottingham to receive routine data for the GBS3 Trial. After the end of the trial, these agreements will be periodically renewed in order to continue to hold these data. These may be amended,for further linkage to data on the child's health and development as outlined in Section 6.11, subject to further funding. New data providers and sources, such as educational records and GP records, may be required in the future.The routine data sources which will be used for the GBS3 trial are:

19.1.1 Public Health England, Health Protection Scotland, Health Protection Wales

Confirmed cases of all-cause early and late onset neonatal sepsis (section 6.2) and maternal sepsis will be identified through positive-culture of a pathogenic bacteria test. Data on culture-confirmed sepsis (maternal and neonatal) is voluntarily reported by microbiology laboratories to their respective health protection agencies by automatically sending files from their laboratory information management systems.

19.1.1 Badgernet (Maternity and Neonatal)

Badgernet Maternity is available in two versions: as a brief clinical summary record or a complete electronic health record system that captures all aspects of care and outcomes from booking, to discharge from postnatal care. The latter system is used by all maternity units in Scotland and currently about 25% of English units. The providers, Clevermed, under appropriate information security and governance standards, hold the data for all units centrally. Data from the system would enable babies not ill enough to be admitted to a NNU, who remain on the postnatal ward, to be added to the trial dataset. The equivalent information as those admitted to a NNU used to determine clinically suspected all-cause neonatal sepsis and other neonatal outcomes.

Currently, Badgernet Neonatal is the source of Neonatal Dataset for the NNRD, along with additional variables that can add richer data for the primary outcome adjudication and for the economic evaluation. Badgernet may not be the sole provider of the core dataset indefinitely, if other electronic health record providers develop suitable systems that can meet the requirements of the NNRD, therefore we will not replace NNRD with the Badgernet neonatal dataset: the latter will supplement the NNRD.

Badgernet also is incorporating a risk calculator to inform clinical management of infants with clinically suspected neonatal sepsis. We will also obtain any additional input parameters for the risk calculator that are not already required for the definition of neonatal sepsis.

19.1.2 National Neonatal Research Database

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, other secondary neonatal outcomes and further details for the economic assessment will be obtained from this database on a regular basis.

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), currently hosted by Imperial College, London. 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.

19.1.3 Paediatric Intensive Care Audit Network Database (PICANet)

In order to identify newborns not admitted to the neonatal unit or discharged and later readmitted to hospital (within 7 days of birth) with sepsis, information from paediatric intensive care unit's dataset will be requested. PICANet is an audit database recording individual details of the diagnosis and treatment of all critically ill children and babies in paediatric intensive care units. PICANet contains a core dataset of demographic and clinical data on all PICU admissions in the UK since 2008. Admissions and transfers in and out from other hospitals are recorded, enabling tracking of babies via NHS number and other identifiers. Data completeness is nearly 100% for NHS number, primary diagnosis and neonatal mortality. This database will enable verification of the final outcome of a subset of ill babies and provide economic data.

19.1.4 Maternity Data

Information on secondary outcomes and other descriptive details of the mothers and babies involved in the trial will be extracted from the relevant maternity datasets.

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. Version 2.0 of the MSDS (Amendment 10/2018) has been accepted as an Information Standard and is mandated. The MSDS is accessible via the Data Access Request Service at NHS Digital.

In Scotland, the Scottish Birth Record (SBR) records details of 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.

19.1.5 Hospital Episode Statistics

Information relevant to the economic assessment and further clinical details on the study outcomes, which are missing from the maternity or neonatal data sources, will be extracted from the hospital datasets.

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.

19.2 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 site staff, 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, postcodes and date of births to enable linkage to outcomes obtained from the routine data sources, the routine data will not be visible within the trial database.

19.3 MATERNAL ANAPHYLAXIS

This information will be collected for the secondary outcome maternal intrapartum anaphylaxis due to IAP.

These cases will be collected from the Maternity Governance teams of participating sites. Criteria for which cases to report is detailed in section 17.2. Local maternity governance teams will be asked to send a copy of the corresponding incident forms for any cases of maternal anaphylaxis due to IAP once every three months. The documents will have all identifying information redacted except NHS number, date of birth and postcode (or site code if postcode is not available) that will be needed for linking the data to the final datasets for analysis. After review by medical monitor/ deputy chief investigator, the confirmed cases details will be uploaded to trial database for linkage.

19.4 NEONATAL ADJUDICATION

Full details of neonatal adjudication process and aims will be detailed in the GBS3 Adjudication Committee Protocol and section 6.2.1.

Central neonatal adjudication will be conducted on a sample of clinical suspected sepsis cases to assess the robustness and accuracy of the algorithm developed to extract the primary outcome from routine data.

For sites involved in collecting additional data for the central adjudication, NHS numbers of relevant population will be provided in the first instance to GBS3 trial team to determine which random sample of infants will have further information collected.

The site will then upload full healthcare records of the selected infants, and relevant information about the mother and birth, to a secure web platform with all identifying information redacted except NHS number, date of birth and postcode (or site code if postcode is not available) to enable linkage in main trial database. The maternal and neonatal information will be reviewed by neonatal adjudication panel and the consensus diagnosis linked to the routine data for comparison.

19.5 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. Audio files will be deleted at the end of the study. De-identified transcripts will be held on a secure server at City, University of London, to be available for secondary analysis on request, subject to approval by the study team.

19.6 SOURCE DOCUMENTS

19.6.1 Cluster RCT

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

The source data for the detailed data collection, neonatal adjudication information and maternal anaphylaxis information are the maternal health records neonatal health records and incident reports at the site. There are no informed consent forms (ICF) for the cluster trial.

19.6.2 Qualitative study

The qualitative study team at City, University of London, will receive be able to view the informed consent forms from women and health care professionals invited to participate at selected sites via the qualitative study database.Original informed consent forms will remain at site in the Investigator Site File They will also hold audio files and transcripts of the interviews. These will be kept securely at City, University of London.

19.7 DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and to 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 NHS routine database providers. Any patient identifiable data received (e.g. NHS number) will be deleted once the patient data has been linked between the data sets, so that patientp identifiable information will not be included in the datasets for analysis. The coding list that connects the primary and secondary linkage variables to the trial participant identifier will be retained in a secure drive with access limited to the data analyst(s) performing the linkage. This will be required for linkage of perinatal data with datasets providing long-term outcomes, outlined in Section 6.11.

Access to the information will be limited to the trial staff, investigators and relevant regulatory authorities. Computer held data including the trial database and Qualitative Sub Study database will be hosted by the University of Nottingham password protected and held in accordance with the data providers' security requirements. 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.

At the end of any long-term follow-up, the routine data will be permanently destroyed in accordance with the data sharing agreement requirements set with each data provider and prevailing at that time.

20. QUALITY ASSURANCE AND AUDIT

20.1 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.

20.2 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.

20.3 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.

20.4 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. Further information on retention of audio recordings for the qualitative sub study is detailed in section 15.11. Contact details of participants will be kept by the University of Nottingham and City, University of London, for 3 years after the end of the 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.

20.5 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 TSC and DMC as appropriate in making this decision.

20.6 STATEMENT OF CONFIDENTIALITY

Section 251 approval will be obtained from the CAG 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 NCTU to enable research midwives and PIs at sites participating in the qualitative study to register women and health care professionals' 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. This will enable tracking of women and health care professionals 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 is 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 Chief Investigator, 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 Sponsor's representatives, the REC and local R&D Departments.

21. PUBLICATION AND DATA SHARING POLICY

21.1 PUBLICATIONS

The comprehensive project results will be reported in the Health Technology Assessment journal. 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, Deputy Chief Investigator and TMG; authorship will be determined by mutual agreement and outlined in a publication plan. 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 use GBS3 data and are 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 doing so will not jeopardise the integrity and interpretation of the main results.

Presentations prepared by sites 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. Our PPI groups will assist in preparing plain English summaries of the research. These summaries will be made available on the GBS3 website and the websites of our partner charities. Research findings in plain English will also be widely disseminated to the public via media outlets including the GBS3 social media platforms and those of our charitable partners.

21.2 DATA SHARING AFTER THE END OF THE PROJECT

Requests for data collected for the GBS3 trial (including Qualitative Sub Study) from parties outside the TMG 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 site 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, PICANet, Badgernet or PHE (and devolved nation equivalents) under the terms and conditions under which NCTU receives the data.

22. 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 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
- NCT (www.nct.org.uk), the UK's leading charity for parents, represented by Rachel Plachcinski, User Representative and Research Networker.

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 helplines of both charities will be provided with structured advice regarding the trial and testing strategies, so that they can directly respond to women and their health care professionals' queries.

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

- Review and provision of feedback on all public facing information, both for the cluster randomised trial and the qualitative study
- Review and provision of feedback on all information provided to health care practitioners.
- Helping the qualitative researchers develop the interview schedules.
- Engaging in workshops to develop training packages for midwives in the testing hospitals.
- Developing and potentially participating in video clips, for posting online or showing in antenatal clinic waiting rooms, that supplement written information
- Helping the co-investigators respond to queries about testing policies.
- Advising the co-investigators on the interpretation of the results of the qualitative study
- Creating plain language summaries of the results of the project
- Helping 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.

23. TRIAL FINANCES

23.2 FUNDING SOURCE

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

23.3 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 high street shopping vouchers in recognition of their time commitment to the interviews.

24. SIGNATURE PAGES

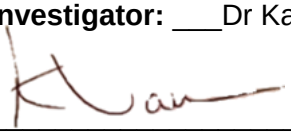
Signatories to Protocol:

Chief Investigator: ____Professor Jane Daniels_____

Signature: 

Date: __24th May 2021_____

Deputy Chief Investigator: ___Dr Kate Walker_____

Signature: 

Date: __24/05/2021_____

Trial Statistician: ___Dr Reuben Ogollah _____

Signature: 

Date: ____23/05/2021_____

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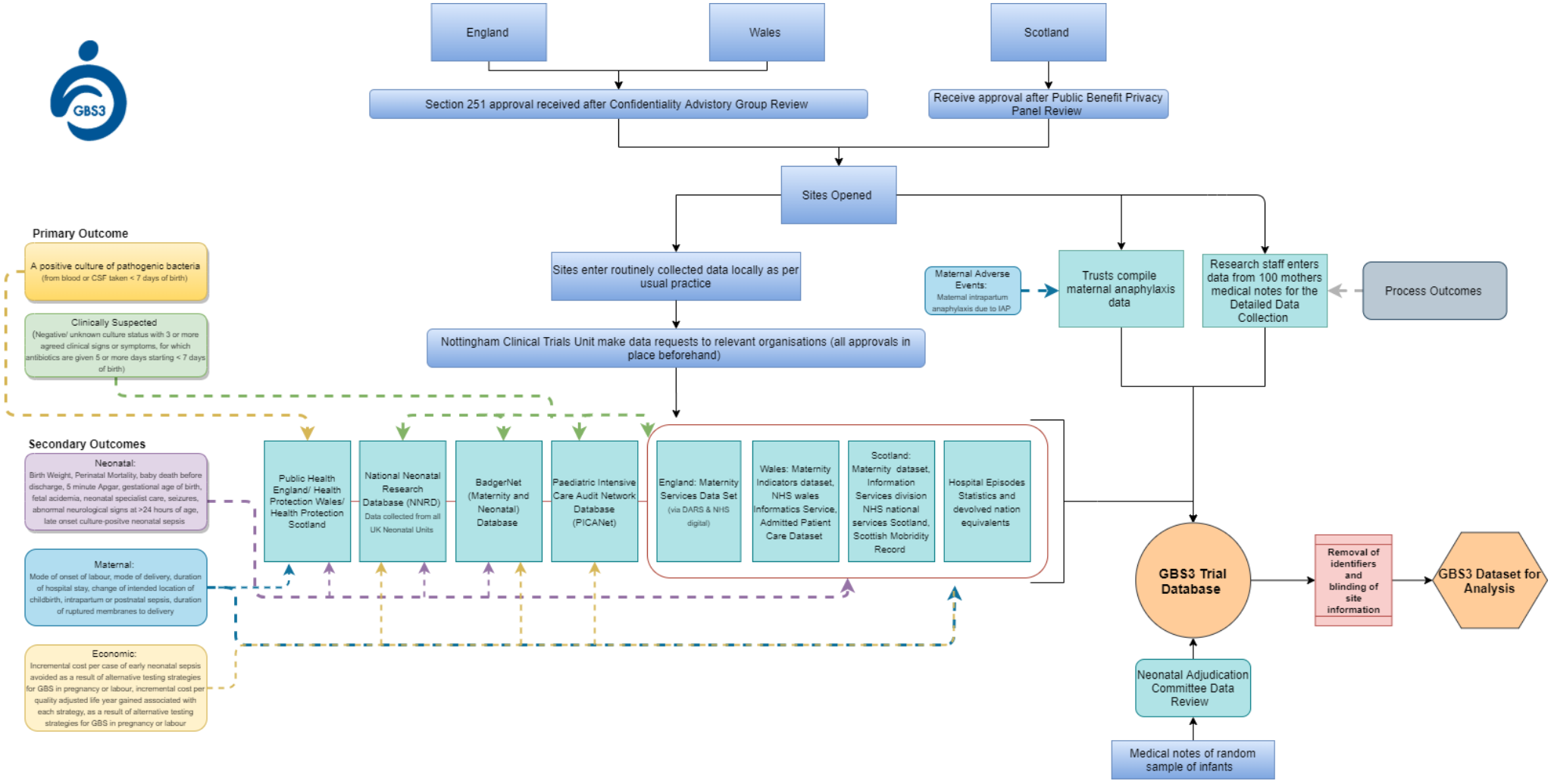
26. APPENDICES

Outcome and Data Sources Flowchart



Summary of Changes

Version	Date	Changes
1.0	2-Sep-2019	First version of approved protocol
2.0	11-Jun-2020	•Primary & secondary outcome wording clarifications (including some new additions to outcomes, secondary questions and descriptors) •Clarification and changes to inclusion and exclusion criteria for testing, data set, detailed data collection, and qualitative sub study •Change to end of trial definition and update to overall trial timelines •Clarification and changes to site management, implementation period, data collection period and trial procedures in all groups (testing and risk factor) •Additional information on positive result pathway, missing results and transport/ processing of swab for both testing groups •Additional information on Quality Assurance process for rapid test site •Clarification on data opt out through the national data opt programme for babies. •Additions of flowcharts throughout protocol to improve readability •Changes to co-applicant details •Clarification on sites, timings of interviews and processes for Qualitative Sub study •Addition of Paediatric intensive care audit network database (PICANet) and Badgernet as a routine data source and clarification on what is to be collected from each data source Addition of information collected and process for maternal anaphylaxis and neonatal adjuciation •Clarification on source data, destruction of data and timings of data retention •Removal of "confidential" in footer and addition of NIHR wording •Minor changes, clarifications and structural changes to document as detailed in track changes to improve readability and flow of document •Addition & changes of references
3.0	26-Jan-2021	• Wording & structure changes throughout document & supporting documents submitted to ensure consistency and improve readability. • Change of co-applicant details • Addition of long term outcome data collection information • Addition of information about pre-trial qualitative interviews • Clarification on location of coding list for primary and secondary variables linkageAdditional information on data sharing agreements in the context of long term follow up • Clarification that routine data will be collected during implementation period but won't be part of analysis (until data collection period begins at site) • Clarification that the duration of internal pilot and criteria for continuation may be amended following consultation with oversight committees and funder. • Clarification of information collected from Badgernet routine data source • Clarification that 80% testing coverage during implementation period is based on birth rates