The clinical and cost-effectiveness of testing for Group B Streptococcus in pregnancy: a cluster randomised trial with economic and acceptability evaluations (GBS3)

Statistical Analysis Plan

Final version 1.0
(28 February 2024)

Based on Protocol version 6.0 (dated 13 December 2023)

Trial registration: ISRCTN49639731

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents				
Name	**Job title**	**Trial Role**	**Signature**	**Date**
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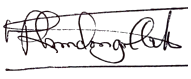
Reuben Ogollah	Associate Professor of Medical Statistics and Clinical Trials	Senior Trial Statistician		Feb 28, 2024
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Abbreviations

Abbreviation	Description
CACE	Complier Average Causal Effect
CI	Chief Investigator
CV	Coefficient of Variation
DMC	Data Monitoring Committee
ECM	Enriched Culture Medium
EOGBS	Early Onset group B Streptococcus
GBS	Group B Streptococcus
HIC	Health Informatics Centre
IAP	Intrapartum Antibiotic Prophylaxis
ICC	Intracluster correlation coefficient
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
SAP	Statistical Analysis Plan
TMG	Trial Management Group
TRE	Trusted Research Environment
TSC	Trial Steering Committee

Changes from protocol

The table below details changes to the planned analyses in the SAP compared to the protocol which after discussion with the TMG are not considered to require a protocol amendment.

Protocol version and section	Protocol text	SAP version and section	SAP text	Justification

Amendments to versions

Version	Date	Change/comment	Statistician

Additional contributors to the SAP (non-signatory)

Name	Trial role	Job Title	Affiliation
Shalini Ojha	Co-applicant Co-lead for neonatology aspects of trial	Clinical Associate Professor of Neonatology	University of Nottingham
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Name	Trial role	Job Title	Affiliation
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David Torgerson	TSC chair	Professor Co-Director of York Trials Unit	Department of Health Sciences, University of York

1. INTRODUCTION & PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results addressing the primary objective and secondary objectives for effectiveness from the NIHR HTA funded trial of testing of Group B Streptococcus in pregnancy (NIHR award ID 17/86/06). Analyses related to the secondary objectives for acceptability and implementation will be described in a separate document.

The purpose of the plan is to:

1. Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses respectively is appropriate.

2. Explain in detail how the data will be handled and analysed to enable others to perform or replicate these analyses.

Additional exploratory or auxiliary analyses of data not specified in the protocol may be included in this analysis plan.

This analysis plan will be made publicly available either on the study website or the NIHR project page. It will be uploaded with the main papers, if required, when they are submitted for publication. Additional analyses suggested by reviewers or editors will be performed if considered appropriate. This should be documented in a file note.

Amendments to the statistical analysis plan after approval of the first version and trial datasets being available will be described and justified in the final report of the trial and where appropriate in publications arising from the analysis.

Health economic and qualitative analysis plans are beyond the scope of this document.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

As per protocol version 6.0

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	Professor 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 sub study and parallel economic modelling.
Setting	Up to 80 sites (obstetric unit with or without an alongside midwifery unit) in England 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 at least 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, • 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 their 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 early-onset group B Streptococcus (EOGBS) infection in her baby is identified before or during labour.
Duration of trial	The trial grant started on 01/04/2019 and is planned to finish on 31/05/2024 but may be extended, subject to funding decisions.

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 defined as starting at <7 days of birth: • A culture-positive blood or cerebrospinal fluid, taken at <7 days of birth **or**, • Death <7 days if infection or sepsis was recorded on the death certificate **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 (a stillbirth or early neonatal death, <7 days~~)~~, extended perinatal mortality (a stillbirth or neonatal death, <28 days), 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 time from ruptured membranes to delivery, duration of hospital stay, change of intended location of birth, maternal intrapartum anaphylaxis, systemic infection confirmed with a positive blood culture or suspected maternal sepsis within 42 days of birth (subset of patient data collected), maternal death, cause of maternal death. Process: Maternal risk factors for EOGBS infection developing in baby (and which risk factors), 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.

Informed Consent	The allocated testing strategy will be adopted as standard clinical practice by the site. Mothers in the routine testing 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.

2.1. Sample size and justification

Main comparison
The sample size is based on the rate of all-cause early-onset neonatal sepsis between the routine testing and the risk factor based randomised strategies, assuming an all-cause rate of 0.986/1000 live births in the routine testing group. 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 (CV) 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 there be misspecification in any sample size parameters, 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.

During the course of the trial, we reviewed the design effect parameters which were initially specified, to check any changes with time. We noticed that the average cluster size had reduced due to a reduction in birth rates since the original protocol and an increase in the NHS national data opt out for use of data for research purposes in women of child-bearing age in England. As a result, we opted to relax the requirement of a minimum of 3000 deliveries per year to 2000 deliveries per year to increase the pool of potential sites and in addition to allow variable data collection periods for each site from 9 to 16 months, rather than fixed at 12 months. Based on number of deliveries per year for participating sites, the projected length of the data collection period was determined such that by combining information on the average cluster size and CV the effective sample size of 212,960 women would be maintained.

Sub-randomisation comparing antenatal enriched culture medium testing versus intrapartum rapid testing
A second level randomisation will be performed for sites randomised to routine testing. Comparisons for this sub-randomisation will focus on rates of uptake, accuracy in relation to maternal colonisation in labour and abilities to deliver a test in time for adequate IAP that cumulatively influence effectiveness.

Data on the proportion of women providing a swab, and of those, how many test results were available at least four hours before delivery will not be available from routine data sources. Site level individual-level data collection will be required but is not feasible on the total trial population. We therefore propose a 2.5% sample, or data from 100 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.

If the trial recruits less than 80 sites, the number of participants per site will be increased to maintain the effective sample size described above.

2.2. Blinding and breaking of blind

Blinding of women and health care professionals is not possible due to the nature of the strategies. The table below provides an overview of the blinding status of all individuals involved in the management and delivery of the trial.

Trial role	Blinding status	Comments
Participants (pregnant women)	Not blinded	Not possible due to the nature of the intervention.
Principal investigator and site research staff	Not blinded	Not possible due to the nature of the intervention.
Chief Investigator (CI) and Deputy CI	Not blinded	The CI and deputy CI and Deputy Chief Investigator (non-clinical and clinical) have overall responsibility for the trial and oversee all trial management.
Database programmers	Not blinded	The database programmer is responsible for the management of the randomisation system and other databases required for the trial and requires unblinded access in all systems.
GBS Trial Management staff	Not blinded	GBS trial management staff are responsible for training and monitoring sites.
Senior Research Fellow responsible for routine data	Not blinded	Responsible for linkage of the routine datasets from the different sources and providing data set for analysis to trial statisticians
Data management in NCTU	Not blinded	Data management staff will have access to the unblinded datasets within the trial randomisation system and database to ensure data quality and undertake central monitoring activities.
Trial statistician and Senior trial statistician	Blinded	Statisticians will be involved in TMG meetings throughout the trial where information on training and testing uptake is presented. Any data released to the statistics team during the trial will be provided with anonymised site codes. Data will not be linked to treatment allocations until after the final database lock. The trial statistician will be permitted access to the data collected during the detailed data collection at each site (around a 3% sample of overall trial

Trial role	Blinding status	Comments
		sample size) after approval of the statistical analysis plan. Blinding of the Senior Trial Statistician will be maintained as far as possible and any future changes to the SAP will be clearly justified.
Independent statisticians	Not blinded	A statistician independent of the trial management team will be responsible for generating the Data Monitoring committee (DMC) closed reports and other potentially unblinding data and will therefore be unblinded to trial interventions.
Neonatologists on blinded endpoint adjudication committee	Blinded	The committee will be blind to the location of the baby and the GBS3 site allocation.

2.3. Trial committees

A trial management group (TMG), trial steering committee (TSC) and data monitoring committee (DMC) will be assembled to oversee the trial. The general purpose, responsibilities and structure of the committees are described in the protocol. Further details of the roles and responsibilities of the TSC and DMC can be found in their charters agreed prior to the start of recruitment to the trial.

A blinded endpoint adjudication committee of neonatologists will be set up to review the individual level data of a sample of babies with clinically suspected sepsis. Full details are described in the Blinded Endpoint Adjudication Committee Protocol (V1.1, 23 March 2023) and charter (V2.0, 18 April 2023).

2.4. Outcome measures

Primary, secondary clinical and safety outcomes are described in Table 1 below.

With the exception of maternal intrapartum anaphylaxis and suspected maternal sepsis, all neonatal and maternal secondary outcomes will be collected from routine data sources.

Process outcomes collected from detailed data collection at each site are described in Table 3 in Section 9.1.

Table 1: Summary of the primary and secondary outcome measures

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
Primary outcome				
All-cause early neonatal sepsis (starting within < 7 days of birth)	Early neonatal sepsis is defined as: • A positive culture of a pathogenic bacteria from blood or cerebrospinal fluid taken at <7 days of birth, or • Death <7 days if infection or sepsis was recorded on the death certificate • Negative/ unknown culture status with ≥3 agreed clinical signs or symptoms (see list in protocol), for which intravenous antibiotics are given for ≥5 days, starting within 7 days of birth.	Binary	Frequencies and percentages in each group Babies who die in utero (antepartum stillbirth) will not be included.	Mixed-effect logistic regression model adjusting for the minimisation variables as fixed effects and including a random effect for sites and mother to account for clustering due to sites and correlation between outcomes for babies from a multiple pregnancy. The estimated between-group effect will be presented using both relative (risk ratio) and absolute (risk difference) measures of effect.
Neonatal secondary outcomes				
Birthweight (grams)		Continuous	Means and standard deviations in each group for liveborn babies	Descriptive only
Perinatal mortality	Stillbirth or livebirth and baby death before 7 completed days after birth	Binary	Frequencies and percentages in each group	As described above for primary outcome

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
Extended perinatal mortality	Stillbirth or livebirth and baby death before 28 completed days after birth	Binary	Frequencies and percentages in each group	As described above for primary outcome
Baby death before discharge	Livebirth and baby died prior to being discharged from hospital	Binary	Frequencies and percentages in each group for liveborn babies	As described above for primary outcome
5 minute Apgar	Score based on five criteria (appearance, pulse, grimace, activity and respiration) assessed be medical professional to summarise the health of a baby. Each criteria is scored 0, 1 or 2 and scores are summed to give a total score between 0 and 10 (higher scores indicating better health). Scores of 7 and above are considered normal and scores below 7 are considered abnormal, the lower the score the greater the need for the baby to receive additional support.	Continuous	Median and interquartile range in each group for liveborn babies Frequencies and percentages in each group for the following categories: < 4, 4 to 6 and 7 to 10.	Apgar scores are left skewed. The 5 minute Apgar will be analysed as a binary variable to compare the number of babies in each group with a score <4 and <7 (i.e. a poor outcome on the Apgar) using the method described above for the primary outcome.
Fetal acidaemia	Fetal acidaemia is defined as cord arterial pH < 7.05	Binary	Frequencies and percentages in each group for liveborn babies	As described above for primary outcome
Gestational age at birth	Number of days that the baby was in gestation prior to birth based on the estimated date of delivery	Continuous	Means and standard deviations in each group. Frequencies	Linear mixed-effect model adjusting for the minimisation variables as fixed effects and including a random effect for sites and mother to account for

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
			and percentages in the following categories: 24 to < 28 weeks, 28 to < 32, 32 to < 37, 37/38, 39/40 and ≥ 41 weeks	clustering due to sites and correlation between outcomes for babies from a multiple pregnancy.
Admission for neonatal specialist care (length of stay, level of care)	Whether the baby was admitted to neonatal specialist care after birth and prior to hospital discharge If admitted the total length of stay in any neonatal specialist care (days) and highest level of neonatal specialist care received (intensive care, high dependency care, special care)	Admission – binary Length of stay – Continuous Level of care - categorical	Admission for neonatal specialist care – frequencies and percentages in each group for liveborn babies Length of stay – mean and standard deviation in each group and frequency and percentage who stay for more than 4 days Highest level of care – frequencies and percentages in each category and group	Admission for neonatal care will be analysed as three binary outcomes including all liveborn babies as follows: • Admitted to neonatal specialist care • Length of stay of 4 days or more • Admitted to neonatal intensive care. using the methods described above for the primary outcome with additional adjustment for the neonatal assessment policy in the cluster at randomisation (NICE or Kaiser-Permanente Neonatal Early-Onset Sepsis Calculator).
Seizures	Whether baby had a seizure ≤ 28 completed days after birth	Binary	Frequencies and percentages in each group for liveborn babies	As described above for primary outcome

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
Abnormal neurological signs at > 24 hours of age	Abnormal neurological signs defined as hypotonia or abnormal level of consciousness between > 24 hours of age and ≤ 28 days.	Binary	Frequencies and percentages in each group for babies alive at > 24 hours of age	As described above for primary outcome
Late onset culture-positive neonatal sepsis	Late onset culture-positive neonatal sepsis defined as blood or cerebrospinal fluid taken from 7 days to ≤ 28 days of birth including clearly pathogenic organisms and excluding skin organisms (e.g. coagulase-negative staphylococci).	Binary	Frequencies and percentages in each group for liveborn babies	As described above for primary outcome
Maternal secondary outcomes				
Mode of onset of labour	The method by which the process of labour began, or delivery by caesarean section occurred. The following categories will be presented: spontaneous, induction and caesarean section.	Categorical	Frequencies and percentages in each category in each group	Mode of labour will be analysed as a binary variable for induction in the sample of women whose labour was spontaneous or induced.
Mode of delivery	Method by which the baby was delivered to be presented in the following categories: spontaneous vaginal delivery, assisted vaginal delivery, elective caesarean section and emergency caesarean section. Mode of delivery may be different for each baby in multiple pregnancies and so will be	Categorical	Frequencies and percentages in each category in each group	Mode of delivery will be analysed as a binary variable for emergency caesarean section in the sample of women whose labour was spontaneous or induced.

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
	presented accordingly (e.g. combined vaginal-caesarean delivery).			
Duration from ruptured membranes to delivery (hours)	Hours from first rupture of membranes to birth of baby (first born baby for multiple pregnancies) Note this outcome is not available from routine data in Wales	Continuous	Means and standard deviations in each group	Linear mixed-effect model adjusting for the minimisation variables as fixed effects and including a random effect for sites
Duration of hospital stay (days)	Days between admission to hospital for labour/caesarean section and discharge from hospital following labour and delivery	Continuous	Means and standard deviations in each group	As described above for duration of ruptured membranes to delivery.
Change of intended location of childbirth	Whether the baby was born in a different place to the location of the planned delivery. The following will be presented: - Change of hospital - Change of setting (e.g. AMU to obstetric unit and vice versa, home to hospital etc …)	Binary	Frequencies and percentages in each group	Descriptive only
Maternal intrapartum anaphylaxis due to intrapartum antibiotic prophylaxis	Maternal intrapartum anaphylaxis assessed as being due to intrapartum antibiotic prophylaxis at ≥ 32 weeks' gestation	Binary	Frequencies and percentages in each group for women giving birth at ≥ 32 weeks' gestation	Mixed-effect logistic regression model adjusting for the minimisation variables as fixed effects and including a random effect for sites.

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
In a subset of participants for whom detailed data is collected, systemic infection confirmed with a positive blood culture or suspected maternal sepsis within 42 days of birth	Systemic infection confirmed with a positive blood culture taken from the onset of labour to within 42 days of birth or suspected maternal sepsis as defined by 1 or more of the following within 42 days of birth: • A new prescription of IV antibiotics for presumed perineal wound-related infection, endometritis or uterine infection, urinary tract infection with systemic features (pyelonephritis or sepsis) or other systemic infection (clinical sepsis) but NOT antibiotics for other any indication.	Binary	Frequencies and percentages in each category in each group	As described above for maternal intrapartum anaphylaxis due to IAP.
Maternal death, from onset of labour to within 42 days post partum	Maternal death from onset of labour to within 42 days post delivery	Binary	Frequencies and percentages in each group	Descriptive only
Cause of maternal death	Maternal cause of death will be categorised using ICD-Maternal Mortality (ICD-MM)	Categorical	Frequencies and percentages in each group	Descriptive only

3. INTERIM ANALYSIS

No interim analyses of clinical outcomes are planned.

4. GENERAL ANALYSIS CONSIDERATIONS

4.1. Analysis sets

The main analysis of the trial will be according to the allocated group of the intended site of delivery of the baby as this determines the plan for antenatal care (and therefore the offer of testing) more closely than actual place of birth. A woman who births in a unit where she has not received antenatal care will only have been offered antenatal testing if both locations have been randomised to ECM testing. The exception to this will be for babies born in Wales as the intended site of delivery is not available as part of the routinely collected data.

Women planning a home birth at sites allocated to routine testing will also be offered a test in order to allow them time to consider their birthing location based upon their GBS colonisation status and so will also be included in the analysis.

Outcome	**Analysis set**
Primary outcome *Secondary neonatal outcomes*	Babies born at ≥24 weeks' gestation during the site's data collection period[1] analysed according to the allocated group of: • the intended site of delivery in England (last recorded prior to delivery) and • actual site of delivery in Wales irrespective of whether testing performed. Babies born with a known congenital anomaly incompatible with survival at birth will be excluded. For women planning a home birth (England)/having a home birth (Wales), analysis will be according to the site responsible for antenatal care (last recorded prior to delivery). The main analysis for each outcome will be for participants with outcome data collected (i.e. without imputation for missing data).

Outcome	Analysis set
Secondary maternal outcomes	Women giving birth at ≥24 weeks' gestation within their site's data collection period[1] analysed according to the allocated group of: • their intended site of delivery in England (last recorded prior to delivery) and • actual site of delivery in Wales irrespective of whether testing performed. For women planning a home birth (England)/having a home birth (Wales), analysis will be according to the site responsible for antenatal care (last recorded prior to delivery).
Secondary outcome - Maternal intrapartum anaphylaxis due to intrapartum antibiotic prophylaxis	Women giving birth at ≥ 32 weeks gestation analysed according to allocated group of site as described above.
Process outcomes	Women and their babies included in the individual data collection at each site as described in protocol section 11.8: consecutive sample of women at gestational age ≥ 32 weeks, excluding elective Caesarean births and women who have opted out of use of data through the national data opt-out.

1 – The dates for the data collection period for each site are documented in the data management plan for the routine data, with each site having a data collection period of between 9 months and 16 months (see protocol section 11.7).

The time between randomisation and opening to data collection was longer than initially expected particularly for sites randomised to the rapid test. The data collection period was therefore extended for risk factor sites that were opened to data collection in 2021 to ensure data used for the comparison of the two strategies is contemporaneous. The start date for the data used in the main analysis for the risk factor sites opened in 2021 will be the date of opening to data collection + 6 months.

4.2. Timing of final analysis

All outcomes will be analysed collectively at the end of the trial after all routine data has been received and blinded endpoint adjudication has been completed.

4.3. Statistical software

Analyses will be performed using Stata version 17 or above or R as appropriate. Analysis will be performed in the accredited Trusted Research Environment (TRE) managed by the Health Informatics Centre (HIC), located at University of Dundee.

4.4. Derived variables

Derivations required for statistical analysis are described in a separate outcome derivation document.

4.5. Procedures for missing data

Missing data will either be due to the whole site dropping out of the trial, women opting out of use of routine data for research or failure to obtain outcome data for some women or babies within participating sites from the routine data sources. The number of clusters dropping out prior to data collection and after starting data collection will be reported. For the primary outcome, the percentage of babies known to be born during the data collection period at each site with missing outcome will be summarised. Demographic and pregnancy characteristics will be compared for babies with and without missing outcome data.

Main analyses 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. Full details are given in section 7.2.

5. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

5.1. Participant flow

A CONSORT diagram will be used to summarise the flow of maternity units into the trial including the number of sites selected, the number randomised and allocated group as well as the reasons if selected sites were not randomised (if available). For each allocated group, the flow diagram will also show the number of women giving birth during the site data collection period and the number of babies born, the number of women and babies included in the analysis of the primary outcome and reasons if babies are not included in the analysis.

The cluster sizes for the primary outcome analysis set will be summarised descriptively by allocated group, including the coefficient of variation.

5.2. Baseline characteristics

Baseline characteristics for the cluster and the women in the analysis set will be summarised both overall and by allocated group using appropriate descriptive statistics for continuous (mean, standard deviation, median, lower & upper quartiles, minimum, maximum and number of observations) and categorical (frequency counts and percentages) characteristics. Characteristics will also be summarised according to the testing strategy for sites randomised to routine testing.

Cluster level characteristics will include:

- Country (England or Wales)
- Type of unit (obstetric led or midwifery led)
- Number of deliveries per year (as used for randomisation, summarised as continuous and in categories: < 4000, 4000 - < 5000, ≥ 5000)
- Neonatal unit level of care (special care, local neonatal unit, neonatal intensive care unit)
- Presence of alongside midwifery unit at the time of randomisation
- Neonatal sepsis assessment at randomisation (NICE guidelines or Kaiser-Permanente Neonatal Early-Onset Sepsis Calculator)

Individual level characteristics of the women will include:

- Country of site at booking
- Age at booking
- Ethnicity

- Decile of Index of Multiple Deprivation (based on postcode)
- Parity
- Pregnancy type (single or multiple)
- Smoking status at booking

In addition, neonatal sex will be presented for the babies.

6. ASSESSMENT OF STUDY QUALITY

6.1. Randomisation

Eligible sites are 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. The minimisation variables are: number of deliveries per year (<4000, 4000– <5000 and ≥5000), neonatal unit level of care tier associated with the participating maternity unit (Special Care Unit, Local Neonatal Unit or Neonatal Intensive Care Unit) and presence of alongside midwifery unit, at the time of randomisation (yes/no).

There is a further second-level randomisation of the routine testing sites to one of the two testing strategies using the same minimisation variables as above with no random element.

Sites can be randomised after completion of the pre-randomisation green light checklist. The trial team aim to randomise all sites with a completed pre-randomisation green light checklist in a batch at the end of each month. Prior to minimisation, the randomisation system randomly orders the sites within the batch. The number of randomisations conducted will be summarised with the number of sites randomised and the allocations.

6.2. Adherence

Compliance with the testing strategy will be assessed as one of the process outcomes using data from the detailed data collection (see Section 9.1).

At a site level the following information will be summarised by testing strategy for sites allocated to routine testing using data collected during central monitoring by the GBS-3 co-ordinating centre:

- Number of sites beginning the implementation period
- Testing coverage at the end of the implementation period (defined as either when the site reaches 80% coverage or after 12 weeks of implementation phase, whichever earlier)
- Number of sites who discontinue testing and reasons
- Number of sites who are unable to test for more than one week during data collection period with reasons
- Testing coverage during the data collection period (summarised using descriptive statistics overall and also according to month of data collection in a graph)

6.3. Follow-up and discontinuations

The data used in the trial will be collected from routine data sources as detailed in the protocol. Data linkage across the different data sources and completeness of data will be summarised by the Senior Research Fellow in eHealth.

6.4. Protocol deviations

Non-compliances related to being unable to test at sites allocated to routine testing will be summarised as described in Section 6.2. Other non-compliances with the protocol are collected during central monitoring by the GBS-3 co-ordinating centre. The number of sites with protocol deviations will be summarised by allocated group along with the type of deviation. Protocol deviations will also be listed.

7. ANALYSIS OF EFFECTIVENESS

The analysis and reporting of the trial will be in accordance with CONSORT guidelines for cluster randomised trials (1) and trials using routinely collected data (2). Primary comparative analyses will be based on intention-to-treat principle, with all eligible women and her babies analysed according to the allocation of the site as described in Section 4.1. Comparisons will be based on individual-level (woman/baby) data rather than cluster-level summaries unless otherwise specified. Analyses will be based on observed data (see Section 4.5) unless otherwise specified. All tests will be two-tailed with point estimates and 95% confidence intervals for the intervention effect presented. Secondary outcomes will be considered supportive to the primary outcome. No formal adjustment for multiple significance testing will be applied.

7.1. Primary analysis

The number and percentage of babies with early neonatal sepsis will be summarised in each group as well as breaking down according to the components of the protocol definition:

- Positive culture of a pathogenic bacteria from blood or cerebrospinal fluid taken at <7 days of birth
- Death <7 days if infection or sepsis was recorded on the death certificate
- Negative/ unknown culture status with ≥3 agreed clinical signs or symptoms, for which intravenous antibiotics are given for ≥5 days, starting within 7 days of birth (see protocol section 6.2 for details).

For babies with culture positive early neonatal sepsis, details of the pathogens will be summarised descriptively.

The primary estimand for the trial is the relative risk of all-cause early neonatal sepsis between a risk based strategy versus routine testing for offer of IAP to the baby's mother, regardless of adherence at site or individual level for babies born at ≥24 weeks' gestation with no known congenital anomaly incompatible with survival at birth. See Table 2 below for further details.

Table 2: Details of estimand

Estimand component	Definition
Target population	Babies born at ≥24 weeks' gestation with no known congenital anomaly incompatible with survival at birth
Variable/endpoint	All-cause early neonatal sepsis as defined in Table 1.
Treatment condition	Comparator: Risk factor based strategy with offer of IAP to the baby's mother if a maternal risk factor for EOGBS infection in her baby is identified before or during labour. Intervention: Routine testing strategy using either antenatal ECM testing or intrapartum rapid testing using the Cepheid GeneXpert system (according to site randomisation), with IAP offered if the test is positive for GBS presence in the sample taken

Estimand component	Definition
Population level summary measure	Relative risk and risk difference of all-cause early neonatal sepsis between the two treatment strategies
Handling intercurrent events	1. *Intervention discontinuation (at site level) – treatment policy*: babies included irrespective of discontinuation of routine testing at site 2. *Test not offered to mother at intervention sites (individual level) – treatment policy:* babies included irrespective of whether mother offered test 3. *Baby death in utero – principal stratum*: i.e. treatment effect in the subpopulation of babies who would survive, regardless of treatment condition

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 risk factor sites, adjusting for the cluster level minimisation factors (number of deliveries per year at randomisation (treated as continuous), neonatal unit level of care tier associated with participating maternity unit and presence of alongside midwifery unit at the time of randomisation) as fixed effects and accounting for the clustering effect due to sites and the correlation between outcomes for babies from a multiple pregnancy. Multiple births will be nested within site using random effects.

The comparison will be presented as an adjusted risk ratio and risk difference with corresponding 95% confidence intervals obtained using Stata's margins command with standard errors computed using the delta method (3). The maternity unit intracluster correlation coefficient with 95% confidence interval will also be presented.

In the case of non-convergence with the model specified above, minimisation variables may be collapsed into fewer categories (for example collapsing neonatal level of care tier into two categories (intensive care unit yes/no) or a simpler covariance structure will be used. If adjustment for minimisation variables is not possible, unadjusted estimates will be presented.

7.2. Sensitivity analysis of primary outcome

The following sensitivity analyses will be performed for the primary outcome:

- Using cluster level analysis
- Using multiple imputation for missing outcomes (see Section 4.5)
- According to allocation of actual site of delivery
- Further adjustment for baseline variables (including baseline sepsis rate)
- Accounting for paired opening of sites

Further details are described in Sections 7.2.1 to 7.2.5 below.

In addition, there is the potential that women may have more than one pregnancy during the trial data collection period. The number of women with more than one pregnancy in the analysis dataset will be summarised. Sensitivity analysis may be conducted to explore the robustness of the results to the specification of the random effects for siblings from different pregnancies in the model for the primary analysis.

7.2.1. Using cluster level analysis

Analysis on aggregate cluster-level infection rate will be performed to check the conclusions are robust. The percentage of babies with early neonatal sepsis at each site will be summarised by

allocated group (using mean, standard deviation, median, lower quartile, upper quartile, minimum and maximum). Analysis at the cluster level will use a two-stage procedure: first fitting a linear regression model for the percentage of babies with early neonatal sepsis 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 a t-test to obtain the between group differences in the risk.

7.2.2. Using multiple imputation for missing primary outcome data

Multiple imputation will be used to impute data for babies known to be born during the site data collection period with missing primary outcome data. This analysis will assume that unobserved outcomes are missing at random (MAR) and depend on observed characteristics included in the imputation model but not the unobserved outcomes. Imputations will be done using multilevel joint imputation to account for the multilevel structure of the data.

Variables included in the imputation model will be:

- Cluster level minimisation variables: number of deliveries per year, neonatal unit level of care tier associated with the participating unit and presence of alongside midwifery unit
- Pregnancy characteristics associated with early neonatal sepsis including gestational age, mode of delivery and duration of rupture of membranes to delivery (*NICE guideline*)
- Maternal characteristics, as described in Section 6.8 additional descriptors section of the protocol, associated with missing primary outcome data (by examination only)

If the imputation model fails to converge including the variables above, a simpler model will be used. The number of datasets imputed will be based on the proportion of babies with a missing outcome.

Between group effects in each imputed dataset will be estimated using the mixed effects logistic regression model described in Section 7.1. The adjusted risk differences and adjusted risk ratios will be computed using the delta method in each imputed dataset and combined using Rubin rules for multiply imputed data.

7.2.3. According to allocation of actual site of delivery

The analysis specified in Section 7.1 will be repeated replacing the intended site of birth and it's allocation for the GBS-3 trial with the actual site of birth and it's allocation for the GBS-3 trial. Babies who were not born at GBS-3 sites will not be included in this sensitivity analysis.

7.2.4. Further adjustment for prognostic baseline variables

Baseline sepsis rate at each site (if the data is available) will additionally be included as a fixed effect in the model specified in Section 7.1.

In addition, baseline maternal variables will be examined for imbalances between the two groups. Any characteristics where a marked imbalance is observed (based on comparison of summary statistics only, not statistical testing) that is predictive of neonatal sepsis will additionally be included as covariates in the model specified in Section 7.1.

7.2.5. Accounting for paired opening of sites

Risk factor and testing sites were opened to data collection in batches to ensure contemporaneous data collection. An additional variable will be created to group sites opening at the same time. This variable which will be included as an additional random effect in the mixed effects logistic regression model described above in Section 7.1.

7.3. Secondary analysis of primary outcome

7.3.1. Complier average causal effect analysis

Should there be any non-compliance with some sites refusing to implement the new intervention then an analysis to estimate the complier average causal effect will be performed to account for any non-compliance.

7.3.2. According to testing coverage at the end of the implementation period

At 12 weeks, sites allocated to routine testing will be deemed to be open to data collection regardless of testing coverage with data included in the primary analysis. However, a secondary analysis will be conducted, using the methods described in Section 7.1, excluding sites which failed to reach 80% uptake (see protocol section 11.6) if sufficient sites reach this threshold. For this analysis, the corresponding risk factor site opened at the same time as the routine testing site who failed to reached 80% testing coverage will be excluded.

An additional secondary analysis will be conducted excluding sites with a very poor testing coverage. Different testing uptake thresholds (e.g., 25%, 50%) will be used for this analysis to assess how sensitive the results are depending on testing coverage.

7.3.3. Excluding periods where sites could not perform routine testing

A secondary analysis will be conducted, using the methods described in Section 7.1, excluding data from sites allocated to routine testing during dates where the site was unable to test women during the data collection period. For this analysis, data will be excluded for the same time period for a randomly selected risk factor site.

7.3.4. Effect of each routine testing strategy

A secondary analysis will be conducted to estimate the effect of each routine testing strategy compared to the risk factor based strategy by including a three level variable for allocation (risk factor, antenatal ECM testing, intrapartum rapid test) in the mixed effects model described in Section 7.1.

7.4. Subgroup analysis of primary outcome

Subgroup analysis for the primary outcome will be conducted according to maternal ethnicity in the following categories: White, South Asian, Black, Mixed and Other. The analysis will be conducted by including appropriate interaction terms in the analysis model for the primary outcome. Between-group effects will be provided for each subgroup, but interpretation of any subgroup effects will be based on the treatment allocation-subgroup interaction and 95% confidence interval. Since the trial is powered to detect overall differences between the groups rather than interactions of this kind, this subgroup analysis will be regarded as exploratory and will be conducted regardless of the results of the main analysis.

7.5. Secondary outcomes

Table 1 lists all the neonatal and maternal secondary outcomes and the type of variables. Secondary outcomes will be analysed using mixed-effects regression models appropriate for the type of outcome variable, adjusting for minimisation variables as fixed effects with a random effect for site.

For neonatal outcomes the correlation between outcomes for babies from a multiple pregnancy will be accounted for by using an additional random effect for the pregnancy nested within site.

Continuous outcomes will be analysed using linear mixed-effect models. The between group comparison will be presented using the adjusted difference between means, along with a 95% confidence interval. Binary outcomes will be analysed and presented as described for the primary outcome in Section 7.1.

For the secondary effectiveness question for neonatal unit admission, the admission for neonatal specialist care secondary outcome will be compared between the two testing strategies in addition to comparing routine testing with the risk factor based strategy.

8. ANALYSIS OF SAFETY

Maternal intrapartum anaphylaxis due to IAP is a secondary outcome for the trial and will be analysed as described in Table 1 and Section 7.5. No other adverse event data will be collected.

Details of any unexpected adverse events occurring as a result of participation in the trial that are reported to the trial coordinating centre will be included in the final report.

9. OTHER ANALYSIS

9.1. Process outcomes

Process outcomes collected from detailed data collection at each site are described in Table 3. Comparisons for the process outcomes for the sub-randomisation to the different testing strategies will focus on rates of uptake, accuracy in relation to maternal colonisation in labour and ability to deliver a test in time for adequate IAP that cumulatively influence effectiveness. Table 3 specifies the outcomes which will be compared between the two different testing strategies using the methods described in Section 7.1. Estimates of the between group differences for the two different testing strategies will be presented as intrapartum rapid testing versus antenatal enriched culture medium testing.

Table 3: Summary of process outcomes

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
Number of women with risk factors for EOGBS infection developing in the baby and which risk factors they have	RCOG Greentop Guideline 36, 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	Binary	Frequencies and percentages according to allocated group (control, intervention) and allocated testing strategy.	Descriptive only Number of women with at least one risk factor for EOGBS developing in the baby will be presented as well as number and percentage of women with each of the individual risk factors for both the risk factors identified by the clinical care team and all risk factors identified through review of records.
Number of women having a swab taken (of all those eligible for testing) including site of swab (vaginal-rectal, vaginal only, rectal only) and person performing the swab (self-swab, health care professional swab).	Whether swab taken for women booked at a site allocated to routine testing, who were eligible for a test	Binary	Frequencies and percentages according to allocated testing strategy (antenatal enriched culture medium or intrapartum rapid test)	The proportion of women having a swab taken will be analysed using a mixed-effect logistic regression model adjusting for the minimisation variables as fixed effects and including a random effect for site (to account for clustering). The estimated between-group effect will be presented using both relative (risk ratio) and absolute (risk difference) measures of effect.
Number of women who decline a swab when offered (and reasons why)	Whether swab declined for women offered a swab in sites allocated to routine testing. Number of women declining by site of swab (vaginal-rectal, vaginal only, rectal only) will be	Binary	Frequencies and percentages according to allocated testing strategy using the	Descriptive only

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
	presented as well as the number of women declining any type of swab.		number of women offered a swab as the denominator.	
Number of women having a swab taken at the appropriate time (of all those swabbed and all those eligible)	Whether swab taken at appropriate time (as defined in protocol) in sites allocated to routine testing based on date/time of first swab taken.	Binary	Frequencies and percentages according to allocated testing strategy using the number of women where swab taken as denominator.	Descriptive only
Number of women with a test result available ≥ 4 hours before time of birth	Whether test result (positive/negative) is available at least 4 hours before baby born in sites allocated to routine testing. Derived from date and time of delivery (first born for multiple pregnancies) and: • Date and time positive/negative result available on machine for intrapartum rapid test sites or • Date and time positive/negative result reported in antenatal ECM sites Date and time of positive/negative result from a second swab will be used for women at intrapartum rapid test sites with an initial negative test result	Binary	Frequencies and percentages according to allocated testing strategy using the number of women eligible for testing as denominator.	Analysis as described above for swab taken

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
	who do not progress to labour within 5 days of the first test.			
Number of women with a test result available ≥ 2 hours before time of birth	As described above for at least 2 hours before baby born	Binary	As above	Analysis as described above for swab taken
Number of women receiving GBS-specific IAP	Whether women received intrapartum antibiotic prophylaxis for GBS infection.	Binary	Frequencies and percentages according to allocated group and allocated testing strategy	Analysis as described above for swab taken. Between group effects will be presented for both routine testing compared to risk factor strategy and intrapartum rapid testing compared to antenatal ECM for sites allocated to routine testing
Number of women receiving antibiotics for prophylaxis before operative (Caesarean or instrumental) birth	Whether women with operative birth received antibiotics prior to start of procedure	Binary	As above	Descriptive only
Number of women receiving intrapartum antibiotics for any other reason	Whether women who did not receive antibiotics for IAP for GBS or antibiotics for prophylaxis before operative birth, received antibiotics prior to childbirth for reasons other than prophylaxis for GBS or before operative birth	Binary	As above	Descriptive only

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
Number of women with first dose of GBS-specific IAP administered at least 4 hours before childbirth	Whether first dose of IAP for GBS given at least 4 hours before baby born. Time between first dose of IAP and childbirth derived from: • date and time of delivery (first born for multiple pregnancies) and • date and time of first dose of IAP for GBS	Binary	As above	Analysis as described above for swab taken. Between group effects will be presented for both routine testing compared to risk factor strategy and intrapartum rapid testing compared to antenatal ECM for sites allocated to routine testing.
Number of women with first dose of GBS-specific IAP administered at least 2 hours before childbirth	As described above for with time period at least 2 hours before baby born	Binary	As above	
Total dose of administered IAP per woman	*N/A – to be summarised as part of health economic evaluation*		*N/A*	*This outcome will be summarised as part of the economic evaluation to provide estimates of resource use and cost profiles associated with IAP*
The proportion of women who tested positive for GBS, tested negative for GBS or who did not have an available test result	Summary of test result for GBS for women in sites allocated to routine testing derived from testing information. The final test result will be used for the summary (i.e. retest result if initial test failed or result from second swab for women at intrapartum rapid test sites with an initial negative test result who do not progress to labour within 5 days of the first test)	Categorical	Frequencies and percentages according to allocated testing strategy	Descriptive only

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
The proportion of failed tests.	Summary of test result failures where a swab was taken. Failures will be summarised separately for the initial swab and any repeat tests.	Binary	Frequencies and percentages according to allocated testing strategy	Descriptive only
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	Summary of whether IAP offered for women who had a positive test result for GBS or risk factors as described in protocol section 11.1 to 11.5	Binary	Frequencies and percentages according to allocated group and allocated testing strategy	Descriptive only. Offer of IAP will be summarised according to test result if available or risk factors if no test result available at testing sites and according to risk factors at risk factor sites.
Number of women declining IAP when offered and reason why	Summary of whether woman accepted the offer of IAP (regardless of reason) and reason if women did not accept IAP	Binary for accept/decline Categorical for reason	As above	Descriptive only
Number of women with a negative test result or no documented risk factors who are offered and accept IAP (and reasons)	Summary of offer of IAP to women and whether accepted for women who had a negative GBS test result or no risk factors identified (see protocol section 11.1 to 11.5)	Binary for offer and acceptance Categorical for reason	As above	Descriptive only

Outcome measure	Description	Type	Method of aggregation	Methods of analysis
Number of babies of mothers who A) tested positive for GBS (testing sites) B) with documented risk factors (risk factor sites) whose vital signs and clinical condition were observed for at least 12 hours	Summary of whether baby vital signs and clinical condition observed for at least 12 hours for babies with a positive GBS test result or documented risk factors where no test result available (testing sites) or documented risk factors (risk factor sites)	Binary	As above	Descriptive only
Number of babies of mothers who A) tested positive for GBS (testing sites) B) with documented risk factors (risk factor sites) who were investigated for infection and/or had intravenous antibiotics commenced	Summary of whether baby had: • clinical assessment for sepsis or • septic screen or • antibiotics in hospital within 7 days of birth for babies with a positive GBS test result or documented risk factors where no test result available (testing sites) or documented risk factors (risk factor sites)	Binary	As above	Descriptive only. Frequency of each assessment will be summarised separately as well as the number of babies who had any investigation for infection and/or IV antibiotics within 7 days of birth.

10. FINAL REPORT TABLES AND FIGURES

See separate dummy table document – 1736GBS3 dummy tables version 1.0 20240228.docx

11. REFERENCES

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