PReCePT Study Evaluation
Statistical Analysis Plan

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List of abbreviations

Acronym	Details
AHSN	Academic Health Science Network
CI	Confidence Interval
ARC	Applied Research Collaboration
CP	Cerebral Palsy
CTU	Clinical Trials Unit
GA	Gestational Age
GCP	Good Clinical Practice
ITS	Interrupted Time Series analysis
MgSO4	Magnesium Sulphate
NDAU	Neonatal Data Analysis Unit
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNAP	National Neonatal Audit programme
NNRD	National Neonatal Research Database
NPP	PReCePT National Programme
OR	Odds Ratio
PReCePT	Prevention of Cerebral Palsy in pre-term labour
RCT	Randomised Control Trial
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

1. INTRODUCTION TO SAP

1.1 Scope

This document details information regarding the statistical analysis of the PReCePT Study (cluster randomized controlled trial). The analysis will be conducted by the National Institute for Health Research Applied Research Collaboration (NIHR ARC West).The purpose of this trial is to assess the effectiveness of an enhanced support implementation of the PReCePT quality improvement toolkit aimed to increase the uptake of magnesium sulphate in pre-term deliveries (<30 weeks gestational age) in comparison with the standard support implementation delivered via national PReCePT programme (NPP) delivered by Academic Health Science Networks (AHSNs). This analysis plan only includes the quantitative analysis.

1.2 Editorial changes

Any changes made to this statistical analysis plan (SAP) after approval must be clearly justified and documented as an amendment at the end of this document. The SAP should then be re-approved.

1.3 SAP document approval

The NIHR ARC West effectiveness team lead (Dr. Theresa Redaniel), the PReCePT Trial Evaluation Lead (Dr. Brent Opmeer) and the NIHR ARC West Applied Data Science workstream theme lead Prof. Tim Peters will authorise this document. Other members of the study team will also be invited to comment prior to approval.

1.4 Skeleton tables and figures

Throughout this document references are made to any skeleton tables and figures to be used in the reporting of the study (e.g. **Figure 1** or **Table 1**). Such tables and figures can be found in **Appendix A** of this document and are intended as a guide for evaluation reporting. Final versions of the tables/figures may differ- tables may be combined, and/or their layout or numbering may change. However, the content should be consistent with **Appendix A.**

2. STUDY BACKGROUND AND OBJECTIVES

2.1 Study background

Preterm birth is the leading cause of brain injury and Cerebral Palsy (CP) with lifelong impact on children and families. Magnesium sulphate (MgSO4) given to eligible mothers during preterm birth is an effective treatment for protecting the baby's brain. High quality evidence suggests a relative risk reduction of one-third for acquiring CP. One third of UK premature babies (36% in 2017) are not receiving the benefit of this highly cost-effective treatment. The dose costs approximately £1.

A Quality Improvement (QI) package, PReCePT1, was co-designed with patients and staff in 2014/15 and implemented across five maternity units in the West of England, increasing average uptake from 21% to 85%. PReCePT1 used a multifaceted approach to increase awareness and knowledge about MgSO4 as brain protection in preterm deliveries. It provided practical tools and training to support staff in acute clinical settings to consider MgSO4 in eligible pregnancies.

The National PReCePT Programme (NPP) is the national adoption and spread of the PReCePT QI Toolkit. The NPP is funded by NHS England and is led by the West of England Academic Health Science Network (WEAHSN). WEAHSN is supporting the other 14 AHSNs across England to implement the PReCePT QI toolkit in all maternity units. In the NPP, the PReCePT QI toolkit is considered to be implemented using a standard support model.

To assess whether a standard support model of implementation is effective, or whether an enhanced support model of implementation (includes a micro-level QI support) is necessary to improve rates of MgSO4 uptake, the PReCePT Study was embedded within the NPP. Forty-eight maternity units in England were randomised to either receive the enhanced support model (16 units) or be observed while implementing the standard support model (32 units) during a 9-month implementation period.

The NIHR ARC West will evaluate the implementation and effectiveness of the PReCePT QI toolkit in maternity units across England, comparing an enhanced support model for implementation with a standard support model. For the evaluation of comparative effectiveness, we will be using an anonymised extract from the National Neonatal Research Database (NNRD). Data will also be collected using study questionnaires and and reports from QI coaches. Only the quantitative analysis plan for the effectiveness evaluation will be presented in this document.

2.2 Study objectives

PReCePT Study evaluation aims to assess the impact of an enhanced support implementation and a standard support implementation of the PReCePT QI toolkit on the uptake of MgSO4 in pre-term deliveries (<30 weeks GA) for the prevention of neurodisabilities.

2.3 Primary outcome

Proportion of MgSO4 uptake in mothers with deliveries bellow 30 weeks gestation at the maternity unit level in the 9 months after the implementation of the QI intervention adjusting for the proportion in the 12 months before implementation.

2.4 Secondary outcomes (all measured as proportion of all mothers eligible for MgSO4)

- Trend in the MgSO4 uptake
- Reasons for not administering MgSO4 (e.g. mother refused, imminent delivery etc.)
- Data completeness

2.5 Changes to the study objectives during the course of the study

N/A

2.6 Changes to the study outcomes during the course of the study

N/A

3. STUDY POPULATION

The study population is mothers with preterm (<30 weeks GA) deliveries presenting at maternity units in England that are participating in the PReCePT Study. The study includes 40 units that were randomly selected from 84 maternity units in England with minimum 10 preterm (<30 weeks GA) births in 2017 and 70% or less MgSO4 uptake in 2017, participating in the NPP with and have not previously participated in PreCePT1. Primary analysis will be at the level of the maternity units, aggregated from the data at the level of the mothers. Secondary analyses will be at the level of mothers and maternity units.

3.1 Analysis groups

The study is set up as a cluster randomised controlled trial (non-blinded). The term "cluster" refers to the maternity units. Two groups are being evaluated and compared in the trial and are recruited among eligible maternity units in England. Randomisation procedures were applied to eligible maternity units to reduce imbalance between intervention groups. Units were stratified by MgSO4 uptake in 2016 (four strata of 0-39.9%, 40-49.9%, 50-59.9%, and 60-70.9%). Depending on study allocation, units received:

Group 1 (control): Implementation of the PReCePT QI toolkit according to the standard support model, as defined and deployed by the local AHSN within the NPP. This includes provision of PReCePT QI materials, regional level QI training cascaded from the AHSNs, some support funding for the regional neonatal lead and clinical backfill (local midwife);

Group 2 (intervention): Implementation of the PReCePT QI toolkit according to the enhanced support model. After participating in the initial implementation stage of the PReCePT Programme, the level of support will be intensified for units in this group, providing individual unit-level coaching by an experienced QI coach, access to learning and celebration events, funded time for local clinical champions (neonatologist and midwife), over and above the backfill provided by the NPP, and a small fund to purchase study collateral.

Since implementation of the NPP were expected to start at different times in different units, the PReCePT Study randomisation procedure and implementation were aligned with NPP timeframe to accommodate unit readiness for the roll-out of the NPP and resulted in two implementation waves. 9-months implementation period for enhanced support in units in the first study wave were started in December 2018; for units in the second study wave, implementation started in January 2019. The follow-up periods to evaluate the outcomes will reflect the same time-delay associated with waves.

The data from 12 months pre-randomisation, 1-9 months post-randomisation and 10-18 months post-randomisation represents the pre- during and post- implementation periods, respectively, and will be referred to as such for the remainder of this SAP.

3.2 Consent

Maternity units that agreed to participate in the trial PReCePT have provided written informed consent at unit level before commencing the study. Consent have been provided

by the clinical service lead for maternity and neonatal care for each unit (or an authorised delegate). No informed consent is sought from individual women delivering in maternity units for their participation in this study, as health care provided is according to current practice, following the clinical practice NICE guideline (NG25). Data used in this evaluation are routinely collected and anonymous and therefore this does not require patient consent.

3.3 Withdrawals

Withdrawal from the evaluation is not possible as only routine data are being used and patient care will not be affected by the evaluation. However, patients who have opted to have their data removed from data registries will be excluded from analyses as their data will not be available.

4. DATA SOURCES

Data for this evaluation will be from routine data sources, study questionnaires and report from QI coaches delivering enhanced support model. These sources are listed below.

Pseudonymised patient level routine data is obtained from UK National Neonatal Research Database (NNRD), which is maintained and updated quarterly by Neonatal Data Analysis Unit (NDAU).

PReCePT Study questionnaires include baseline questionnaire delivered at the start of intervention and teamwork perceptions questionnaire delivered at the start and end of intervention to all intervention and control units.

Variable(s)	Data sources	Further information
Patient (baby) level		
MgSO4 uptake	NNRD/NDAU	
Reasons for not administering MgSO4	NNRD/NDAU	
Patient(baby)/Delivery/Mother/Unit characteristics	NNRD/NDAU	
Unit level (all)		
Experience with other QI projects	Baseline questionnaire; Other sources;	Other sources include participation in MatNeo and VON network;
Number of maternity staff in each unit	Baseline questionnaire; NHS workforce statistics	https://digital.nhs.uk/data-and-information/publications/statistical/nhs-workforce-statistics/october-2018
Number of maternity staff by job role and pay band	Baseline questionnaire;	
Month champion midwife is in place (PReCePT programme)	Baseline questionnaire; WEASHN;	

Variable(s)	Data sources	Further information
Total number of births in each unit	NNRD/NDAU	Using total eligible births per unit as proxy
Numbers and identity of all maternity units (AHSN information)	WEAHSN	
Month unit had a national PReCePT programme 'launch event'	WEAHSN;	
Teamwork perceptions scores: team structure, leadership, situation monitoring, mutual support, communication.	Teamwork perceptions questionnaire;	
Unit level (intervention)		
Month champion midwife is in place (PReCePT study)	Baseline questionnaire;	
Intervention components: implementation	PReCePT Study QI coaching report	Monthly
Intervention components: engagement	PReCePT Study QI coaching report	Monthly
Intervention components: coaching support	PReCePT Study QI coaching report	Monthly
Month unit has PReCePT Study launch/learning events	PReCePT Study team	

5. DERIVATIONS

New variable	Rules
Patient level	
Pre/During/Post implementation periods for analysis	If month of birth ≤ month of implementation start in the unit where the baby was born, then period=pre-implementation If month of birth > month of implementation start and month of birth ≤ month of implementation end in the unit where the baby was born, then period=implementation. If month of birth > month of implementation end in the unit where the baby was born, then period=post-implementation.
Multiple pregnancy	If baby is one of a multiple pregnancy (e.g. twins), then YES. If baby is a single pregnancy, then NO.
Unit level	
Baseline MgSO4	Calculated as the mean percentage of mothers receiving MgSO4 in the 12 months prior to the PReCePT Study starting in each unit.
Post MgSO4	Calculated as the mean percentage of mothers receiving MgSO4 in the 9 months after the PReCePT Study ending in each unit.
Unit size quintiles	Unit size will be determined by the mean number of births in the 12 months prior to the PReCePT Study starting in each unit. Units will then be ordered by size and split into quintiles.

6. STATISTICAL ANALYSES

6.1 Patient, mother and maternity unit characteristics

Patient (baby) characteristics (e.g. sex, gestational age, birth weight etc.) and mother (delivery) characteristics (e.g. age at delivery, mode of delivery, antenatal steroids administration etc.) will be described by trial arm (intervention or control) for the post-implementation period (*Table 1).*

Maternity unit characteristics (e.g. number of beds, number of clinical staff, neonatal unit level, teamwork perception score etc.) will also be described by trial arm (*Table 2*). Continuous variables will be summarised using means and standard deviations (SD) (or medians and interquartile ranges (IQR) if the distribution is highly skewed), and categorical data will be summarised as numbers and percentages. The summary statistic headings given in the skeleton tables are those expected to be used based on a *priori* knowledge of the measurements gained from previous studies.

6.2 Preliminary analysis:

Multivariable linear regression will be used to assess which elements of engagement with the QI intervention are associated with an increase in the MgSO4 uptake in the maternity units which received the intervention. This analysis will only include intervention units and will be done after the implementation period. It is not expected to affect the overall assessment of effectiveness.

6.3 Primary Analyses

MgSO4 uptake

The proportion of mothers receiving MgSO4 over time (monthly) by trial arm will be presented (*Figure 1*).

Linear regression will be used to assess differences between trial arms in post-implementation uptake of MgSO4, adjusted for pre-implementation uptake. As the analysis is at the maternity unit level, the model will be weighted on the number of births contributed by each unit (analytic weights) and will use robust standard errors.

As this is a RCT, we do not anticipate confounding by any other factors. However, we will explore the impact of potential confounders including pregnancy, mother, delivery and baby characteristics (aggregated as proportions at the maternity unit level), unit level (special care, high dependency, or neonatal intensive care unit), AHSN and trial implementation wave. Results will be presented in Table 3. The effect of the intervention will be presented as the percentage increase or decrease in a unit's uptake of MgSO4 associated with the intervention, with a corresponding 95% confidence interval (CI) and p-value.

Missing data on any additional variables in the model will be imputed using chained equations.

6.4 Secondary Analyses

Reasons for not administering MgSO4

Reasons for not administering MgSO4 will be categorised and presented as numbers and percentages by trial arm (pre-, implementation and post-implementation periods) (*Table 4*). No formal analysis will be performed.

Data completeness

The number and percentage of mothers whose MgSO4 status is unknown will be presented over time (monthly) by trial arm (*Figure 2*). No formal analysis will be performed

6.5 Model assumptions

For all methods outlined, underlying assumptions will be checked using standard methods, e.g. residual plots, etc. If assumptions are not valid then alternative methods of analysis will be sought. If outlying observations are found which mean models do not fit the data adequately, we will conduct sensitivity analyses where such observations will be excluded.

6.6 Statistical software

Data management and analyses will be performed in Stata version 15.1 and R version 3.6.1.

7. AMENDMENTS TO THE SAP

Previous version	Previous date	New version	New date	Brief summary of changes
1.0	9th October 2019	2.0	2nd December 2020	Previously the main analysis was going to be a logistic regression at the individual-level. Now we are doing a linear regression at the unit-level. Removed Interrupted Time Series / segmented regression analysis as this is now redundant.

APPENDIX A: SKELETON TABLES AND FIGURES

Table 1: Baby and mother/delivery characteristics at baseline

Characteristic	**Intervention**		**Control**	
	n	**%**	**n**	**%**
Patient (baby) level				
Gestational age, (mean, SD)				
Phenotypic Sex				
Multiples				
Mother/Delivery level				
Age at delivery, years (mean, SD)				
Mode of delivery				
Ethnicity				
IMD quintile				
Hypertension				
Ante-natal steroids given				
Level of birth unit				
MgSO4 data				
MgSO4 given				
MgSO4 data missing				

Table 2: Maternity unit characteristics

Characteristic	**Intervention**		**Control**	
	Median	**IQR**	**Median**	**IQR**
Number of units (n, %)				
Number of beds				
Number of clinical maternity unit staff				
Job roles/ grades of maternity unit staff				
Tertiary or secondary unit (i.e. does it have a neonatal ICU etc)				

Table 3: Mixed-effects model of effectiveness of enhanced support (intervention) compared to standard implementation (control)

Variable	Coefficient	se	p	95%CI
Intervention				
Baseline MgSO4				
Gender				
Gestational age				
Birthweight				
Maternal age				
Maternal ethnicity				
Maternal hypertension				
Anti-natal steroids received				
Delivery mode				
Multiple birth				
Level of birth unit				
AHSN wave				

Table 4: Reasons for not administering MgSO4

Outcome by implementation period	Intervention		Control	
	n	%	n	%
Reason not administering				
Pre				
During				
Post				

Figure 1: Average MgSO4 over time intervention vs. control

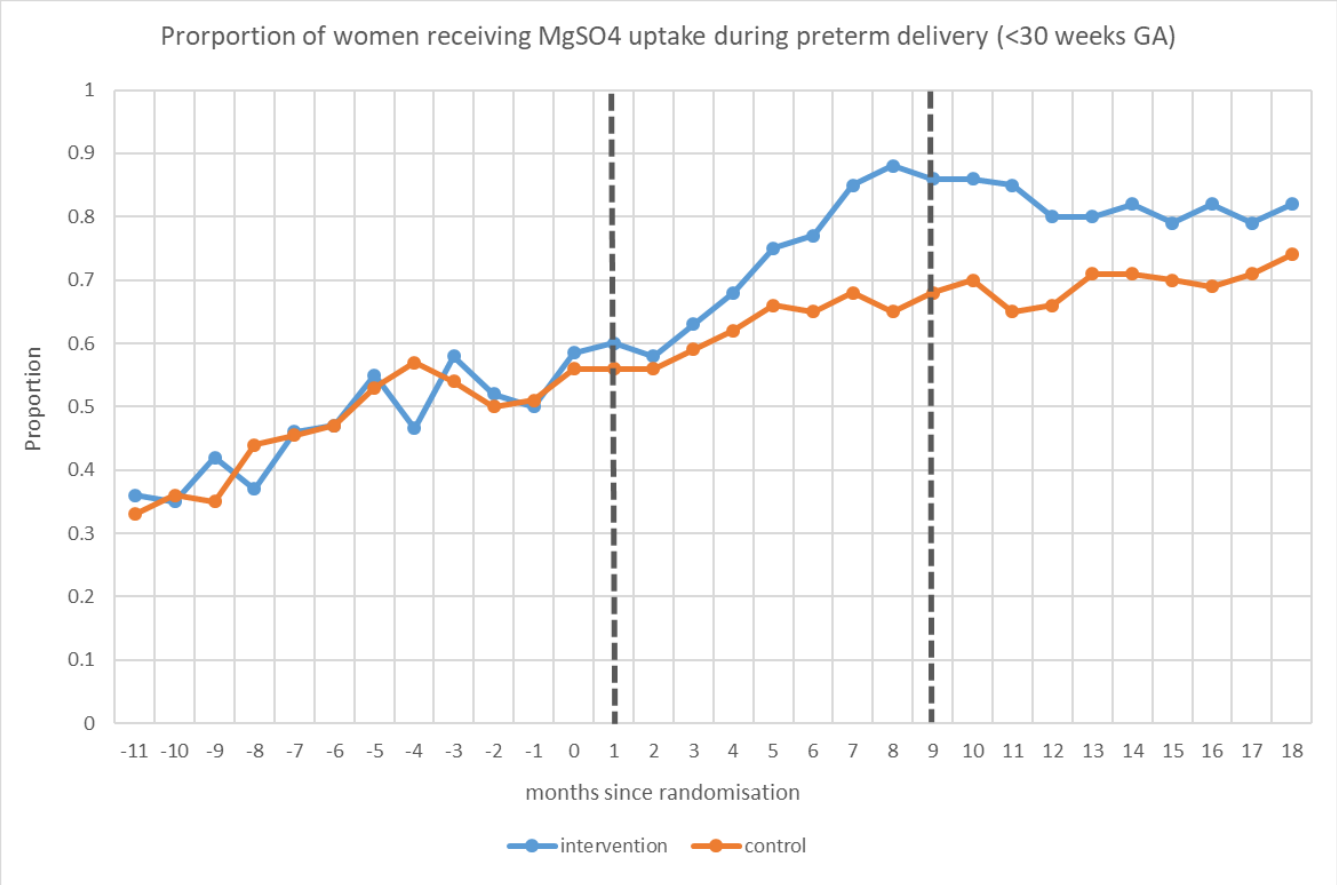
Prorportion of women receiving MgSO4 uptake during preterm delivery (<30 weeks GA)
Proportion
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-11 -10 -9 -8 -7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
months since randomisation
intervention
control

Figure 2: Missing MgSO4 data over time