Bicarbonate for AcidosiS in very pretErm babies: The BASE Studies

Protocol

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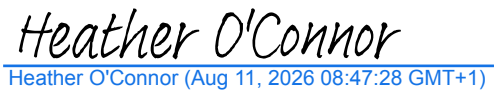
Statistician Signature: 
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Conflict of interest: There are no conflicts of interest to declare

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1 KEY TRIAL CONTACTS

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2 SUMMARY

Metabolic acidosis is a build-up of acid in the bloodstream which has various causes. In the UK, 8,000 babies are born very preterm each year and some will develop metabolic acidosis during their stay on a neonatal unit.

Sodium bicarbonate is widely, but not universally, used to treat metabolic acidosis in very preterm babies but the evidence underpinning its use is poor. Some doctors believe that giving sodium bicarbonate lowers acid levels in the bloodstream and improves the functioning of the heart, but others believe sodium bicarbonate raises acid levels in the cells of the body which can be harmful in the short and long-term by affecting blood flow to the brain and other tissues in the body. There is no accepted standard of care for the use of sodium bicarbonate for metabolic acidosis in premature babies. The two approaches of using sodium bicarbonate, or not, for episodes of metabolic acidosis, are commonly used across the UK. Some doctors also try to prevent metabolic acidosis by giving sodium bicarbonate infusions through an arterial line. The variation in practice persists because the impact and effectiveness of sodium bicarbonate in very preterm babies for metabolic acidosis has never been robustly studied.

The BASE randomised controlled trial (RCT) was developed to answer the question as to whether sodium bicarbonate improved or worsened infant death or major morbidity up to discharge home. The BASE RCT opened to recruitment in February 2024; however it substantially under-recruited. Further work is therefore required to understand the causes of this. The use of alternative research approaches is also necessary to contribute to the evidence-base for the management of metabolic acidosis.

With agreement from the funder, the BASE RCT will convert into a randomised feasibility trial (referred to below as WS1). Two additional studies, an observational study (WS2) and an integrated qualitative study (WS3) will run in parallel to enhance understanding of current practice, identify barriers to recruitment, and support decision-making for future research, including the potential development of a revised future RCT. Collectively, the original BASE RCT, the feasibility trial, the observational study, and the qualitative study will be referred to as *The BASE Studies*.

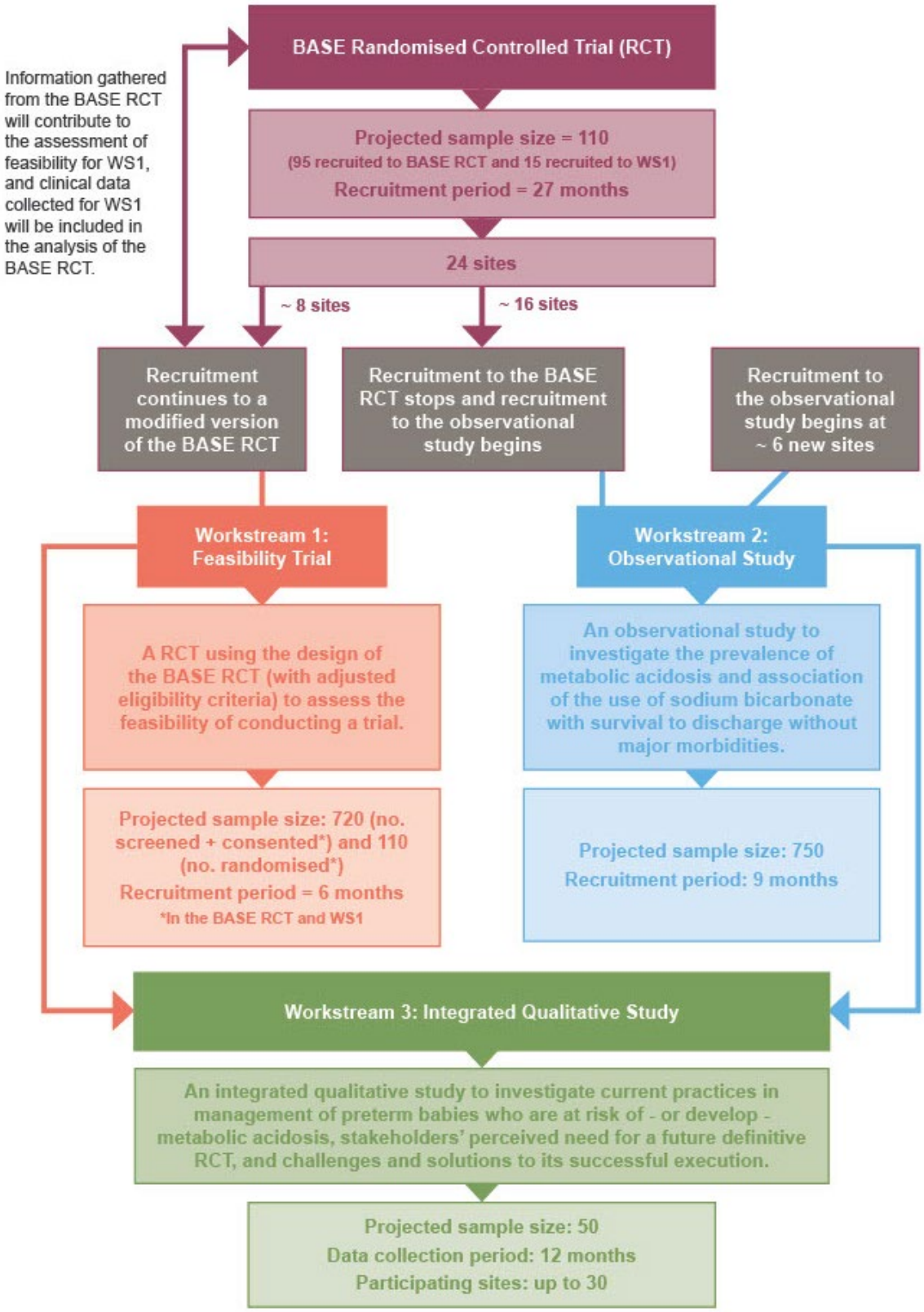
The BASE Studies aim to determine the prevalence of metabolic acidosis in preterm babies, how it is currently managed (including use of sodium bicarbonate), the impact of treatment on health, and the factors that influence or hinder recruitment to an RCT. Analysis and dissemination of the original BASE RCT will proceed as planned, alongside the following workstreams:

- Workstream 1 (WS1): Feasibility Trial
- Workstream 2 (WS2): Observational Study
- Workstream 3 (WS3): Integrated Qualitative Study

Information gathered from the original BASE RCT will contribute to the assessment of feasibility for WS1, and clinical data collected for WS1 will be included in the analysis of the BASE RCT.

This protocol sets out the detail of The BASE Studies; the original BASE RCT and the three workstreams. Including the detail of the original BASE RCT within this protocol supports its completion and provides context for the other workstreams.

3 THE BASE STUDIES FLOWCHART



4 SYNOPSIS

Study Title	Bicarbonate for AcidosiS in very pretErm babies: The BASE Studies
Short title	The BASE Studies
Study registration	ISRCTN Ref: 18260410 Date of Registration: 06/11/2023
Sponsor	University of Oxford
Funder	NIHR Health Technology Assessment (HTA) Programme (NIHR151086)
Clinical Phase	RCT: Phase III WS1: N/A WS2: N/A WS3: N/A
Study Design	Mixed methods comprising of a Randomised Controlled Trial (RCT) and three workstreams: WS1: Feasibility Trial WS2: Observational Study WS3: Integrated Qualitative Study
Study Participants	RCT: Babies born between 23^{+0} and 30^{+6} weeks^{+days} of gestation inclusive with metabolic acidosis defined as blood pH less than 7.2 with pCO_2 that is low or normal for the clinical context (e.g. compensated respiratory acidosis) and a low bicarbonate level. WS1: Study participants will be as detailed for the RCT above but with an option to randomise at a higher blood pH between 7.20 and 7.25. WS2: Babies born between 23^{+0} and 30^{+6} weeks^{+days} of gestation inclusive. WS3: Two groups will be eligible for the qualitative study: 1) Healthcare professionals and other staff members that are on the site delegation log or BASE oversight groups, or who have a role in caring for the eligible patient population, and 2) Parents of babies that have been approached to consider participation in WS1.
Sample Size	RCT: Original planned sample size was 3764, projected final sample size ~110 WS1: 720 (Number of babies screened and consented in the RCT and WS1) and 110 (Number of babies randomised in the RCT and WS1) WS2: 750 WS3: ~ 50 interview participants (30 healthcare professionals/staff, 20 parents), although sample size will be driven by intentions to achieve saturation in relation to the study objectives.

Setting	NHS neonatal units in the UK that care for babies born very preterm (level 2 and 3 units).
Planned Study Period	The total planned duration of the BASE Studies is 56 months, from 01/01/2023 to 31/08/2027. RCT: 01/01/2023 – 31/08/2027 (56 months) WS1: 01/09/2025 – 31/08/2027 (24 months) WS2: 01/09/2025 – 31/08/2027 (24 months) WS3: 01/09/2025 – 30/06/2027 (22 months)
Planned Recruitment period	RCT: 20/02/2024 – 31/05/2026 (27 months) WS1: 01/06/2026 – 30/11/2026 (6 months) WS2: 01/06/2026 – 28/02/2027 (9 months) WS3: 01/06/2026 – 31/05/2027 (12 months)
Primary Objectives	BASE RCT: To evaluate the effect of sodium bicarbonate on survival to discharge from neonatal care without major morbidity in preterm babies with metabolic acidosis up to discharge from neonatal care or 40 weeks postmenstrual age (whichever is sooner), with major morbidity defined as any of the following: • Bronchopulmonary dysplasia (BPD) • Treatment for retinopathy of prematurity (ROP) • Major brain injury (grade 3 or 4 Intraventricular haemorrhage (IVH), periventricular leukomalacia (PVL) or post haemorrhagic ventricular dilatation requiring intervention) • Late-onset sepsis • Severe necrotising enterocolitis (NEC) confirmed at surgery • Major surgery WS1: To determine the proportion of screened and consented babies that are randomised To determine the proportion of randomised babies receiving care as per their allocated treatment arm WS2: To provide a period prevalence estimate of metabolic acidosis in very preterm babies from a range of neonatal units in the UK To investigate the association between exposure to sodium bicarbonate to prevent and/or treat metabolic acidosis and the outcome of survival to discharge from neonatal care without major morbidity for very preterm babies

	WS3: The objectives of the qualitative study are to: i) Investigate healthcare professionals' rationales underpinning their current practices around management of very preterm babies who are at risk of – or develop – metabolic acidosis, their perspectives on the current evidence-base in this area, and implications for a future definitive RCT; ii) Generate a comprehensive understanding of factors that support and hinder recruitment to the feasibility trial, drawing on health care professionals', study team members', and parent/carers' experiences of involvement in the (feasibility) trial (past and present); iii) Combine findings from the above to generate recommendations for the design and conduct of a future definitive RCT in this field, in collaboration with the BASE Project Management Group (PMG) and Parent Advisory Group (PAG).
Secondary Objectives	BASE RCT: To evaluate the impact of sodium bicarbonate on the following, up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner), unless otherwise stated: • Death • BPD • ROP • Major brain injury • Late-onset sepsis • Severe NEC (confirmed at surgery or resulting in death) • Major surgery • Pulmonary haemorrhage resulting in increase in ventilatory requirements or blood transfusion (described using summary statistics only) • Receipt of invasive respiratory support at 36 weeks postmenstrual age (described using summary statistics only) • Receipt of non-invasive respiratory support at 36 weeks postmenstrual age (described using summary statistics only) • Duration of intensive care • Total length of stay in neonatal care • Change in weight z-scores in survivors between birth and discharge from neonatal care or 36 weeks postmenstrual age (whichever is sooner) (described using summary statistics only) • Any receipt of mother's own breast milk To describe the patterns of sodium bicarbonate usage

	WS1: • To determine the rate of recruitment to a randomised controlled trial • To understand the reasons for non-adherence to the allocated treatment arm • To determine how many families are approached and how many give consent for their baby to take part. • To understand the reasons why the babies of parents who consent to the trial are not randomised to the trial • To understand the usage of intra-arterial sodium bicarbonate during the recruitment pathway • To determine how many babies are randomised at a pH between 7.20 and 7.25 • To determine the proportion of randomised families who change their consent status • To determine the level of completeness of clinical outcomes WS2: • To describe current practice of the use of sodium bicarbonate infusion in very preterm babies • To describe the demographic and clinical characteristics of very preterm babies who develop metabolic acidosis • To explore the association between exposure to metabolic acidosis and the outcome of survival to discharge from neonatal care without major morbidity • Provide period prevalence estimate of metabolic acidosis in very preterm babies who have and have not been exposed to intra-arterial sodium bicarbonate • To understand the current practice of the use of intra-arterial sodium bicarbonate in very preterm babies WS3: N/A
For the BASE RCT and WS1: Trial arms to be compared	Two trial arms are being compared; both represent standard clinical practice in neonatal units in the UK. The two trial arms that will be compared are: 1. Routine use of sodium bicarbonate infusion for episodes of metabolic acidosis (intervention) The dose and duration of infusion is at the discretion of the treating clinician. 2. No routine use of sodium bicarbonate infusion for episodes of metabolic acidosis (control)

	Babies will remain allocated to the same trial arm until they reach 40 weeks postmenstrual age or are discharged from neonatal care (whichever is sooner). Once randomised to an arm, all subsequent episodes of metabolic acidosis (unless in the context of cardiopulmonary resuscitation) will be as per the randomised allocation. It is expected that clinical teams will address reversible causes of metabolic acidosis as per usual clinical practice prior to consideration of sodium bicarbonate. Management and treatment of the underlying causes of metabolic acidosis in all babies will be at the discretion of the treating clinician.

5 ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
BASE	Bicarbonate for AcidosiS in very pretErm babies
BPD	Bronchopulmonary dysplasia
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
GCP	Good Clinical Practice
HRA	Health Research Authority
HTA	Health Technology Assessment
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IP	Intellectual Property
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
IVH	Intraventricular haemorrhage
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NEC	Necrotising enterocolitis
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Health and Care Research
NNRD	National Neonatal Research Database
NPEU	National Perinatal Epidemiology Unit
pCO_2	Partial Pressure of Carbon Dioxide
PI	Principal Investigator
PIL	Participant/Parent Information Leaflet
PMG	Project Management Group
PPI	Patient and public involvement
PVL	Periventricular leukomalacia
QRI	QuinteT Recruitment Intervention
QuinteT	Qualitative Research Integrated within Trials
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance
ROP	Retinopathy of prematurity
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction

SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
VEGF	Vascular endothelial growth factor
WS	Workstream

6 BACKGROUND AND RATIONALE

Sodium bicarbonate is widely, but not universally, used in the management of metabolic acidosis in very preterm babies despite very low grade of evidence underpinning its use (1). Both using and not using sodium bicarbonate for the correction of metabolic acidosis exist in standard clinical practice in the UK (2). Practice varies between clinicians in the threshold of pH below which sodium bicarbonate is used, the dosage and duration of infusion. Sodium bicarbonate is believed to correct metabolic acidosis and so improve cardiac function. It is also used to replace renal losses of bicarbonate in very preterm babies. However, the use of sodium bicarbonate can lead to worsening of intracellular acidosis with consequent adverse outcomes including fluctuations in cerebral blood flow, diminished tissue oxygenation and deterioration of cardiac function (3-5). It is plausible, therefore, that both approaches of not treating metabolic acidosis using sodium bicarbonate or using sodium bicarbonate to treat metabolic acidosis could lead to an increase in short-term morbidities that lead to adverse long-term neurodevelopmental impairment (6-8).

Most medicines in routine neonatal care are used off-label. Care is delivered to babies by neonatal teams and practice can vary within the teams depending on clinician preference. For these reasons, neonates are regularly exposed to different treatments during their stay on a neonatal unit, and consequently, very few treatments can be determined as standard care in neonates. This applies to the use of sodium bicarbonate for metabolic acidosis in the preterm population.

Therefore, there is no accepted ‘standard of care’ for the administration of sodium bicarbonate for the prevention and correction of metabolic acidosis, as clinical practice varies among treating clinicians and between and within neonatal teams, reflected in the varying guidelines on administration (9, 10). This demonstrates how in real-world practice, babies receive their treatment based on clinician preference. This is evidenced in our UK survey of 125 neonatal consultants from 57 neonatal units conducted to inform the design of this trial. Of the respondents, 80% reported using sodium bicarbonate but the indications and thresholds varied. In the survey, the most common threshold of pH below which clinicians would use sodium bicarbonate to correct acidosis was 7.2. The survey indicated that only 12% of respondents used sodium bicarbonate to *prevent* metabolic acidosis and 56% of all respondents indicated that they would not randomise a baby to a trial of sodium bicarbonate to prevent metabolic acidosis. Similar variation in care was seen in a national survey carried out in Italy showing a wide range of practice, including in dosage, duration of administration, and thresholds of intervention in the 45% of units that used sodium bicarbonate (11). The BASE RCT was therefore designed to evaluate the correction, not the prevention, of metabolic acidosis with sodium bicarbonate.

In response to a NIHR commissioned call (21/536 Sodium Bicarbonate in Neonatal Care), the BASE RCT was designed to investigate the use of sodium bicarbonate for metabolic acidosis in very preterm babies. The trial opened to recruitment in February 2024 and recruitment was substantially below target from when the first site opened. The trial team worked with site staff and collected enhanced screening log data to better understand the patient population and identify the barriers to recruitment.

The key challenges identified were: i) lower than expected prevalence of metabolic acidosis (as there are no published data on this and the prevalence rate used to calculate the original sample recruitment projection was based on the experience of the co-investigator group), ii) lack of equipoise among clinicians with regards to giving or not giving sodium bicarbonate to treat metabolic acidosis, and iii) the use of sodium bicarbonate in arterial line infusions for prevention of metabolic acidosis (there has been therapeutic creep

of this practice since our original survey conducted prior to the initial grant application which has meant babies do not reach the trial blood pH threshold for randomisation).

Neonatal units and clinicians vary in their practice of using sodium bicarbonate in arterial line infusions. Arterial lines are commonly placed in extremely and very preterm babies for a varying period of time after birth to monitor blood pressure and to allow for non-invasive blood sampling. It is usual to infuse these lines with heparin and sodium chloride to ensure patency. In the UK there is an increasing trend towards substituting normal saline with sodium bicarbonate in arterial lines with the intention of preventing the development of metabolic acidosis or treating mild metabolic acidosis. This practice is based on a perception that intra-arterial sodium bicarbonate is safer than intravenous sodium bicarbonate for the treatment of metabolic acidosis, despite a lack of supporting evidence. The use of sodium bicarbonate rather than sodium chloride in arterial line infusions during the early postnatal period may also have contributed to a reduced observed prevalence of metabolic acidosis.

Another factor which affected the trial's success was that it did not meet the target for participating sites. Many sites declined to participate due to lack of equipoise, with some units believing that sodium bicarbonate therapy is safe and other believing it is harmful. Conducting a large observational study across a range of neonatal units that use and do not use sodium bicarbonate would allow for studying the association between use of sodium bicarbonate and exposure to metabolic acidosis and important clinical outcomes. There is also a need to understand health care professionals' views on the use of sodium bicarbonate or not and parental perspectives on why they chose to participate or decline participation in the BASE RCT. There is a need to describe the prevalence rate of metabolic acidosis and clinician use of sodium bicarbonate both to prevent and treat metabolic acidosis.

The trial team worked with the NIHR on potential ways to amend the trial design to help understand the recruitment issues and successfully address the research question. The NIHR approved a trial re-design in the form of three workstreams (WS), and analysis and dissemination of the BASE RCT. The re-design has been submitted as an amendment to the BASE RCT protocol, and the project will transition to the following workstreams:

- Workstream 1 (WS1): Feasibility Trial
- Workstream 2 (WS2): Observational Study
- Workstream 3 (WS3): Integrated Qualitative Study

Information gathered from the BASE RCT will contribute to the assessment of feasibility for WS1, and clinical data collected for WS1 will be included in the analysis of the BASE RCT. This protocol sets out the detail of the original BASE RCT and the three workstreams.

7 BASE RANDOMISED CONTROLLED TRIAL (RCT)

This section describes the BASE RCT to support its completion and provide context for the other workstreams.

7.1 BACKGROUND AND RATIONALE FOR THE BASE RCT

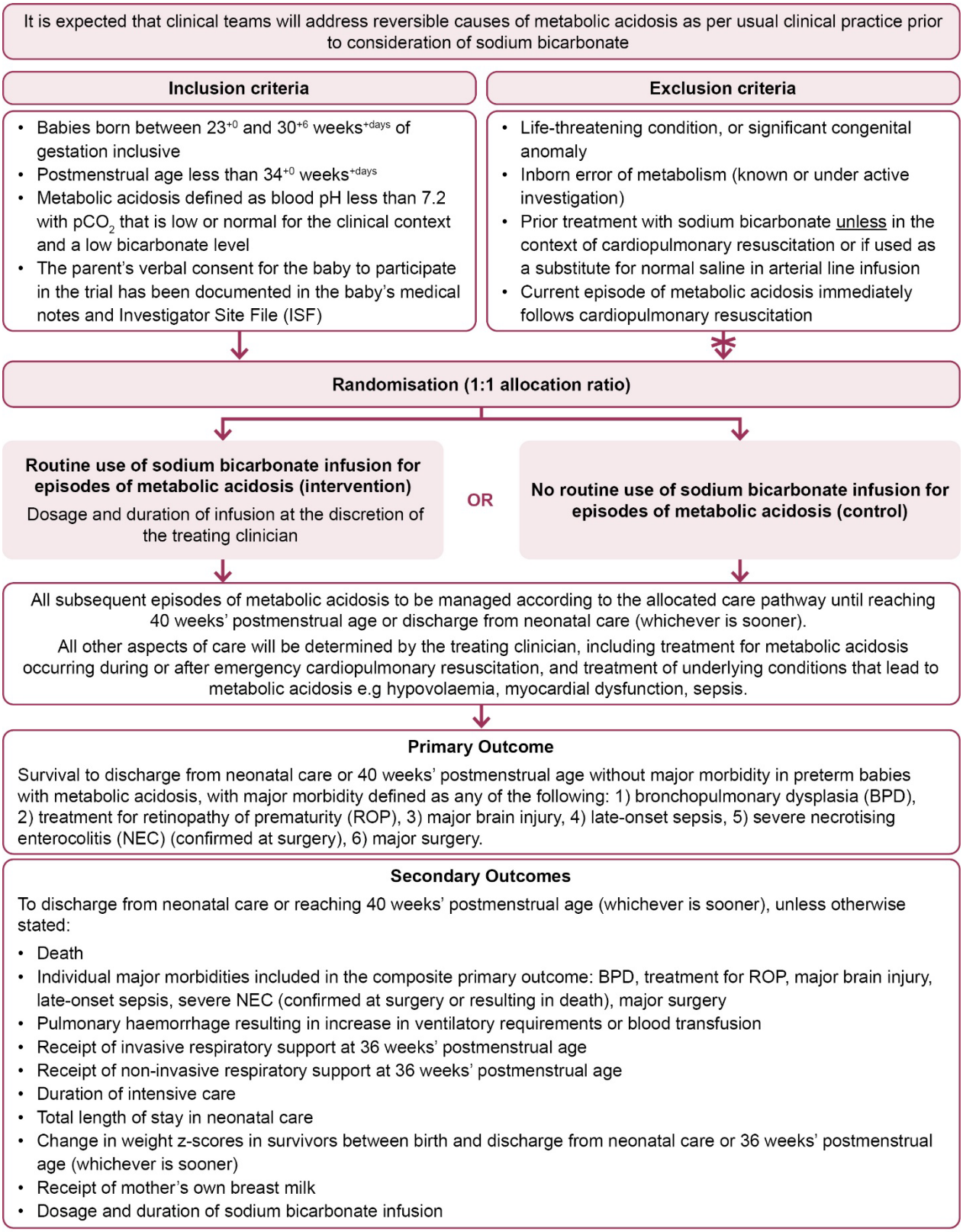
The 2005 Cochrane review of sodium bicarbonate for preventing mortality and morbidity in preterm babies with metabolic acidosis found one small Randomised Controlled Trial (RCT) comparing the use of sodium bicarbonate versus no treatment and another comparing to a fluid bolus. The authors concluded that there was insufficient evidence and recommended a large RCT to address the issue (12).

In response to this uncertainty in neonatal care, the Health Technology Assessment programme of the UK National Institute for Health and Care Research commissioned a clinical trial to evaluate the use of intravenous sodium bicarbonate in metabolic acidosis. The BASE RCT was designed to meet the criteria set out in the commissioning brief. Of note, the brief only covered *intravenous* sodium bicarbonate and not the use of oral sodium bicarbonate. The BASE RCT would be the first adequately powered trial to study the clinical effectiveness, both in the short and long-term, of the use of sodium bicarbonate for metabolic acidosis in very preterm babies. If the use of sodium bicarbonate, an inexpensive drug, improves outcomes, there could be significant benefits in terms of survival and neurodevelopment of a vulnerable group of babies who are at high risk of mortality and long-term neurodevelopmental sequelae. If instead sodium bicarbonate does not improve outcomes or even makes them worse, then omitting sodium bicarbonate to correct metabolic acidosis in very preterm babies would prevent harm that currently many of the 8,000 very preterm babies born each year in the UK (and many more around the world) are exposed to. The BASE RCT is designed as a comparative effectiveness trial rather than an efficacy trial, exploring the natural variation in clinician treatment. As such there is no stipulated dose of sodium bicarbonate nor duration of infusion. The trial seeks to reflect the use of sodium bicarbonate in a real-world setting to make the results generalisable to the entire population of preterm babies (13). Apart from improving healthcare and outcome of very preterm babies this is also assumed to be cost-effective, through avoiding the costs of sodium bicarbonate and the costs associated with increased long-term morbidity.

7.2 RESEARCH QUESTION FOR THE BASE RCT

In very preterm babies born between 23^{+0} and 30^{+6} weeks of gestation inclusive with metabolic acidosis (Population), does a pathway of routine use of intravenous sodium bicarbonate (Intervention) compared to no routine use of intravenous sodium bicarbonate (Comparator) increase or decrease the risk of survival to discharge from neonatal care without major morbidity (Outcome)?

7.3 TRIAL FLOWCHART FOR THE BASE RCT



7.4 OBJECTIVES AND OUTCOME MEASURES OF THE BASE RCT

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
Primary Objective To evaluate the effect of sodium bicarbonate on survival to discharge from neonatal care without major morbidity in preterm babies with metabolic acidosis.	Survival without major morbidity, with major morbidity defined as any of the following: • Bronchopulmonary dysplasia (BPD) (defined as any respiratory or ventilatory support or supplemental oxygen at 36 weeks postmenstrual age); • Treatment for retinopathy of prematurity (ROP) (defined as cryotherapy, laser therapy or injection of anti-VEGF therapy for retinopathy of prematurity in either or both eyes); • Major brain injury (grade 3 / 4 IVH, periventricular leukomalacia (PVL) or post haemorrhagic ventricular dilatation requiring intervention); • Late-onset sepsis (defined as one or more episodes of a positive blood or cerebrospinal fluid culture with either a pure or mixed growth of a known pathogenic organism after the first 72 hours following birth); • Severe necrotising enterocolitis (defined as necrotising enterocolitis confirmed at surgery); • Major surgery (defined as any major surgical procedure recorded during neonatal admission).	Up to discharge from neonatal care or 40 weeks postmenstrual age (whichever is sooner)
Secondary Objectives To evaluate the impact of sodium bicarbonate on death and individual major morbidities during neonatal care, duration of neonatal unit stay and acceptability	• Death	Up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
	• Bronchopulmonary dysplasia (BPD)	At 36 weeks postmenstrual age
	• Treatment for retinopathy of prematurity	Up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)

	• Major brain injury (grade 3 or 4 IVH, periventricular leukomalacia (PVL) or post haemorrhagic ventricular dilatation requiring intervention)	Up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
	• Late-onset sepsis	Up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
	• Severe necrotising enterocolitis (necrotising enterocolitis confirmed at surgery or resulting in death)	Up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
	• Major surgery	Up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
	• Pulmonary haemorrhage resulting in increase in ventilatory requirements or blood transfusion (described using summary statistics only)	Up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
	• Receipt of invasive respiratory support (described using summary statistics only)	At 36 weeks postmenstrual age
	• Receipt of non-invasive respiratory support (described using summary statistics only)	At 36 weeks postmenstrual age
	• Duration of intensive care (level 1 care as defined by BAPM) as a proportion of total length of stay in the neonatal unit	Up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
	• Total length of stay in neonatal care	Up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)
	• Change in weight z-scores in survivors (described using summary statistics only)	Between birth and discharge from neonatal care or 36 weeks postmenstrual age (whichever is sooner)
	• Any receipt of mother's own breast milk	Up to discharge from neonatal care or reaching

		40 weeks postmenstrual age (whichever is sooner)
To describe the patterns of sodium bicarbonate usage	• Dosage and duration of sodium bicarbonate infusion (described using summary statistics only)	Up to discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner)

7.5 TRIAL DESIGN OF THE BASE RCT

A multicentre, pragmatic, open-label, two-arm, parallel-group, randomised controlled trial, with an internal pilot. The research will take place in NHS neonatal units in the UK.

It is a comparative effectiveness trial.

The trial flowchart and schedule of events are summarised in sections 7.3 and 7.8 respectively.

7.5.1 Internal Pilot and Progression Criteria

A 12-month internal pilot was due to be conducted to test and refine the components and processes of the trial. The key progression criteria for the internal pilot were site and participant recruitment, and adherence to the intervention, with the decision to progress to full trial based on a traffic light system presented in Table 1. Safety and completeness of data collection was also due to be assessed.

Substantially lower than expected recruitment initiated discussions to redesign the trial 6 months into the recruitment period of the trial. A formal evaluation of the pilot progression criteria at 12 months was therefore not required.

Table 1: Internal pilot trial progression criteria

	Green	**Amber**	**Red**
Number of sites			
Number of sites open for recruitment	≥45	25–44	<25
% of sites open	100%	56–99%	<56%
Recruitment			
Total participants recruited	≥665	372–664	<372
Target recruitment per site per month	≥2.9	1–2.8	<1
% of target recruited	100%	56–99%	<56%
Adherence to allocated intervention			
Combined crossover from control to intervention and intervention to control (% of babies)	≤12%	13%–20%	>20%
Completion of primary outcome	100%	70–99%	<70%

Green: continue into the main trial;
Amber: open new sites, identify and address site specific issues through site visits, training and newsletters, consider review in 6 months;
Red: urgent detailed review of options with the SSC and HTA.

7.6 PARTICIPANT IDENTIFICATION FOR THE BASE RCT

7.6.1 Trial Participants

Babies born between 23^{+0} and 30^{+6} weeks^{+days} of gestation inclusive, satisfying the following criteria:

7.6.2 Inclusion Criteria

- Babies born between 23^{+0} and 30^{+6} weeks^{+days} of gestation inclusive
- Postmenstrual age less than 34^{+0} weeks^{+days}
- Metabolic acidosis defined as blood pH less than 7.2 with pCO_2 that is low or normal for the clinical context and a low bicarbonate level
- The parent's verbal consent for the baby to participate in the trial has been documented in the baby's medical notes and Investigator Site File (ISF)

7.6.3 Exclusion Criteria

- Life-threatening condition, or significant congenital anomaly
- Inborn error of metabolism (known or under active investigation)
- Prior treatment with sodium bicarbonate unless in the context of cardiopulmonary resuscitation or if used as a substitute for normal saline in arterial line infusion
- Current episode of metabolic acidosis immediately follows cardiopulmonary resuscitation

7.7 TRIAL INTERVENTIONS FOR THE BASE RCT

7.7.1 Trial arms to be Compared

Two trial arms are being compared; both exist in routine clinical practice within different neonatal units across the UK. It is expected that clinical teams will address reversible causes of metabolic acidosis as per usual clinical practice prior to consideration of sodium bicarbonate. Management and treatment of the underlying causes of metabolic acidosis in all babies will be at the discretion of the treating clinician. Babies will remain allocated to the same trial arm until they reach 40 weeks postmenstrual age or are discharged from neonatal care (whichever is sooner).

During their neonatal unit stay babies can have more than one episode of metabolic acidosis, defined as blood pH less than 7.2 with pCO_2 that is low or normal for the clinical context and a low bicarbonate level. Once randomised to an arm, all subsequent episodes of metabolic acidosis (unless in the context of cardiopulmonary resuscitation) will be as per the randomised allocation.

The two trial arms that will be compared are:

1. Routine use of sodium bicarbonate infusion for episodes of metabolic acidosis (intervention)

2. No routine use of sodium bicarbonate infusion for episodes of metabolic acidosis (control). Sodium bicarbonate infusions should not be used for episodes of metabolic acidosis except in the clinical scenarios described in section 7.7.4.1

7.7.2 Investigational Medicinal Product(s) (IMP)

In current neonatal practice, administration of sodium bicarbonate is embedded within the delivery of standard intensive care. As an open-label trial comparing standard care pathways, the trial will use Neonatal Intensive Care Unit (NICU) stock of sodium bicarbonate for intravenous infusion. Storage, accountability and destruction of sodium bicarbonate will be as for standard clinical care according to NHS hospital policy.

7.7.2.1 Dosage

Dosage and duration of infusion will be decided by the treating clinician. For units who do not already have existing guidance on administering intravenous sodium bicarbonate, guidance on dosage and administration is provided in Appendix 1. This will also be presented to sites during Site Initiation Visits (SIVs) and training.

Treating clinicians should refer to the current summary of product characteristics (SmPC) for sodium bicarbonate for the consideration of contraindications and warnings/precautions for use.

Most babies who develop metabolic acidosis are likely to have a cannula as part of routine care. However, occasionally when a baby does not have a cannula, the placement of a cannula in order to administer sodium bicarbonate would be required.

7.7.2.2 Post-trial treatment

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

7.7.3 Concomitant Care

All other aspects of care will be determined by the treating clinician, including treatment for metabolic acidosis occurring during or after emergency cardiopulmonary resuscitation, and treatment of underlying conditions that lead to metabolic acidosis e.g. hypovolaemia, myocardial dysfunction, sepsis.

Treating clinicians should refer to the current SmPC for sodium bicarbonate for interactions and incompatibilities when determining all other aspects of care.

7.7.4 Adherence to the Allocated Trial Arms

Adherence to the allocated trial arm will be recorded in the Daily Dosing Log by recording the date and time of episodes of metabolic acidosis that meet the definition in section 7.6.2 and the use of sodium bicarbonate (with indication) from randomisation until discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner). The use of oral sodium bicarbonate, and sodium bicarbonate infusion for clinical reasons set out below (section 7.7.4.1), will not be considered non-adherent.

Babies should, where possible, be maintained according to their allocated trial arm alone. In either group, if alternatives for treating metabolic acidosis are required for another reason, they can be given if the attending clinician deems this necessary. Use of alternative treatments will be collected on CRFs and monitored by the CI, Data Monitoring Committee (DMC) and Study Steering Committee (SSC).

7.7.4.1 Allowed uses of intravenous sodium bicarbonate

The use of intravenous sodium bicarbonate is allowed in any of the following circumstances for either arm. This is not an exhaustive list. Uses outside of the trial indication for circumstances other than these will be reviewed by DMC as indicated in the DMC charter.

- Use as a substitute for normal saline in arterial line infusion
- Use during cardiopulmonary resuscitation
- Severe acidaemia and continued clinical deterioration despite escalating intensive care management and supportive treatment with volume cardiovascular support and antibiotic therapy with a persistently low pH below 7.1
- Nephrologist diagnosis of renal tubular acidosis
- Confirmed diagnosis of an underlying inborn error of metabolism made after randomisation
- Chronic renal failure

7.7.4.2 Definition of non-adherence to trial arm

The study team will monitor patterns of any non-adherent episodes of metabolic acidosis (that meet the definition in section 7.6.2) by site. A non-adherent episode is where the baby does not receive management as per allocated trial arm. For babies on the no routine use arm, the use of oral sodium bicarbonate, and sodium bicarbonate infusion for clinical reasons set out in section 7.7.4.1 will not be considered non-adherent.

For the purposes of per protocol analysis and defining crossover from control to intervention and intervention to control for the internal pilot study progression criteria (see section 7.5.1) a baby will be described as being non-adherent to their allocated trial arm if it meets the following criteria:

Routine use of sodium bicarbonate infusion for episodes of metabolic acidosis: As a proportion of the total number of episodes of metabolic acidosis (that meet the definition in section 7.6.2), if 50% or more of the episodes occur where infusion of sodium bicarbonate **is not** administered between randomisation and discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner).

No routine use of sodium bicarbonate infusion for episodes of metabolic acidosis: As a proportion of the total number of episodes of metabolic acidosis (that meet the definition in section 7.6.2), if 30% or more episodes occur where infusion of sodium bicarbonate **is** administered between randomisation and discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner). The use of oral sodium bicarbonate, and sodium bicarbonate infusion for clinical reasons set out in section 7.7.4.1, will not be considered non-adherent.

Whilst both trial arms i.e. giving intravenous sodium bicarbonate for metabolic acidosis and not giving sodium bicarbonate may be beneficial, harmful or have no impact on outcomes, there is more concern over the use of sodium bicarbonate and it is plausible that exposure to sodium bicarbonate may be harmful. For this reason and to ensure separation of trial arms, the threshold for non-adherence for the purposes of analysis and the progression criterion is set at 30% for the ‘no routine use of sodium bicarbonate infusion for metabolic acidosis’ and 50% for the ‘routine use of sodium bicarbonate infusion for metabolic acidosis’.

7.8 TRIAL PROCEDURES FOR THE BASE RCT

Table 2: Schedule of procedures

PROCEDURES	BEFORE TRIAL ENTRY	AT TRIAL ENTRY	AFTER TRIAL ENTRY		
	Screening	Randomisation	Baseline	Intervention and Data collection	
				Post-randomisation	Discharge from neonatal unit or 40 weeks postmenstrual age (whichever is sooner)
Verbal consent	X				
Eligibility assessment	X				
Randomisation		X			
Routine use of sodium bicarbonate infusion for episodes of metabolic acidosis / no routine use of sodium bicarbonate infusion for episodes of metabolic acidosis (unless in the context of cardiopulmonary resuscitation)				X	X
Clinical data collection (from routine data extracted by NNRD)			X	X	X
Clinical data collection (CRF completion/clinical data extraction)			X	X	X
Adverse events assessments (SAEs, SUSARs etc)				X	X

7.8.1 Recruitment

Babies will be recruited from NHS neonatal units in the UK that care for babies born very preterm (level 2 and 3 units). Planned number of recruiting units: 45.

7.8.2 Inter-hospital transfers

Participating neonatal units will be either:

1. A recruiting site where babies may be recruited, randomised, commence, continue and complete participation in the trial;
2. A continuing care site where the allocated trial arm will continue to be followed and data collected if a participating baby is transferred in from a recruiting site before cessation of their allocated trial arm.

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

7.8.3 Screening and Eligibility Assessment

Babies potentially meeting the eligibility criteria will be screened for eligibility by the clinical care team after admission to the neonatal unit.

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

7.8.3.1 Recruitment to other studies

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

7.8.4 Consent

The BASE RCT is a comparative effectiveness trial of an intervention that is already in routine clinical practice, the trial will use a verbal consent approach.

Parents of potential participants will be provided with trial information by members of the clinical care team in the antenatal period or during neonatal admission prior to randomisation. Information will be widely available throughout the neonatal units via posters and banners. Paper and electronic patient information sheets will be provided and trial information videos and animation will be available online. Trained members of staff will have a conversation (may also take place over multiple conversations if appropriate to parents' circumstances and wishes) with parents to discuss the study and answer any questions. It will be made clear to parents that they can withdraw their baby from the study at any time, and they will be given as much time as they wish to consider the study and discuss it with others (e.g. another healthcare professional, other family members, etc) if they wish. The parent will then be asked if they are happy for their baby to participate. Parents will confirm if they are willing for their baby to participate in the study during a verbal conversation with site staff. It will be documented in the baby's medical notes and ISF that information about the study has been provided to the parents and verbal consent has been obtained. This documentation will consist of a signed form, completed by the site staff, to provide evidence that they have taken informed consent. This will be checked by whoever is randomising the baby, prior to randomisation. Parents will also be offered a copy of this form for their own records.

They will also be able to withdraw from the trial at any point after their baby is randomised (further details around withdrawals and discontinuation of the allocated intervention are provided in sections 7.8.9.1 and 7.8.9.2). Acceptability by UK research ethics committees and parents, of consent approaches that do not include a written consent form has been demonstrated, as well as the feasibility of this approach in recent

and ongoing neonatal trials (14-16). Furthermore, there is overwhelming support from our Parent Advisory Group (PAG) led by PPI co-applicants.

Babies meeting the inclusion and exclusion criteria will be eligible for randomisation upon completion and filing of the verbal consent form.

7.8.5 Randomisation

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

Randomisation will occur as soon as a baby becomes eligible, using a 1:1 allocation ratio. Randomisation will use a probabilistic minimisation algorithm. To ensure balance between the randomised groups, minimisation criteria will comprise: recruiting hospital, gestational age week, birth weight centile and multiple births. Twins (or higher order multiple births) will be randomised independently.

Babies will be randomised using an online secure central randomisation service to ensure allocation concealment.

7.8.6 Blinding

BASE is an open-label (unblinded) trial as a placebo would not achieve blinding of the treating clinician since treatment of metabolic acidosis with sodium bicarbonate results in changes in blood pH parameters which are monitored routinely.

7.8.7 Study Data Collection

7.8.7.1 Clinical data collection

Trial data will be collected using electronic or paper CRFs and either entered directly into the secure Clinical Database Management System (OpenClinica) or automatically transferred into it from the bespoke randomisation database. All data will be processed in line with the NPEU CTU Data Management SOPs.

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

Routinely recorded clinical data held in the National Neonatal Research Database (NNRD) and in the trial-specific Case Record Form (CRF) will be used for outcomes. Further details will be fully described in the Data Management Plan and Data Flow Document.

7.8.8 Sample Handling

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

7.8.9 Early Discontinuation/Withdrawal of Participants

7.8.9.1 Withdrawal

Parents/carers can request to withdraw their baby from the trial at any point. Withdrawal from the trial will not affect their baby's ongoing clinical care. Withdrawals will be recorded on an eCRF and the reason detailed, if it has been provided.

Parents/carers have the right to withdraw their baby from some or all of the study data collection (eCRF, baby's medical record). Where parents decline continued data collection (via any method), data collected by that method up to the point of withdrawal will be used in the trial.

If parents/carers agree to ongoing data collection this does not constitute a withdrawal, but a discontinuation of the allocated trial arm (as detailed in section 7.8.9.2).

7.8.9.2 Discontinuation of the allocated trial arm

Parents/carers will have the right to request to discontinue from the allocated trial arm. Following a discontinuation from the allocated trial arm, the care of the baby will revert back to the clinician's preferred method of care (which may be the same as the allocated trial arm they were receiving or not). The decision to discontinue will be recorded on an eCRF and data will continue to be collected unless the parent requests to withdraw their baby from some or all of this (which would then constitute a withdrawal). Discontinuation from the allocated trial arm will not affect their baby's ongoing clinical care.

In addition, if a baby was found to be ineligible for the trial after randomisation (e.g. diagnosed with an inborn error of metabolism), the treating clinician may permanently discontinue the allocated trial arm at any time. The decision to discontinue permanently will be recorded on an eCRF and data will continue to be collected.

7.9 SAFETY REPORTING FOR THE BASE RCT

7.9.1 Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • *consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. * Note, this point does not affect the population under study.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the approved investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

7.9.2 Assessment of Causality

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

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

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

7.9.3 Procedures for Reporting Adverse Events

The safety reporting window for this trial will be from randomisation until discharge from neonatal care or reaching 40 weeks postmenstrual age (whichever is sooner). Events occurring outside of the safety reporting window will only be collected if relevant to outcomes. All trials run by the NPEU CTU follow the unit's safety reporting Standard Operating Procedure (SOP). Sites will be appropriately trained on the safety reporting requirements of the trial.

In this population we anticipate day-to-day fluctuations of pre-existing conditions, new conditions, and deaths. The rate of mortality for the population under study is 10% to discharge from neonatal care. As a result, many adverse events are foreseeable due to the nature of the participant population and their routine care/treatment. Consequently, we are not reporting adverse events unless they are deemed as serious and causally related to the IMP (as assessed by the local investigator). See 7.9.4.

7.9.4 Reporting Procedures for Serious Adverse Events

Only SAEs **deemed causally related to the IMP** (e.g. SARs as assessed by the local investigator) will be reported expeditiously as an SAE. Due to the established use of sodium bicarbonate for this indication within the preterm population, relevant foreseeable Serious Adverse Events will be collected within CRFs for assessment of impact and effectiveness, but will not be expeditiously reported as Serious Adverse Events. In addition to expedited reporting of SARs, safety data for both trial arms will be collected for outcomes and will be reviewed by the DMC according to the charter.

The treatment or no treatment with sodium bicarbonate represents standard clinical practice in neonatal units in the UK. Safety events (as specified in section 7.4) are being collected and reviewed by the DMC as part of the outcomes of the trial. Therefore, only those SAEs that are deemed by the local investigator to be causally related to the IMP will be reported. These will be reported using the SAE Reporting Form to the Sponsor or delegate (NPEU CTU) immediately or within 24 hours of the site study team becoming aware of the event being defined as serious and related (as described in section 7.9.4.1). All events meeting the criteria of an SAE but deemed not to be causally related to the IMP should not be reported as an SAE but should be recorded in the baby's medical notes, as per usual care practice.

7.9.4.1 Procedure for immediate reporting of SAEs

All SAEs deemed causally related to the IMP must be reported on the SAE Reporting Form to the NPEU CTU trial team as soon as possible and within 24 hours of the site becoming aware of the event being defined as serious and related.

Sites may use one of the following SAE reporting methods:

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

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

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

Follow-up SAE information should be reported as necessary by the site staff and sent back to the NPEU CTU electronically or by email.

7.9.5 Expectedness

For SAEs that require reporting, expectedness of SARs will be determined according to the list of undesirable effects in section 4.8 of the most up-to-date, MHRA approved for use in this study SmPC for sodium bicarbonate injection. The RSI used (SmPC) will be the current Sponsor and MHRA approved version at the time of the event occurrence. For assessment of expectedness in the Development Safety Update Report, see section 7.9.7 below.

7.9.6 SUSAR Reporting

All SUSARs will be reported by the Sponsor or NPEU CTU delegate to the MHRA and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the NPEU CTU is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

NPEU CTU will ensure the Sponsor is sent copies of all reports at the time of submission to the MHRA.

7.9.7 Development Safety Update Reports

A Development Safety Update Report (DSUR), or necessary regulatory annual report, will be submitted once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

7.10 STATISTICS FOR THE BASE RCT

7.10.1 Sample Size Determination

Original sample size calculation

Since the use of sodium bicarbonate infusion for episodes of metabolic acidosis could result in an increase or decrease in the risk of the primary outcome, the sample size calculated provides 90% power, assuming a two-sided 5% level of significance, to detect a treatment effect in either direction. To detect an absolute risk difference of 6% in the primary outcome rate (from 53% to 47%, or 53% to 59%) a total of 2,916 babies is required. Inflating by 1.29 to allow for 12% combined crossover (i.e. non-adherence as defined in section 7.7.4.2) from control to intervention and from intervention to control would require 3,764 babies in total (1,882 per group) (17). We anticipate loss to follow-up to be negligible as data will be collected using routine data sources. The event rate is based on NNRD data of 65,000 babies born less than 31 weeks of gestation (incidence rate 53%, 95% CI 52.4% to 53.2%) (18). Multiple births will be randomised independently; therefore the impact of correlation of outcomes will have a negligible effect on the sample size (19).

A 6% difference in the primary outcome is considered the minimal clinically important difference to result in a change in clinical practice and is conventionally used for these outcomes in neonatal trials. Views from the study parent focus groups indicate that any difference, however small, would be valuable.

The sample size has been inflated by 29% to allow for 12% crossover (i.e. non-adherence). If the original sample size before inflation is retained (2,916) the impact on the required sample size after inflation due to combined crossover is given in Table 3.

Table 3: Inflation of sample size due to crossover (i.e. non-adherence as defined in section 7.7.4.2)

Combined crossover rate	Inflation factor[a]	Total sample size
5%	1.108	3230
10%	1.235	3600
12%	1.291	3764
15%	1.384	4036
20%	1.563	4556
25%	1.778	5184

[a] Adjustment for crossovers based on formula: $n\ adj = n \times 10{,}000 / (100 - c)^2$
where c is the combined percent crossover in the control and intervention group. (17)

Projected sample size

All babies randomised into the BASE RCT, along with any babies recruited to WS1, will contribute to the analysis of the BASE RCT outcomes. Based on recruitment as at 7 October 2025 and projected recruitment rates, it is expected that a total of ~110 babies will contribute data to the analysis of the BASE RCT outcomes.

7.10.2 Statistical Analysis Plan (SAP)

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

7.10.3 Description of Statistical Methods

7.10.3.1 Descriptive statistics

The flow of participants through each stage of the trial will be summarised by randomised group using a CONSORT diagram (20). The number and percentage of babies lost to follow-up will be reported with the reasons recorded. Demographic factors and clinical characteristics at baseline will be summarised with counts (percentages) for categorical variables, mean (standard deviation [SD]) for normally distributed continuous variables, or median (interquartile [IQR] or entire range) for other continuous variables. There will be no tests of statistical significance performed for differences between randomised groups on any baseline variable.

7.10.3.2 Comparative statistics

The achieved sample size is substantially lower than was originally planned, and therefore the BASE RCT is not powered to detect the originally specified treatment effect. All analyses will be considered exploratory and results will be interpreted cautiously.

The primary analysis will be based on a modified intention-to-treat approach; participants with outcome data will be analysed in the groups to which they are assigned, regardless of deviation from the protocol or procedure received. The no sodium bicarbonate group will be used as the reference group in all analyses. For binary outcomes, risk ratios and confidence intervals will be calculated using a mixed binomial or Poisson model with a log link. Risk differences will also be calculated using a mixed binomial model with an identity link. The primary outcome and other continuous outcomes will be analysed using mixed linear regression with mean differences and confidence intervals presented, where model assumptions are satisfied. Skewed continuous outcomes will be analysed using quantile regression models, with median differences and confidence intervals presented. Site will be treated as a random effect in the model, and all other factors as fixed effects. Correlation between siblings from multiple births will be accounted for by nesting the ‘multiple’ cluster within site, where technically possible. Analyses will also be adjusted for the randomisation minimisation factors where possible; recruiting hospital, gestational age week, birth weight centile and multiple birth. Both crude and adjusted effect estimates will be presented, but the primary inference will be based on the adjusted estimates.

7.10.3.3 Secondary analysis

A per-protocol analysis will be performed on the primary outcome and its components, excluding babies who were non-adherent according to the definition set out in section 7.7.4.2. A pragmatic definition of non-adherence has been chosen to allow for the inclusion of babies who received sodium bicarbonate in the no routine use of sodium bicarbonate arm for the allowed clinical reasons described in section 7.7.4.1.

7.10.3.4 Subgroup analysis

The primary outcome will be presented using descriptive statistics (counts and percentages) by gestational age group, number of episodes of metabolic acidosis at trial entry and type of metabolic acidosis episode at trial entry (lactic acidosis or hyperchloraemic acidosis).

7.10.3.5 Level of statistical significance

95% confidence intervals will be used for all pre-specified outcome comparisons including subgroup analysis.

7.10.3.6 Interim data monitoring

Interim analyses of accumulating data will be reviewed by an independent Data Monitoring Committee (DMC) in accordance with a DMC Charter that will be agreed at the start of the trial.

7.10.4 Analysis Populations

The primary analysis will be based on a modified intention-to-treat approach; participants with outcome data will be analysed in the groups to which they are assigned, regardless of deviation from the protocol or procedure received. The analysis population will include all babies randomised to the BASE RCT and all babies randomised in WS1.

8 WORKSTREAM 1: FEASIBILITY TRIAL

8.1 BACKGROUND AND RATIONALE FOR WS1

The original recruitment targets and planned site openings for the BASE RCT were not achieved. To understand the challenges, the study team investigated contributing factors. Site staff provided enhanced screening log data detailing how many parents were approached, how many consented, reasons for non-randomisation and whether any babies experienced an episode of metabolic acidosis during their hospital stay. Several key issues were identified, including lower than expected prevalence of metabolic acidosis, lack of clinician equipoise, use of intra-arterial sodium bicarbonate to prevent metabolic acidosis from occurring and babies receiving prior treatment with sodium bicarbonate, making them ineligible for randomisation.

This feasibility trial will formally evaluate the practicality of conducting a full RCT in this area, including generating estimates of recruitment and adherence rates, and testing revised eligibility criteria. Enhanced screening log data will continue to be collected to monitor approach and consent rates. This will also allow the conduct of an integrated qualitative study (WS3) to explore factors that support or hinder recruitment and retention based on examination of healthcare professionals' (HCPs'), BASE study staff members', and parents' perspectives and experiences of the feasibility trial, and analysis of audio-recordings of HCP/parent recruitment discussions (see Section 10 for detail).

8.2 AIM AND RESEARCH QUESTION FOR WS1

8.2.1 Aim

The aim of the feasibility trial is to assess the feasibility of conducting a randomised controlled trial in very preterm babies with metabolic acidosis.

8.2.2 Research Question

In a trial in very preterm babies born between 23^{+0} and 30^{+6} weeks^{+days} of gestation inclusive with metabolic acidosis (Population), comparing a pathway of the routine use of sodium bicarbonate for the treatment of metabolic acidosis (Intervention) versus no routine use of sodium bicarbonate (Comparator) on survival to discharge from neonatal care without major morbidity, what are the rates of recruitment and adherence (Outcomes)?

8.3 OBJECTIVES AND OUTCOME MEASURES FOR WS1

Objectives	Outcome Measures
Primary Objectives	
To determine the proportion of screened and consented babies that are randomised	Proportion of babies randomised out of babies that are screened and consented
To determine the proportion of randomised babies receiving care as per their allocated treatment arm	Proportion of randomised babies that are adherent (as defined in section 7.7.4.2) to their allocated treatment arm
Secondary Objectives	
To determine the rate of recruitment to a randomised controlled trial	Average number of babies recruited per site per month
To understand the reasons for non-adherence to the allocated treatment arm	Reasons for non-adherence
To determine how many families are approached and how many give consent for their baby to take part.	• Proportion of families approached to discuss the trial out of babies within the gestational age eligibility criteria • Reasons not approached • Proportion of families that give consent for their baby to take part out of those approached • Reasons why consent was not obtained
To understand the reasons why the babies of parents who consent to the trial are not randomised to the trial	• Proportion of families that give consent and their baby is not randomised • Reasons why consented babies were not randomised
To understand the usage of intra-arterial sodium bicarbonate during the recruitment pathway	• Proportion of babies within the gestational age eligibility criteria who receive intra-arterial sodium bicarbonate • Proportion of consented babies who receive intra-arterial sodium bicarbonate • Proportion of randomised babies who receive intra-arterial sodium bicarbonate

To determine how many babies are randomised at a pH between 7.20 and 7.25	• Proportion of randomised babies that were randomised at the optional eligibility criterion of a higher pH between 7.20 and 7.25*
To determine the proportion of randomised families who change their consent status	• Proportion of randomised babies who change consent for any element of their participation
To determine the level of completeness of clinical outcomes	• Proportion of randomised babies with missing clinical outcomes for each outcome listed in section 7.4

*Assessed in babies randomised following the introduction of the optional eligibility criterion

8.4 TRIAL DESIGN FOR WS1

Multicentre, pragmatic, open-label, two-arm, parallel-group, randomised controlled feasibility trial. The research will take place in eight NHS neonatal units in the UK. Relevant data from the BASE RCT will be included in the analysis.

8.5 PARTICIPANT IDENTIFICATION FOR WS1

Babies born between 23^{+0} and 30^{+6} weeks^{+days} of gestation inclusive satisfying the criteria stated in section 7.6. The only difference is there will be an option to randomise at a higher blood pH between 7.20 and 7.25.

8.6 TRIAL INTERVENTIONS FOR WS1

As detailed in section 7.7 above. Information relating to the optional blood pH threshold is detailed below.

For a baby to be randomised with a blood pH between 7.20 and 7.25, there must be an intention to treat at this threshold for the eligible episode.

Once randomised to an arm, all subsequent episodes of metabolic acidosis (unless in the context of cardiopulmonary resuscitation) should be managed according to the allocated trial arm. For babies allocated to routine use of sodium bicarbonate, sodium bicarbonate may be administered at the discretion of the treating clinician when the blood pH is between 7.20 and 7.25 and should be administered when the blood pH is less than 7.20.

For babies allocated to routine use of sodium bicarbonate, not giving sodium bicarbonate when blood pH is between 7.20 and 7.25 will not be classed as non-adherent.

8.7 TRIAL PROCEDURES FOR WS1

All trial procedures will be as detailed for the BASE RCT in section 7.8 above.

8.8 SAFETY REPORTING FOR WS1

All safety reporting will be as detailed in section 7.9 above.

8.9 STATISTICS FOR WS1

8.9.1 Sample Size Determination

Proportion of screened and consented babies that are randomised

Data from all babies on the enhanced screening log for the BASE RCT and all babies recruited to WS1 will be included in the analysis of this outcome.

To estimate the expected proportion of screened and consented babies that are randomised, the enhanced screening logs for the BASE RCT were used. As of 7 October 2025, data was available for 22 sites who had screened and consented 397 babies, and randomised 67 babies. The proportion of screened and consented babies that were randomised was therefore estimated to be 16.9% (67/397).

Data from the enhanced screening logs for the BASE RCT was used to inform the number of babies expected to be screened and consented for the WS1 analysis, and is projected to be 720 babies. With this sample size, the margin of precision (21) achievable for an expected proportion of screened and consented babies that are randomised of 16.9% would be ±2.74%.

Proportion of randomised babies receiving care as per their allocated treatment arm

Data from all babies randomised to the BASE RCT and all babies randomised to WS1 will be included in the analysis of this outcome.

From the data collected for the BASE RCT as at 7 October 2025, the proportion of randomised babies receiving care as per their allocated treatment arm was estimated to be 55%.

Data from the enhanced screening logs for the BASE RCT was used to inform the number of babies expected to be randomised for the WS1 analysis, and is projected to be 110 babies. With this sample size, the margin of precision (21) achievable for an expected adherence rate of 55% would be ±9.30%.

All calculations assume a 95% confidence interval.

8.9.2 Statistical Analysis Plan (SAP)

The statistical aspects of the feasibility trial are summarised here with details fully described in a statistical analysis plan that will be finalised before final data lock takes place.

8.9.3 Description of Statistical Methods

8.9.3.1 Descriptive statistics

The flow of participants through each stage of WS1 will be summarised by randomised group using a CONSORT diagram. The number and percentage of babies with no primary outcome data will be reported with reasons recorded. Demographic factors and clinical characteristics at baseline will be summarised with counts (percentages) for categorical variables, mean (standard deviation [SD]) for normally distributed continuous variables, or median (interquartile range [IQR]) or entire range) for skewed continuous variables. There will be no tests of statistical significance performed for differences between randomised groups on any baseline variable.

All primary and secondary outcomes will be presented combining the two randomised groups and summarised with proportions and associated 95% confidence intervals. In addition, outcomes relating to post-randomisation metrics (adherence rate, withdrawal rate, clinical outcome completeness) will be summarised by trial arm.

8.9.3.2 Comparative statistics

Outcomes relating to adherence and missing data will be presented by trial arm, based on an intention-to-treat approach; participants will be analysed in the groups to which they are assigned, regardless of deviation from the protocol or procedure received.

8.9.3.3 Interim data monitoring

There is no planned interim data monitoring.

8.9.4 Analysis Populations

The analysis population will include all babies screened for the BASE RCT and all babies screened as part of WS1.

9 WORKSTREAM 2: OBSERVATIONAL STUDY

9.1 BACKGROUND AND RATIONALE FOR WS2

When the BASE RCT was being developed, little was known about how metabolic acidosis was managed in very preterm babies in the UK, including its prevalence and the clinical thresholds for administering sodium bicarbonate. The limited existing evidence consists mainly of two retrospective observational studies. One study conducted in the United States investigated the short-term outcomes of bicarbonate therapy in 165 of 984 preterm babies who received sodium bicarbonate for metabolic acidosis in the first 7 days of life. After adjusting for potential confounders, sodium bicarbonate infusion was associated with an increased risk of death or intraventricular haemorrhage. The threshold at which sodium bicarbonate was given changed over the course of the study with more selective criteria being applied. No details on other adverse outcomes were collected (22).

A second retrospective observational cohort study in Switzerland of 138 extremely preterm babies found that metabolic acidosis (defined as pH <7.2 with base excess < -10 mmol/L or standard bicarbonate < 12 mmol/L in the first week) was associated with higher odds of mortality and/or bronchopulmonary dysplasia at 36 weeks postmenstrual age. The paper did not specifically refer to treatment with sodium bicarbonate being administered to the babies nor did it differentiate between hyperchloraemic and lactic metabolic acidosis (23).

Neither of these studies reported on the prevalence of metabolic acidosis.

Given the lack of existing evidence, this observational study will provide valuable information about the prevalence of metabolic acidosis in very preterm babies and the current approaches to its treatment.

9.2 AIM AND RESEARCH QUESTION FOR WS2

9.2.1 Aim

The aim of the observational study is to investigate the prevalence of metabolic acidosis in the target population and the association of the use of sodium bicarbonate with survival to discharge without major morbidities in the target population.

9.2.2 Research Questions

- In very preterm babies born between 23^{+0} and 30^{+6} weeks^{+days} of gestation inclusive (Population), what is the prevalence of metabolic acidosis (Disease)?
- In very preterm babies born between 23^{+0} and 30^{+6} weeks^{+days} of gestation inclusive (Population), is the use of sodium bicarbonate (Exposure) to prevent and/or treat metabolic acidosis compared with no sodium bicarbonate (Comparator) associated with increased or decreased survival to discharge from neonatal care without major morbidity (Outcome)?

9.3 OBJECTIVES AND OUTCOME MEASURES FOR WS2

9.3.1 Primary Objectives

- To provide a period prevalence estimate of metabolic acidosis in very preterm babies from a range of neonatal units in the UK
- To investigate the association between exposure to sodium bicarbonate to prevent and/or treat metabolic acidosis and the outcome of survival to discharge from neonatal care without major morbidity for very preterm babies

9.3.1.1 Primary exposure for the primary objective

- Any use of sodium bicarbonate infusions to prevent or treat metabolic acidosis (including intravenous and intra-arterial infusions)

9.3.1.2 Comparator for the primary objective

- No use of sodium bicarbonate for metabolic acidosis

9.3.1.3 Outcomes for the primary objective

- Proportion of babies within gestational age criteria with at least one episode of metabolic acidosis defined as blood pH less than 7.25 with pCO_2 that is low or normal for the clinical context and a low bicarbonate level (episodes with blood pH < 7.20 and blood pH 7.20–7.25 will be assessed separately)
- Survival without major morbidity, with major morbidity defined as any of the following:
    - Bronchopulmonary dysplasia (BPD) (defined as any respiratory or ventilatory support or supplemental oxygen at 36 weeks postmenstrual age);
    - Treatment for retinopathy of prematurity (ROP) (defined as cryotherapy, laser therapy or injection of anti-VEGF therapy for retinopathy of prematurity in either or both eyes);
    - Major brain injury (grade 3 / 4 IVH, periventricular leukomalacia (PVL) or post haemorrhagic ventricular dilatation requiring intervention);
    - Late-onset sepsis (defined as one or more episodes of a positive blood or cerebrospinal fluid culture with either a pure or mixed growth of a known pathogenic organism after the first 72 hours following birth);
    - Severe necrotising enterocolitis (defined as necrotising enterocolitis confirmed at surgery);
    - Major surgery (defined as any major surgical procedure recorded during neonatal admission).

9.3.2 Secondary Objectives

- To describe current practice of the use of sodium bicarbonate infusion in very preterm babies

- To describe the demographic and clinical characteristics of very preterm babies who develop metabolic acidosis
- To explore the association between exposure to metabolic acidosis and the outcome of survival to discharge from neonatal care without major morbidity
- Provide period prevalence estimate of metabolic acidosis in very preterm babies who have and have not been exposed to intra-arterial sodium bicarbonate
- To understand the current practice of the use of intra-arterial sodium bicarbonate in very preterm babies

9.3.2.1 Primary exposure for the secondary objective

- At least one episode of metabolic acidosis defined as blood pH less than 7.25 with pCO_2 that is low or normal for the clinical context and a low bicarbonate level

9.3.2.2 Comparator for the secondary objective

- No episode of metabolic acidosis defined as blood pH less than 7.25 with pCO_2 that is low or normal for the clinical context and a low bicarbonate level

9.3.2.3 Outcomes for the secondary objective

- Number, dosage and duration of sodium bicarbonate infusions received
- Demographic characteristics e.g. gestational age, small for gestational age, ethnicity, sex
- Clinical characteristics e.g. exposure to antenatal steroids, delivery room interventions
- Survival without major morbidity, with major morbidity defined as any of the following:
    - Bronchopulmonary dysplasia (BPD) (defined as any respiratory or ventilatory support or supplemental oxygen at 36 weeks postmenstrual age);
    - Treatment for retinopathy of prematurity (ROP) (defined as cryotherapy, laser therapy or injection of anti-VEGF therapy for retinopathy of prematurity in either or both eyes);
    - Major brain injury (grade 3 / 4 IVH, periventricular leukomalacia (PVL) or post haemorrhagic ventricular dilatation requiring intervention);
    - Late-onset sepsis (defined as one or more episodes of a positive blood or cerebrospinal fluid culture with either a pure or mixed growth of a known pathogenic organism after the first 72 hours following birth);
    - Severe necrotising enterocolitis (defined as necrotising enterocolitis confirmed at surgery);
    - Major surgery (defined as any major surgical procedure recorded during neonatal admission).
- Metabolic acidosis defined as blood pH less than 7.25 with pCO_2 that is low or normal for the clinical context and a low bicarbonate level
- Exposure to intra-arterial sodium bicarbonate

9.3.3 Covariates

Directed acyclic graphs (DAGs) will be used to guide which covariates will be included in the analysis, and whether they are considered confounders, mediators or moderators. Possible covariates include but are not limited to: antenatal factors, maternal characteristics, infant characteristics and hospital (21).

9.4 STUDY DESIGN FOR WS2

Multicentre, prospective cohort study. The research will take place in 22 NHS neonatal units in the UK.

9.5 PARTICIPANT IDENTIFICATION FOR WS2

Babies born between 23^{+0} and 30^{+6} weeks^{+days} of gestation inclusive, satisfying the following criteria.

9.5.1 Inclusion criteria

- Babies born between 23^{+0} and 30^{+6} weeks^{+days} of gestation inclusive
- Born at a recruiting site or transferred within 24 hours of being born

9.5.2 Exclusion criteria

- A parent has opted out of their baby's participation

9.6 STUDY PROCEDURES FOR WS2

Table 3: Schedule of Procedures

PROCEDURES	BEFORE STUDY ENTRY	AT STUDY ENTRY	AFTER STUDY ENTRY
	Screening	Entry form	Birth – discharge from neonatal unit or 40 weeks postmenstrual age (whichever is sooner)
Eligibility assessment	X		
Enrolment		X	
Clinical data collection (from routine data extracted by NNRD)			X
Clinical data collection (CRF completion/clinical data extraction)			X

9.6.1 Sampling

Babies will be recruited from NHS neonatal units in the UK that care for babies born very preterm. All babies will be included if they satisfy the eligibility criteria in section 9.5 from the date a site receives greenlight until the end of recruitment period. Admission data collected in the NNRD will be used to check that all babies who meet the eligibility criteria have been enrolled.

Sampling frame: a selection of neonatal units that were previously participating in the BASE RCT will participate in WS2, selected using a non-probability sampling method. Additional neonatal units that did not participate in the BASE RCT will also be invited to participate. The primary sampling unit is a hospital (cluster); all babies meeting the age criteria who are born in one of these clusters, or transferred in within 24 hours from birth, will be included (if parent does not opt out).

9.6.2 Inter-hospital transfers

As detailed in section 7.8.2 but for data collection only.

9.6.3 Screening and Eligibility Assessment

Babies meeting the eligibility criteria will be screened for eligibility by the clinical care team after admission to the neonatal unit. Assessment of eligibility is accepted to be within the scope of competency of appropriately trained member of the baby's clinical care team, as delegated by the Principal Investigator.

9.6.4 Consent

As participation in the study will only involve data collection, an opt-out consent approach will be used. As outlined in section 15.6, there is strong support for opt-out consent in neonatal trials. The data used in this study is routinely recorded in baby's medical notes.

Parents will have the option to opt out if they do not want their baby enrolled into the study. They will also be able to opt out of the study at any point after their baby is enrolled (further details around withdrawals are given in section 9.6.7). The opt-out nature means that there will not be a signed consent form.

Parents of potential participants will be provided with study information by members of the clinical care team in the antenatal period or during neonatal admission, prior to enrolment. Information will be widely available throughout the neonatal units via posters. Paper and electronic patient information sheets will be provided and study information will be available online.

9.6.5 Enrolment

Enrolment of babies will be managed via a secure web-based program hosted by the National Perinatal Epidemiology Unit Clinical Trials Unit (University of Oxford) with telephone backup available at all times (365 days per year). A Senior Trials Programmer at the NPEU CTU will write the web-based program.

Babies can be enrolled as soon as they are identified as eligible.

9.6.6 Study Data Collection

The source of data for the cohort will be the NNRD and study specific CRFs. The NNRD is a database of routine health data, electronically recorded for all babies admitted to neonatal units across the UK. For data not routinely recorded in the NNRD, study specific CRFs will be used and serve as the data source for these data items. Data collection will occur as detailed in section 7.8.7 above.

9.6.7 Withdrawal of Participants

Parents/carers can request to withdraw their baby from some or all of the study data collection (eCRF, baby's medical record) at any point. Data collected by that method up to the point of withdrawal will be used in the study. Withdrawal will not affect their baby's ongoing clinical care. Withdrawals will be recorded on an eCRF and the reason detailed, if it has been provided.

9.7 SAFETY REPORTING FOR WS2

As this is an observational study, there will be no safety reporting.

9.8 STATISTCS FOR WS2

9.8.1 Sample Size Determination

Prevalence estimate

To estimate the expected population at these sites, 2021 and 2022 birth and admissions numbers for very preterm babies (23^{+0} to 30^{+6} weeks^{+days} gestation) in the expected observational study sites was acquired from the NNRD. From this, an estimated 750 babies are expected to be eligible for inclusion over the 9-month study period. Allowing for a 10% opt-out rate and 10% missing data, approximately 600 will contribute to the prevalence estimate. This sample size allows the prevalence for metabolic acidosis to be estimated with a margin of precision (21, 24) of approximately ±3% assuming a prevalence of 19% (from the BASE RCT enhanced screening log data).

Association of primary exposure

As above, approximately 600 babies will contribute data to the analysis for the association of the primary exposure. After deflating to allow for a design effect based on a Variance Inflation Factor (VIF) of 1.429 (21), to account for the potential reduction in power resulting from adjusting the logistic regression model for factors which are not strongly prognostic, we expect a sample size of approximately 420 babies. This effective sample size will allow a difference of approximately 16.5% between groups to be detected, assuming a control group rate of 53% (as used for the BASE RCT and taken from NNRD data) and 20% receiving sodium bicarbonate (from the BASE RCT enhanced screening log data).

All calculations assume 80% power and 5% significance level.

9.8.2 Statistical Analysis Plan (SAP)

The statistical aspects of the observational study are summarised here with details fully described in a statistical analysis plan that will be finalised before final data lock takes place.

9.8.3 Description of Statistical Methods

9.8.3.1 Descriptive statistics

Demographic factors and clinical characteristics at baseline will be summarised with counts (percentages) for categorical variables, mean (standard deviation [SD]) for normally distributed continuous variables, or median (interquartile range [IQR]) or entire range) for skewed continuous variables. A descriptive analysis will be carried out on all outcomes, and on any potential confounders, mediators and moderators. Demographic and clinical characteristics and covariates associated with the development of metabolic acidosis, including gestational age and illness severity will be described for babies who develop metabolic acidosis. The amount of missing data and any variables which may be associated with 'missingness' will be explored.

Prevalence

The prevalence of metabolic acidosis overall and by exposure status to intra-arterial sodium bicarbonate, and the prevalence of the use of sodium bicarbonate, will be estimated using appropriate statistical methods. For example, prevalence ratios would be calculated using a generalised linear model (GLM) with a binomial family and log link, or using a GLM with a Poisson family, log-link and robust variance estimator if the binomial GLM fails to converge. All prevalence ratios will be presented with associated 95% confidence intervals.

To account for the method used to select hospitals for inclusion in WS2 not being probability based, methods to improve the external validity of the prevalence estimates will be considered. These methods may include inverse probability weighting or inverse propensity score weighting, and will use aggregate infant and maternal characteristics from a publicly available research database, such as the National Neonatal Audit Programme (NNAP) or the NNRD, for all NHS neonatal units across England, Wales and Scotland as their external reference.

9.8.3.2 Comparative statistics

For all outcomes, the association between exposure of interest and the defined outcomes will be presented using both crude and adjusted effect estimates. All outputs will be presented with coefficients, 95% confidence intervals and p-values reported for each variable. DAGs will be used to represent the assumed causal relationships between the variables of interest and suitable modelling strategy will be identified.

For binary outcomes, including the association between the use of sodium bicarbonate and survival without major morbidity, risk ratios will be presented with 95% confidence intervals. Crude effect estimates will be estimated with a suitable model, such as a log binomial regression model, or should that model fail to converge, a Poisson regression model with a robust variance estimator. Adjusted risk ratios and 95% confidence intervals will then be calculated using an appropriate multivariate model, adjusting for potential confounders, mediators and moderators as defined in the DAG. As above, methods to improve the external validity of the outcomes analysis will be considered.

A similar approach will be adopted to explore the associations between exposure to metabolic acidosis and outcomes.

9.8.3.3 Secondary analysis

Any planned secondary analyses will be detailed in the SAP.

9.8.4 Analysis Populations

Analyses will be conducted on all babies enrolled into WS2.

9.8.5 Level of statistical significance

A significance level of 5% will be used to assess any associations between exposures and defined outcomes.

9.8.6 Procedure for accounting for missing, unused and spurious data

The amount of missing data and any variables which may be associated with ‘missingness’ will be explored as part of the descriptive analysis. Where appropriate, we may use statistical methods to address missing data within the analysis, for example, the use of multiple imputation.

10 WORKSTREAM 3: INTEGRATED QUALTIATIVE STUDY

10.1 BACKGROUND AND RATIONALE FOR WS3

As described above, recruitment to the BASE RCT proved to be challenging. While it was possible to gauge some insights into the reasons underpinning the difficulties encountered through analysis of the enhanced screening log and informal interactions with sites, there was still a need to better understand the 'root causes' of recruitment issues to assess if these are remediable in a future trial. Previous research has shown that recruitment is a complex, fragile process that can be shaped by the beliefs and practices of stakeholders that extend beyond the potential participant: from health care professionals who interact with patients/parents throughout the clinical pathway, to public entities (e.g. charities and public information fora) (25). Previous studies have also shown that while there are 'clear obstacles' that may appear to limit recruitment (e.g. lack of eligible babies), these are often underpinned by 'hidden challenges': social and behavioural factors that shape health care professionals' decision-making about whether/when to approach families, their interpretation of eligibility criteria, and the ways in which they convey treatments and trial information to potential participants (26).

The Qualitative Research Integrated within Trials (QuinteT) research group specialises in understanding and addressing the 'root causes' of recruitment and retention issues in clinical trials. The group's principal innovation – 'QuinteT Recruitment intervention' (QRI) – is a complex intervention that seeks to understand the sources of recruitment difficulty in a given RCT (phase 1), with a view to using these insights to design/implement 'tailored solutions' to optimise recruitment. These tailored actions tend to be deployed while the RCT is underway, in trials where the QRI has been integrated from the outset and there is sufficient time to 'take action' and monitor subsequent effects (27). In contexts where time/resource is more limited (e.g. often feasibility studies), QuinteT methods have been used to generate an in-depth understanding of the clear obstacles/ hidden challenges underpinning recruitment, to inform decisions about *future* trial viability, trial design plans, and development of tools/resources to enhance the likelihood of success (28, 29)

The QuinteT research group will deliver a qualitative investigation alongside the feasibility and observational studies (WS1 and WS2), using methods adapted from the QRI to develop an in-depth understanding of: i) current practice in management of babies who are at risk of – or develop – metabolic acidosis, and ii) healthcare professionals' perceived need for a future definition RCT, and iii) factors that may support or hinder recruitment, based on healthcare professionals'/BASE study staffs' and parents' views and experiences of involvement in the BASE RCT and WS1. The evidence arising from the qualitative investigation will be triangulated with quantitative findings from the feasibility trial (WS1) and the observational study (WS2) to inform recommendations for future definitive RCT design(s) that are relevant, feasible, and sensitive to the nuances of current UK practice.

10.2 AIM AND OBJECTIVES FOR WS3

10.2.1 Aim

The overall aim of the integrated qualitative study is to investigate current practices in management of preterm babies with metabolic acidosis, stakeholders' perceived need for a future definitive RCT, and challenges and solutions to its successful execution.

10.2.2 Objectives

Specific objectives of the qualitative study are to:

1. Investigate HCPs' rationales underpinning their current practices around management of very preterm babies who are at risk of – or develop – metabolic acidosis, their perspectives on the current evidence-base in this area, and implications for a future definitive RCT;
2. Generate a comprehensive understanding of factors that support and hinder recruitment to the feasibility trial, drawing on HCPs', study team members' and parent/carers' experiences of involvement in the (feasibility) trial (past and present);
3. Combine findings from '1' and '2' to generate recommendations for the design and conduct of a future definitive RCT in this field, in collaboration with the BASE Project Management Group (PMG) and Parent Advisory Group (PAG)

10.3 STUDY DESIGN FOR WS3

We will use a qualitative design comprising three complementary strands:

i. **Semi-structured interviews with HCPs and BASE study staff** will be conducted to investigate the rationale underpinning current practices around management of the eligible patient population, and views relating to the BASE trial's design and delivery. The latter will largely be derived by drawing on HCPs' and other staff members' experiences of engaging with the trial – whether this is as part of their ongoing involvement (e.g. as a WS1 site, or member of the BASE PMG) or previous involvement in the BASE RCT (i.e. prior to its adaptation to a feasibility trial). Perspectives on the *prospect* of a trial will also be explored with HCPs from sites that did not participate in the BASE RCT and are now participating in WS2.

ii. **Audio-recordings of 'recruitment discussions'** between HCPs and parents who are approached to consider participating in the feasibility trial. These recordings will provide direct insight into how the trial is conveyed and received in practice (sampled from WS1 sites only). Audio-recordings of actual (rather than reported) explanations of the feasibility trial can illuminate parents'/families' responses to different presentations of the trial and its processes, highlighting aspects that may be unclear, open to misinterpretation, or not conducive to conveying equipoise. This will provide insight into challenges and opportunities for optimising communication to BASE and RCTs that follow in this area. The QRI team will examine the findings with a view to assessing whether challenges are remediable through tailored communication training/support, based on prior experience of conducting QRIs in a range of challenging RCTs.

iii. **Interviews with parents who have accepted, declined, and withdrawn/discontinued participation in WS1** to understand decision-making processes around enrolment and continued participation (sampled from WS1 sites only).

10.4 SAMPLING FOR WS3

A bespoke purposeful sampling strategy will be employed for each strand of the qualitative study. Sampling decisions will be dynamic and iterative as the study proceeds, to guide data collection until the team are confident that saturation has been achieved in relation to the study objectives. This will be a team-based

assessment, supported by regular scrutiny of emerging analytical insights and their supporting evidence, and the diversity of the sample from which the evidence is derived.

Initially, sampling decisions for each strand of the qualitative study will proceed as follows:

10.4.1 Semi-structured interviews with HCPs and BASE study staff

Interviews with HCPs and BASE study staff will take place on two levels: at the site level, and at the BASE study oversight level (i.e. the BASE PMG).

We will purposefully sample key informants within the BASE PMG, based on their potential to contribute insights pertaining to current and previous recruitment practices (i.e. drawing on current practices employed for WS1 sites, as well as previous practices prior to the BASE RCT's conversion into a feasibility trial). Sampling of HCPs and other staff operating in recruiting sites will proceed as outlined in 10.4.1.1 and 10.4.1.2.

10.4.1.1 Site selection

Interviews with HCPs and other site staff will be conducted in purposefully-sampled sites from the feasibility trial (WS1) and observational study (WS2). This will maximise opportunities to understand the diversity of practices and perspectives around management of metabolic acidosis in preterm babies. With this broad sampling frame in mind, we will select sites based on:

- **Screening log data collected for the BASE RCT.** We will seek to include neonatal units representing a range of number of babies recruited to the BASE RCT, as well as varying proportions of parents of potentially eligible babies approached among those screened. Previous research has shown that these figures can serve as proxies for HCPs' individual perceptions of equipoise, variable interpretation of eligibility criteria, and discomfort in negotiating research vs clinical roles (30).
- **Monthly scrutiny of enhanced screening log data that are captured throughout the feasibility trial's recruitment period.** This monitoring may reveal changes in screening activity patterns that would warrant further qualitative investigation.
- **Intentions to sample from hospitals serving socio-demographically varied populations** (e.g. in terms of proportion of global majority populations and indices of deprivation).

10.4.1.2 Sampling HCPs/site staff within selected sites

HCPs and other staff members that are on the site delegation log or have a role in caring for the eligible patient population will be eligible for participation in the qualitative study. This is likely to encompass multi-disciplinary team members from medical and nursing backgrounds. Sampling of individual HCPs within selected sites will be guided by key informant and snowball approaches. Key informants will initially comprise site Principal Investigators, given the likelihood that they will have some degree of familiarity with the BASE RCT and/or studies and their operationalisation within their localities. In WS1 sites, key informants will comprise Principal Investigators and any HCP with a role in supporting or conducting recruitment to the trial.

Key informants will initially be identified through liaison with the BASE Study Team and site delegation logs. Additional informants will be identified through snowball sampling techniques, where individuals interviewed are asked to pass on study information to other relevant members of their local team.

10.4.2 Audio-recordings of recruitment discussions

Audio-recording of recruitment discussions will solely take place in sites that are taking part in the feasibility trial (WS1). Personnel within these sites who have a role in explaining the trial to parents/families prior to randomisation will be invited to routinely record their discussions with parents/families (subject to parental consent as detailed in section 10.5.2). As the feasibility trial progresses, we will target sites with the highest and lowest consent rates (i.e. the *percentage of approached families who consent*), captured via regular monitoring of screening log data.

10.4.3 Interviews with parents

As above, interviews with parents will solely take place in sites that are taking part in the feasibility trial (WS1). Any parent that is approached to consider participation in the feasibility trial will be eligible for the qualitative study. Decisions about whether parent interviews have potential to yield new insights – and if so, whom to approach – will be driven by emerging insights from analysis of audio-recorded trial recruitment discussions (as described above) and scrutiny of reasons recorded on the screening log for why consent was not obtained. We will prioritise approaching parents who decline trial participation, on the basis that these cases are most likely to generate new insights into recruitment barriers and ways in which they might be overcome. We will also seek to interview those who accept trial participation, as a means of comparing perspectives and experiences with decliners. A concerted effort will be made to approach any parents who withdraw from the trial or discontinue participation, to understand their decision and explore ways in which their experience of participation could have been improved.

Decisions about trial participation/continuation, as outlined above, will be a principal factor driving purposeful sampling decisions, in addition to efforts to sample parents from a range of sites taking part in the feasibility trial (WS1).

10.5 RECRUITMENT FOR WS3

We will follow distinct processes for recruiting HCPs, BASE study staff and parents/carers for the qualitative study. In both cases, there will be an effort to streamline study information/paperwork to minimise participant burden.

10.5.1 Recruitment of HCPs and BASE study staff

A multi-faceted recruitment strategy will be employed for HCPs and BASE study staff.

- At the site-level, HCPs and other staff members who meet the sampling criteria (outlined above) will be informed about the qualitative study via Site Initiation Visits (SIVs), email correspondence, and word-of-mouth communication via local members of the research team, e.g. research nurses. Potential participants will receive an electronic copy of a dedicated information sheet outlining the qualitative study. Bespoke information sheets will be used, depending on whether the individual is operating within a feasibility trial site or observational study site. Information sheets for staff operating within feasibility trial sites will cover the interviews and audio-recording process, whereas

information sheets for staff in observational study sites will only cover the interview element of the qualitative study. The QRI researcher or members of the local research team (e.g. research nurses, Associate Principal Investigators) will obtain written or verbal consent from HCPs/site staff who express an interest in taking part in the qualitative study. Dedicated consent forms will be used for staff operating within feasibility trial sites and observational study sites. The consent form for individuals approached within feasibility trial sites will provide separate clauses pertaining to each element of the qualitative study as relevant (i.e. interviews, audio-recording of recruitment discussions). Potential participants may opt to participate in just one, both, or neither of these elements.

- BASE study staff operating at a trial oversight level (i.e. selected individuals within the BASE PMG) will receive an information sheet about taking part in an interview. This will be the same information sheet as the document used for observational study staff (given that the exact same study processes are relevant to both groups). The QRI researcher will send this information sheet via email and obtain verbal consent from individuals who express an interest in taking part.

10.5.2 Recruitment of parents

Recruitment of parents will be led by local site staff (e.g. research nurses, Associate PIs, recruiting HCPs) who are trained and delegated in taking consent for the feasibility trial. The recruitment process will take place as follows:

- Healthcare professionals (e.g. recruiting HCPs) or local research staff (e.g. research nurses, Associate PIs) will introduce the qualitative study during the same encounters in which parents are approached to consider taking part in the feasibility trial.
- The staff member leading the discussion will inform parents that they would like to discuss potential participation in a research study (the feasibility trial) and seek verbal permission to audio-record the discussion to support the team's training/development around explaining research opportunities to parents, patients, and the public.
- The recorder (a digital encrypted handheld recording device) will be switched on, subject to the parent's agreement. The staff member will sign a disclosure form to confirm that they have sought and received verbal consent from the parent to record the discussion.
- A copy of a dedicated participant information sheet that fully explains the audio-recording process will be provided to parents during or after this initial encounter. A member of the local research team (e.g. a research nurse) will seek consent for participation in the qualitative study (use of audio-recordings and interview), ideally during the same encounter that consent is sought for the feasibility trial. On receipt of consent, any audio-recordings previously obtained will be shared with the QuinteT research team for research purposes. If consent is not given, any recordings previously obtained will be permanently deleted.

The above information sheet and associated consent form will also cover the interview element of the qualitative study. The consent form will have separate clauses asking parents if they are willing to take part in a telephone or web-based interview with a member of the QuinteT team, and whether they are happy for their contact details to be shared with the QuinteT team for the purposes of arranging the interview.

10.6 DATA COLLECTION PROCESSES FOR WS3

10.6.1 Interviews with HCPs and BASE study staff

Semi-structured interviews will take place via telephone or a secure web-platform that is approved for research according to the latest University of Bristol guidance (e.g. Microsoft Teams). Interviews are anticipated to last between 30–60 minutes and will be audio-recorded using an encrypted recording device and/or the recording feature on a secure web platform. Where web platforms are used, both audio and video-recordings may be captured if participants switch their video on, but only the audio file will be retained for research purposes.

An experienced qualitative methodologist with training in QuinteT approaches (i.e. the 'QRI researcher') will conduct the interviews, under the supervision of Professor Rooshenas (who leads the QuinteT research group). Distinct topic guides will be used to guide the interviews: one for HCPs/site staff operating in feasibility trial sites, and one for HCPs/site staff operating in observational study sites, and one for members of the staff who have been approached by virtue of their role on the BASE PMG. The topic guides will cover some core common questions, such as perspectives on the current evidence base aligned with the scientific questions underpinning BASE and perceptions of equipoise around management options in this field and how these relating to different subsets of the eligible population. Healthcare professionals/other staff with experience of recruiting to BASE will also be asked about their interpretations of the eligibility criteria, application of the criteria in practice, the 'local recruitment pathway', and experiences of approaching parents for potential participation.

10.6.2 Audio-recording recruitment discussions

HCPs/site staff will be provided with an encrypted audio-recorder to record their discussions with parents relating to WS1. Efforts will be made to capture all relevant discussions, starting with the first point at which BASE is discussed (e.g. during antenatal consultations, although this will vary by site). Subject to full consent having been obtained, recordings will be securely sent to the University of Oxford and the University of Bristol QuinteT team.

10.6.3 Interviews with parents

Interviews with parents will take place remotely, via telephone or secure web-platform depending on the individual's preferences. Encrypted audio-recorders or the recording function of secure web platforms will be used to capture the interview. Where web platforms are used, both audio and video-recordings may be captured if participants switch their video on, but only the audio file will be retained for research purposes. Interviews are anticipated to last 30–60 minutes and will be conducted by the QuinteT researcher (as described above). A dedicated parent-interview topic guide will be used as a loose framework to guide the discussion, with opportunities to explore new lines of enquiry as these arise. The topic guide will encourage parents to share a narrative summary of their experiences of being approached about the trial, beginning with the first point at which they heard about the study. Questions will probe around different aspects of recruitment / trial participation, including: the timing of being approached about the trial; the quality of information provision (both written and verbal information); perceptions of how supported parents felt in being able to make an informed decision; other sources consulted to support decision-making about (continued) participation; concern(s) relating to (continued) trial participation, and ways in which these could be mitigated or addressed

10.7 SAFETY REPORTING FOR WS3

There will be no safety reporting for WS3.

10.8 ANALYSIS FOR WS3

All qualitative interviews will be audio-recorded using digital encrypted recorders, transcribed verbatim, and edited to ensure anonymity. Audio-recordings will be transcribed by internal University of Bristol staff or an external transcription company which has signed the necessary University of Bristol confidentiality agreements. Transcripts will be pseudo-anonymised. Interview data will be managed using NVivo software (QRS International) and analysed thematically using constant comparative approaches adopted from Grounded Theory (31). Audio-recorded recruitment discussions will be subjected to content, thematic, and novel analytical approaches, including targeted conversation analysis. There will be a focus on aspects of information provision that are unclear, disrupted, or potentially detrimental to recruitment and/or adherence. Standard approaches to enhancing rigour, such as double-coding, triangulating, and seeking out 'negative cases', will be employed throughout the conduct of the qualitative study. A detailed description of how the QRI methodology achieves rapid analysis whilst maintaining rigour is detailed elsewhere (32).

11 DATA MANAGEMENT

The data management aspects of the studies are summarised here with details fully described in the Data Management Plan and Data Flow document.

11.1 SOURCE DATA

Source documents are where data are first recorded, and from which babies' CRF data are obtained. CRF entries will be considered source data if the CRF is the site of the original recording (i.e. there is no other written or electronic record of data).

The majority of the RCT data and for WS1 and WS2 will be obtained from routinely recorded clinical data held in the NNRD, following the NNRD application process, and will be considered source data. Principal Investigators at recruiting sites will be responsible for data completeness of NNRD items that will be used for the studies; the Data Monitoring Plan (DMP) will detail data cleaning processes.

For WS3, the audio-recordings of the recorded discussions and interviews, and the transcripts will be considered source data.

11.2 ACCESS TO DATA

Direct access will be granted to authorised representatives from the Sponsor, host institution, research team and the regulatory authorities to permit trial-related monitoring, audits and inspections.

For BASE RCT, WS1 and WS2, site staff will have authenticated and restricted access to the secure Clinical Database Management System (OpenClinica), ensuring they are only able to see data on participants recruited at their site. Access to the electronic data is strictly controlled using individual passwords for all staff accessing the electronic databases.

11.3 DATA RECORDING AND RECORDING KEEPING

11.3.1 BASE RCT, WS1 and WS2

The majority of trial-specific data and data for the BASE RCT, WS1 and WS2 will be collected using electronic CRFs and either entered directly into the secure Clinical Database Management System (OpenClinica) or automatically transferred into it from the bespoke randomisation database. Daily dosing logs for the BASE RCT, WS1 and WS2 will be a paper CRF with completed logs entered directly into the secure clinical database. The clinical database will be validated and maintained in accordance with NPEU CTU Standard Operating Procedures (SOPs). Data will be entered and at the point of entry will undergo a number of validation checks to verify the validity and completeness of the data captured. A separate administrative database application will be used to store participant identifiable details. Study participants will be identified by a unique trial number, which is used to link the clinical and administrative database applications.

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

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

11.3.2 WS3

The integrated qualitative research will require site staff to share identifiable information of individuals who consent to be contacted about the qualitative study. These details will be stored on the University of Oxford's administrative database application and will be shared with the QuinteT team at the University of Bristol.

The qualitative research will entail collection of audio-recorded interviews and recruitment discussions, which will be transcribed by a University of Bristol employee or a University of Bristol-approved transcription service that has signed the necessary University of Bristol confidentiality agreement. Audio-recordings and transcripts will be labelled with participant identification numbers in file names, and the content of transcripts will be de-identified (e.g. removal of information that may compromise an individual's anonymity). Electronic data files will be saved in restricted folders only accessible to the QuinteT research team, on secure University of Bristol network space that adheres to the University of Bristol's data security policies. Audio-recordings will be stored for 12 months after the study end date and transcripts will be stored for 25 years, after which they will be deleted in accordance with the applicable data protection guidelines.

11.4 DEFINITION OF END OF TRIAL

The end of trial will be defined as the date when the BASE Studies database(s) are locked.

12 QUALITY ASSURANCE PROCEDURES

12.1 RISK ASSESSMENT

The studies will be conducted in accordance with the current approved protocol, GCP, relevant regulations and Standard Operating Procedures (SOPs). A risk assessment (RA) and monitoring plan (MP) will be prepared before the studies open and will be reviewed as necessary over the course of the studies to reflect significant changes to the protocol or outcomes of monitoring activities.

12.2 MONITORING

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

Recruitment patterns at sites and within the data will be monitored. Any unexpected patterns, issues, or outlier data will be investigated and may trigger 'for cause' site monitoring.

12.3 STUDY COMMITTEES

The studies will be run on a day-to-day basis by the Project Management Group (PMG), which reports to the Study Steering Committee (SSC), which in turn is responsible to the NIHR HTA programme. The PMG will consist of the Chief Investigator, CTU Director, Clinical CTU Director, Head of Operations, Senior Trials Manager, Trial Statistician, Trials IT Development and Data Management Team and other project staff. The PMG will meet every month.

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

The BASE Studies will be overseen by a SSC consisting of an independent chair and other members, to include clinicians, statisticians and PPI representatives. Committee members will be deemed independent if they are not involved in study enrolment. The chair and members of the SSC will be nominated as per the guidance outlined by the NIHR HTA for their approval. The SSC will aim to meet at least annually.

The SSC will monitor the progress of the BASE Studies and its conduct and advise on its scientific credibility. Details about the roles, responsibilities and conduct of the committee with be set out in a SSC Charter, which will be agreed at the first meeting.

The DMC will be in place for the BASE RCT and WS1. The DMC members will be independent of the trial team and the SSC, and will include a chair, clinician and statistician. During the recruitment phase, the committee will meet annually or more often as appropriate, review trial conduct, progress, and accumulating data, and make recommendations to the SSC. Details about the roles, responsibilities and conduct of the committee with be set out in a DMC Charter, which will be agreed at the first meeting.

13 PROTOCOL DEVIATIONS

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

14 SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the study protocol which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within one working day. In collaboration with the CI the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, regulatory authority and the relevant NHS host organisation within seven calendar days.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 DECLARATION OF HELSINKI

The Investigator will ensure that the studies are conducted in accordance with the principles of the Declaration of Helsinki.

15.2 GUIDELINES FOR GOOD CLINICAL PRACTICE

The Investigator will ensure that these studies are conducted in accordance with relevant regulations and with Good Clinical Practice, as applicable for the specific workstreams.

15.3 APPROVALS

Following Sponsor approval the protocol, consent forms, participant information sheets and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.

The NPEU CTU will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

15.4 REPORTING

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the host organisation, funder (where required) and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor.

15.5 TRANSPARENCY IN RESEARCH

Prior to the recruitment of the first participant, the BASE RCT was registered on a publicly accessible database. The sub-studies (WS1-3) will be included on this existing registration

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

15.6 CONSENT MODEL

There was unanimous support for an opt-out consent approach from the PPI co-applicants and focus groups involved in development of the proposal, who felt that it would normalise participation and minimise the decision-making and emotional burden on parents during an already very stressful time. Acceptability by UK research ethics committees and parents to opt-out consent has been demonstrated, as well as the feasibility of this approach in neonatal trials (WHEAT Pilot, WHEAT International and neoGASTRIC trials (33). There has also been overwhelming support from the trial's Parent Advisory Group (PAG). As the BASE RCT and WS1 are CTIMPs, a verbal consent approach will be used, to ensure that consent is documented, whilst still reducing the burden on parents, as recommended by PPI members. The qualitative study will use a written and verbal consent model. The observational study will use an opt-out consent model.

15.7 PARTICIPANT CONFIDENTIALITY

The studies will comply with the UK General Data Protection Regulation (GDPR) and Data Protection Act 2018. All documents will be stored securely and only accessible by the research team and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

For BASE RCT, WS1 and WS2, personal identifiers will be stored in a separate database also held at the NPEU CTU. These databases will only be linked by the baby's study number. After the trial has been completed and the reports published, the data will be archived in a secure physical or electronic location with controlled access. For WS3, personal identifiers will be stored and held by the QuinteT team at the University of Bristol.

15.8 EXPENSES AND BENEFITS

Parents/carers of babies enrolled in the BASE RCT will receive a voucher as a thank you for their participation in the trial. There will be no payments in WS1–3.

16 FINANCE AND INSURANCE

16.1 FUNDING

The studies are funded by the NIHR Health Technology Assessment (HTA) programme Funder Reference: NIHR151086. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

16.2 INSURANCE

University of Oxford is the sponsor for the studies. The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment which is provided.

16.3 CONTRACTUAL ARRANGEMENTS

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

17 PUBLICATION POLICY

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

Authorship of the primary results papers will take the form "[name], [name] and [name] on behalf of the BASE Studies Collaborative Group". The drafting of each paper will be the responsibility of a writing committee. All contributors to the studies will be listed at the end of each paper, with their contribution identified. It is the intention of the BASE Studies Collaborative Group to publish the protocol and peer-reviewed articles. All published material will contain an acknowledgement of funding, as required by the NIHR HTA.

Full details of the studies will be made available through the trial website: https://www.npeu.ox.ac.uk/base. The studies will also be registered on relevant public databases where applicable. Study results will also be made available to parents, clinicians, provider organisations and policy makers through Bliss (the national charity for babies born premature or sick), social media, professional conferences, and lay and peer-review publications. A full dissemination plan will be developed by the PMG.

18 DEVELOPMENT OF A NEW PRODUCT / PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

19 ARCHIVING

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

Archiving of identifiable data will follow the completion of the trial and publication of results for a maximum of 25 years, to allow for contact in the unlikely event of very long-term treatment effects being discovered. Parents are aware that we will hold identifiable data for long-term use. Long-term follow-up using linked routine data is not within the scope of this protocol. A separate protocol and funding application and Confidentiality Advisory Group (CAG) application may be submitted for linkage to routinely recorded long-term outcome data (including Hospital Episode Statistics, neurodisability registers and the National Pupil Database).

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

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21 APPENDICES

APPENDIX 1: Guidance on dosage and administration of intravenous sodium bicarbonate

The following is a suggested guide to the use of intravenous sodium bicarbonate in neonatal units that do not have pre-existing guidance in place.

To calculate the dose of sodium bicarbonate, use the following formulae. The dosage to correct the base deficit is at the discretion of the treating clinician.

Mmol of $NaHCO_3$= (0.3 to 0.6) x weight (kg) x base deficit (mmol/L)

The rate of the infusion depends on the clinical situation. Acceptable duration of infusion ranges from 30 min to 4 hours.

8.4% sodium bicarbonate injection contains 1 mmol/ml.

Prepare infusions for corrections by diluting 4.2% sodium bicarbonate with equivalent volume of water for injection.

APPENDIX 2: Amendment history

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Non-substantial amendment 2 (NSA2)	2.0	9 February 2024	Rebecca Dennis (Trial Manager)	a) Additional sentence added into Section 10.2.1 (Dosing), in line with request from the MHRA in their approval letter dated 8 December 2023: “Treating clinicians should refer to the current SmPC for sodium bicarbonate for the consideration of contraindications and warnings / precautions for use." b) Change to Appendix 2, to remove yellow highlighting which was in error.
Substantial Modification 4	V3.0	2 June 2026	Catherine Thompsett	a) Protocol has been amended to reflect trial re-design changes. Details about three new workstreams have been added. b) Reference to the two-year follow up has been removed as it will no longer go ahead. c) Safety reporting requirements has been amended in line with new Clinical Trial Regulations.

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

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

BASE Protocol V3.0 02Jun2026

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