BASE

Bicarbonate for AcidosiS in very pretErm babies

Bicarbonate for AcidosiS in very pretErm babies: a randomised clinical trial: The BASE Trial

Protocol

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Chief Investigator (CI):	Dr Sabita Uthaya Imperial College London
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CI Signature:	
Statistician Signature:	

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

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1 KEY TRIAL CONTACTS

Chief Investigator	Dr Sabita Uthaya Clinical Senior Lecturer and Consultant in Neonatal Medicine Chelsea and Westminster Hospital / Imperial College London Neonatal Unit 369 Fulham Road London SW10 9NH Email: s.uthaya@imperial.ac.uk Phone: 0203 3158000
Sponsor	University of Oxford Research Governance, Ethics and Assurance (RGEA) Boundary Brook House Churchill Drive Headington Oxford OX3 7GB Email: RGEA.Sponsor@admin.ox.ac.uk Phone: 01865 289886
Funder(s)	NIHR Health Technology Assessment (HTA) Programme (NIHR151086)
Clinical Trials Unit	NPEU Clinical Trials Unit National Perinatal Epidemiology Unit Nuffield Department of Population Health University of Oxford Old Road Campus Oxford OX3 7LF Email: base@npeu.ox.ac.uk Phone: 01865 289716
Statistician	Heather O'Connor NPEU Clinical Trials Unit National Perinatal Epidemiology Unit Nuffield Department of Population Health University of Oxford Old Road Campus Oxford OX3 7LF Email: heather.oconnor@npeu.ox.ac.uk Phone: 01865 289743
Committees	**Trial Steering Committee (TSC) Chair** Professor Sailesh Kotecha Professor and Head of Child Health Cardiff University School of Medicine

	UHW Main Building Heath Park Cardiff CF14 4XN kotechas@cardiff.ac.uk tel: +44 29207 44187 **Data Monitoring Committee (DMC) Chair** Professor Karel Allegaert Professor at KU Leuven and Senior Clinical Consultant at Erasmus MC Rotterdam KU Leuven UZ Herestraat 49 - box 7003 3000 Leuven Belgium karel.allegaert@kuleuven.be tel:+32 16 23 04 32

2 TRIAL 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 many will develop metabolic acidosis during their stay on a neonatal unit.

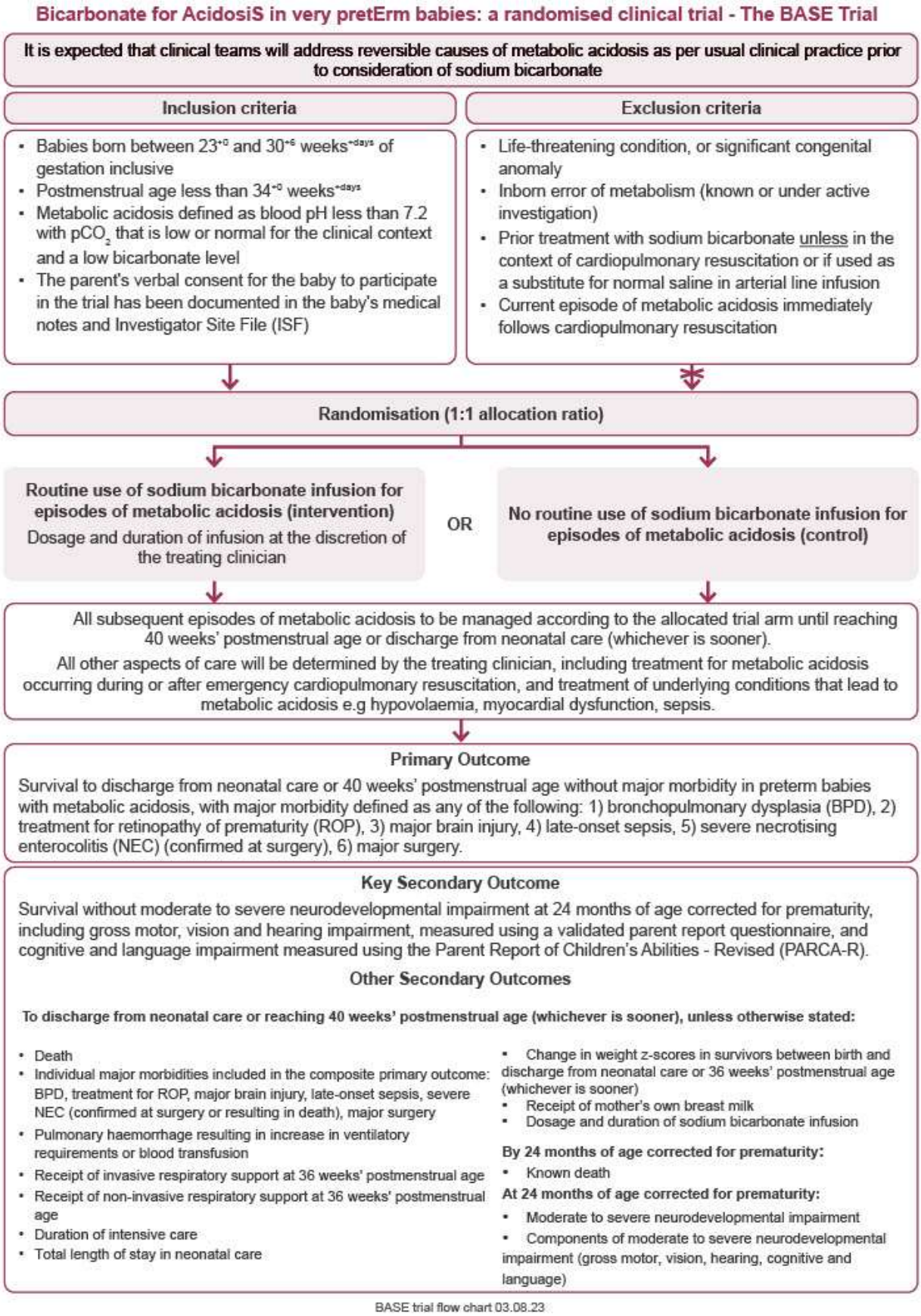
Sodium bicarbonate is widely, but not universally, used to treat metabolic acidosis in very preterm babies but the evidence underpinning its use is poor. Some doctors believe that giving sodium bicarbonate lowers acid levels in the bloodstream and improves the functioning of the heart, but others believe 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. The two approaches of using sodium bicarbonate, or not, for episodes of metabolic acidosis, are commonly used across the UK, so there is nothing new about either type of care. The reason practice differs widely is because the impact and effectiveness of sodium bicarbonate in very preterm babies has never been properly studied.

We want to answer the question, 'In very preterm babies with metabolic acidosis, does giving sodium bicarbonate or not impact on their health and development in the short and long term?'

In this randomised controlled trial, 3,764 very preterm babies with metabolic acidosis will be allocated at random to either routine use of sodium bicarbonate infusion or no routine use of sodium bicarbonate infusion. We will compare survival to discharge from neonatal care without the occurrence of major illnesses during neonatal care between the two groups to find out whether giving sodium bicarbonate or not affects very preterm babies' health in the short term. Babies will also be followed up until they are 24 months of age corrected for prematurity to assess whether there are any longer-term effects of giving sodium bicarbonate or not on children's development.

This is a multicentre, pragmatic, open-label, two-arm, parallel-group, randomised controlled trial. The trial includes a 12-month pilot phase, with criteria at the end of this period to decide whether or not to progress to the main trial. The trial overall has a 3-year recruitment period.

3 TRIAL FLOWCHART



BASE trial flow chart 03.08.23

4 SYNOPSIS

Trial Title	Bicarbonate for AcidosiS in very pretErm babies: a randomised clinical trial: The BASE Trial
Short title	The BASE Trial
Trial registration	ISRCTN Ref: 18260410 Date of Registration: 06/11/2023
Sponsor	University of Oxford
Funder	NIHR Health Technology Assessment (HTA) Programme (NIHR151086)
Clinical Phase	Phase III
Trial Design	Multicentre, pragmatic, open-label, two-arm, parallel-group, randomised controlled trial, with an internal pilot.
Trial Participants	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. Setting: NHS neonatal units in the UK that care for babies born very preterm (level 2 and 3 units).
Sample Size	3,764 babies (1,882 per group) individually randomised in approximately 45 neonatal units in the UK.
Planned Trial Period	The total planned duration of the trial is 75 months, from 01/01/2023 to 31/03/2029. Enrolled babies will be randomised to a trial arm when they meet the inclusion criteria of metabolic acidosis. 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). Final follow-up assessment by parent questionnaire will be conducted at 24 months of age corrected for prematurity.
Planned Recruitment period	36-month recruitment period, starting approximately November 2023, including a 12-month internal pilot.
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 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 / 4 IVH, periventricular leukomalacia (PVL) or post haemorrhagic ventricular dilatation requiring intervention) • Late-onset sepsis • Severe necrotising enterocolitis (NEC) confirmed at surgery

	• Major surgery
Key Secondary Objective	To evaluate the impact of sodium bicarbonate on survival without moderate to severe neurodevelopmental impairment, including gross motor, vision and hearing impairment measured using a validated parent report questionnaire, and cognitive and language impairment measured using the Parent Report of Children's Abilities - Revised (PARCA-R), at 24 months of age corrected for prematurity.
Other Secondary Objectives	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 • Bronchopulmonary dysplasia • Treatment for retinopathy of prematurity • Major brain injury • Late-onset sepsis • Severe necrotising enterocolitis (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) • Receipt of mother's own breast milk • Known death (by 24 months of age corrected for prematurity) • Moderate to severe neurodevelopmental impairment (at 24 months of age corrected for prematurity) • Components of moderate to severe neurodevelopmental impairment (at 24 months of age corrected for prematurity) To describe the patterns of sodium bicarbonate usage
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
BERC	Blinded Endpoint Review Committee
BPD	Bronchopulmonary dysplasia
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CRF	Case Report Form
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
IRB	Independent Review Board
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
NPEU	National Perinatal Epidemiology Unit
NEC	Necrotising enterocolitis
NICU	Neonatal Intensive Care Unit
NIHR	National Institute for Health and Care Research
NNRD	National Neonatal Research Database
PARCA-R	Parent Report of Children's Abilities - Revised
PHVD	Posthemorrhagic ventricular dilatation (PHVD)
PI	Principal Investigator
PIL	Participant/Parent Information Leaflet
PMA	Postmenstrual age
PMG	Project Management Group
PPHN	Persistent pulmonary hypertension of the newborn
PPI	Patient and public involvement
PVL	Periventricular leukomalacia
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
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TSC	Trial Steering Committee
VEGF	Vascular endothelial growth factor

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 (2). Both using and not using sodium bicarbonate for the correction of metabolic acidosis exist in standard clinical practice in the UK (3). 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 (4-6). 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 (7-9).

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.

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 (11). The review noted that neither trial assessed longer-term neurodevelopmental outcomes, which is a core outcome of importance to professionals and parents alike (12). There have been no published studies since then. Despite increased survival rates to over 90% for extremely preterm babies over the last two decades, long-term morbidity and neurodevelopmental outcomes (particularly cognitive) have not shown similar improvements (13-16).

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 (17, 18). 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. This trial was therefore designed to evaluate the correction, not the prevention of metabolic acidosis with sodium bicarbonate. 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 (19).

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. This trial 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. This study will be the first adequately powered trial to study the clinical and cost-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. This is a comparative effectiveness trial not 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 (20). 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. Regardless of the study's result, the BASE trial will lead to more evidence-based practice and cost-effective care of very preterm babies worldwide.

6.1 Research Question

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 OBJECTIVES AND OUTCOME MEASURES

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);	Up to discharge from neonatal care or 40 weeks postmenstrual age (whichever is sooner)

	• 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).	
Other 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 weekspostmenstrual 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 / 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)
	• 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)
Key Secondary Objective To evaluate the impact of sodium bicarbonate on survival without moderate to severe neurodevelopmental impairment at 24 months of age corrected for prematurity.	Key secondary outcome: • Survival without moderate to severe neurodevelopmental impairment, including gross motor, vision and hearing impairment measured using a validated parent report questionnaire, and cognitive and language impairment measured using the Parent Report of Children's Abilities - Revised (PARCA-R).	At 24 months of age corrected for prematurity
	Other secondary outcomes: • Known death	By 24 months of age corrected for prematurity

	• Moderate to severe neurodevelopmental impairment	At 24 months of age corrected for prematurity
	• Components of moderate to severe neurodevelopmental impairment (gross motor, vision, hearing, cognitive and language; presented descriptively)	At 24 months of age corrected for prematurity

Assessment of acceptability to parents of the intervention will be developed using the Parent Advisory Group (PAG) with amendments made to the protocol and study documents as required.

8 TRIAL DESIGN

BASE is 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.

BASE is a comparative effectiveness trial.

The trial flowchart and schedule of events are summarised in sections 3 and 11 respectively.

8.1 Internal Pilot and Progression Criteria

A 12-month internal pilot will be conducted to test and refine the components and processes of the trial. Any substantial amendments, if required, will be submitted. The key progression criteria for the internal pilot are 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. We will also assess safety and completeness of data collection.

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 centres, 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 TSC and HTA.

9 PARTICIPANT IDENTIFICATION

9.1 Trial Participants

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

9.2 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)

9.3 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

10 TRIAL INTERVENTIONS

10.1 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 10.4.1

10.2 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.

10.2.1 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 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.

10.2.2 Post-trial treatment

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

10.3 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.

10.4 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 9.2 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 10.4.1), 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 Trial Steering Committee (TSC).

10.4.1 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

10.4.2 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 9.2) 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 10.4.1 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 8.1) 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 9.2), 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 9.2), 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 10.4.1, 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'.

11 TRIAL PROCEDURES

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)	24 months corrected age
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	X*
Parent reported neurodevelopmental outcomes						X
Adverse events assessments (SAEs, SUSARs etc)				X	X	

* Data will be requested from sites for participants at 24 months corrected age where the parent questionnaire has not been completed, was completed outside of the timeframe required or where data items are missing (section 11.7)

11.1 Recruitment

Babies will be recruited from NHS neonatal units in the UK that care for babies born very preterm (level 2 and 3 units). It is expected that approximately 45 neonatal units in the UK will take part.

11.1.1 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.

11.2 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.

11.2.1 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.

11.3 Consent

As BASE 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 11.9.1 and 11.9.2). 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 (21-23). Furthermore, there is overwhelming support from our Parent Advisory Group (PAG) led by PPI co-applicants.

Cot cards indicating that the baby is potentially eligible to be randomised (before randomisation and if parent has provided verbal consent) and after randomisation will be placed on the baby's cot as an ongoing reminder to parents and staff.

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

Before discharge from the neonatal unit, a discussion will take place with parents to remind parents about follow-up and that the trial team will contact them at 24 months of age corrected for prematurity for parent-reported outcome data.

11.4 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.

11.5 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.

11.6 Study Data Collection

11.6.1 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.

11.6.2 Neurodevelopmental outcome at 24 months corrected age (parent-reported)

Neurodevelopmental outcome at 24 months of age corrected for prematurity will be collected remotely via parent questionnaire completed electronically using a bespoke secure online trial questionnaire, with alternative methods offered for those not wishing to complete online, i.e. on paper via postal questionnaire or over the telephone with a member of the trial team. Parents will also be given an option of completing the questionnaire over telephone via Language Line translation services where they do not read or speak English sufficiently enough to complete the questionnaire.

Parents of all surviving participants will be contacted by the trial team to complete the questionnaire when their child reaches 24 months of age (corrected for prematurity). Questionnaires will be sent electronically by default, however, parents can request different completion methods. Contact and reminders may be made by email, text message, phone call and post.

Where required, data relating to the child's 24-month clinical follow-up assessment will be requested from sites for review by the Blinded Endpoint Review Committee (BERC) (section 11.7).

11.7 Blinded Endpoint Review

Blinded Endpoint Review will be used to classify neurodevelopmental outcome at 24 months of age corrected for prematurity for participants for whom: (1) a 24-month questionnaire was not completed; (2) a 24-month questionnaire was completed outside of the timeframe required for deriving PARCA-R standard scores (less than 23.5 months or more than 27.5 months corrected age); (3) where there are missing data on questionnaire items precluding classification of one or more of the individual components of the main 24-month neurodevelopmental outcome. Data relating to the child's 24 month clinical follow-up assessment will be requested from sites and will be reviewed by the Blinded Endpoint Review Committee (BERC) to classify the main 24-month outcome. Reviews will be conducted in accordance with a BERC Charter, written and

agreed by the PMG and TSC. The BERC reviewers will be professionals who are expert in the fields of conditions for which endpoint data is being collected for analysis.

11.8 Sample Handling

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

11.9 Early Discontinuation/Withdrawal of Participants

11.9.1 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, completion of the 24-month follow-up questionnaire). 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 11.9.2).

11.9.2 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.

11.10 Definition of End of Trial

The end of trial will be defined as the date when the trial database is locked after completion of the 24-month (corrected for prematurity) follow-up.

12 SAFETY REPORTING

12.1 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.

12.2 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.

12.3 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 12.4.

12.4 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 collected within CRFs for assessment of impact and effectiveness, but will not be expeditely 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) 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 12.4.1). 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.

12.4.1 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 other 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.

12.5 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 Summary of Product Characteristics (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 12.7 below.

12.6 SUSAR Reporting

All SUSARs will be reported by the Sponsor or NPEU CTU delegate to the MHRA and to the REC 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 REC.

12.7 Development Safety Update Reports

As this has been categorised as a Type A study, and is not part of a multi-study development programme, as an alternative to producing a full Development Safety Update Report (DSUR) for the trial, NPEU CTU will use the Health Research Authority's Annual Progress Report (APR) form as is available on the HRA website.

13 STATISTICS

13.1 Sample Size Determination

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 10.4.2) from control to intervention and from intervention to control would require 3,764 babies in total (1,882 per group) (24). 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%) (25). Multiple births will be randomised independently, therefore the impact of correlation of outcomes will have a negligible effect on the sample size (26).

For the key secondary outcome (survival without moderate to severe neurodevelopmental impairment to 24 months of age corrected for prematurity) assuming 13% mortality rate by 24 months corrected age (22, 27) (i.e. 489 deaths) would mean 3,275 (3,764-489) follow-up questionnaires would be sent out to parents. With a loss to follow-up of 15% (28), outcome data would be collected for 3,273 babies, including deaths ((0.85 x 3,275)+489)). With crossover (non-adherence) rates as above, and assuming a control group rate of 73%, approximately 2,537 (3,273/1.29) babies would provide 90% power to detect an absolute risk difference of 6% in moderate to severe neurodevelopmental impairment (from 73% to 67%, or 73% to 79%). The event rate in the control group and 24-month follow-up rate are based on NNRD data and NIHR HTA Speed of Increasing milk Feeds Trial and the PANDA Study (29, 30).

A 6% difference in both the primary and key secondary 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% cross-over (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 10.4.2)

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 × 10,000 / (100 - c)^2
where c is the combined percent crossover in the control and intervention group. (24)

13.2 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.

13.3 Description of Statistical Methods

13.3.1 Descriptive statistics

The flow of participants through each stage of the trial will be summarised by randomised group using a CONSORT diagram (28). 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.

13.3.2 Comparative statistics

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. Centre 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 centre, 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.

13.3.3 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 10.4.2. 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 10.4.1. The sample size calculation has allowed for these potential cross-overs.

13.3.4 Subgroup analysis

The consistency of the treatment effect on the primary outcome 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) will be assessed using the statistical test of interaction.

13.3.5 Level of statistical significance

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

13.3.6 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.

13.4 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.

14 DATA MANAGEMENT

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

14.1 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).

Parent-reported data (for example 24-month study questionnaires) will be considered source data. Source data used by the BERC will also include the summary downloaded from routine data collection sources (BadgerNet or equivalent) providing an outline of the results of the child's two-year follow-up assessment, or a completed proforma based on the National Neonatal Audit Programme (NNAP) form, including any clinic letters related to the 24 month assessment where available.

The majority of trial data will be obtained from routinely recorded clinical data held in the National Neonatal Research Database (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 as trial data; the trial Data Monitoring Plan (DMP) will detail data cleaning processes.

14.2 Access to Data

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

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.

14.3 Data Recording and Record Keeping

The majority of trial-specific data 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. The daily dosing log will be a paper CRF with completed logs entered directly into the secure clinical database. The 24-month parent questionnaire data will be entered into OpenClinica either directly by parents or by the study team from returned paper questionnaires or parents' responses obtained via a telephone call. 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 the participant's name and any other identifiable details. Trial 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 is 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.

15 QUALITY ASSURANCE PROCEDURES

15.1 Risk assessment

The trial 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 trial opens and will be reviewed as necessary over the course of the trial to reflect significant changes to the protocol or outcomes of monitoring activities.

15.2 Monitoring

The Principal Investigator (17) will be responsible for the running of the trial at their site. This will include ensuring successful recruitment, staff education and training, and trial data completeness and quality. The NPEU CTU will develop an appropriate central monitoring plan (MP) for the trial, based on the Risk Assessment (RA) for the trial. This will include central monitoring and on-site monitoring by an appropriately qualified research nurse.

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.

15.3 Trial committees

The trial will be run on a day-to-day basis by the Project Management Group (PMG), which reports to the Trial Steering Committee (TSC), 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 trial will be overseen by a TSC 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 trial recruitment. The chair and members of the TSC will be nominated as per the guidance outlined by the NIHR HTA for their approval. The TSC will aim to meet at least annually.

The TSC will monitor the progress of the trial and its conduct and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carry the responsibility for deciding whether the trial needs to be stopped on grounds of safety or efficacy. Details about the roles, responsibilities and conduct of the committee with be set out in a TSC Charter, which will be agreed at the first meeting.

The DMC members will be independent of the trial team and the TSC, 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 TSC. 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.

The BERC reviewers will comprise of neonatal healthcare professionals who are expert in the fields for which blinded endpoint review data is being collected. The BERC have the role of reviewing and classifying endpoints in a blinded and objective fashion. Please refer to section 11.7 for more detail.

16 PROTOCOL DEVIATIONS

A trial-related deviation is a departure from the ethically approved trial protocol or other trial 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.

17 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 trial 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.

18 ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

18.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

18.3 Approvals

Following Sponsor approval the protocol, participant information sheet 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.

18.4 Reporting

The CI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, HRA (where required), 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.

18.5 Transparency in Research

Prior to the recruitment of the first participant, the trial will have been registered on a publicly accessible database.

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

18.6 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). There has also been overwhelming support from the trial's Parent Advisory Group (PAG). As this study is a CTIMP, 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.

18.7 Participant Confidentiality

The trial 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 trial staff and authorised personnel. The trial staff will safeguard the privacy of participants' personal data.

All 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 trial 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.

18.8 Expenses and Benefits

No financial or material incentive or compensation will be provided to parents for enrolling themselves or their baby in this trial.

19 FINANCE AND INSURANCE

19.1 Funding

This trial is 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.

19.2 Insurance

University of Oxford is the sponsor for the trial. 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.

19.3 Contractual Arrangements

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

20 PUBLICATION POLICY

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

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

Full details of the trial will be made available through the trial website: https://www.npeu.ox.ac.uk/base. The trial will also be registered on a public database. Trial results will also be disseminated 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.

21 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.

22 ARCHIVING

Archiving of research data will follow the completion of the trial 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 will 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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24 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	9th 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 8th 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.

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 V2.0 09Feb2024

Final Audit Report 2024-02-13

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