EVALUATION OF INTRAVENOUS THERAPY IN ASTHMA (EVITA): A RANDOMISED TRIAL OF AMINOPHYLLINE, MAGNESIUM SULFATE OR SALBUTAMOL INTRAVENOUS THERAPY FOR ACUTE SEVERE ASTHMA IN CHILDREN AND YOUNG PEOPLE

PROTOCOL v1.0

DATED 02/07/2025

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator and Co-Leads agree to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and CTR's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

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General Information This protocol describes the EVITA clinical trial and provides information about the procedures for entering participants into the trial. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other patients. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

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Trial Co-ordination:

The EVITA trial is being coordinated by the Centre for Trials Research (CTR) Cardiff University, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

Data management and statistical analysis are being coordinated by the Liverpool Clinical Trials Centre, University of Liverpool, a United Kingdom Clinical Research Collaboration (UKCRC) registered trials unit.

This protocol has been developed by the EVITA Trial Management Group (TMG).

For **all queries,** please contact the EVITA team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator and Co-Leads, or Co-Investigators

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Registration and randomisations:

Patient randomisation for this trial will be through the use of a web-based system:

https://redcap02.lctc.org.uk/EVITA/

Details of how to access the system will be supplied to Investigators as part of the trial set-up.

If any problem with the web-based system or it is unavailable, please contact the trial team:

evita@liverpool.ac.uk (See section 17 for more details).

Serious Adverse Events:

SAE reporting

Where the adverse event meets one of the serious categories, an SAE form should be completed by the

responsible clinician and submitted to CTR Safety team within 24 hours of becoming aware of the event (see section 14).

Serious Adverse Event (SAE) email address:

CTR-Safety@cardiff.ac.uk

Table of Contents

Glossary of abbreviations

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AIM	Acceptability of Intervention Measure
ANCOVA	Analysis of Covariance
AR	Adverse Reaction
ASS	Asthma Severity Score
BNFc	British National Formulary for Children
BTS	British Thoracic Society
CA	Competent Authority
CARRii	Centre for Applied Respiratory Research Innovation & Implementation
C&C	Capacity and Capability
CENTRAL	Cochrane Central Register of Controlled Trials
CF	Consent Form
CFIR	Consolidated Framework for Implementation Research
CHU-9D	Child Health Utility instrument
CI	Chief Investigator
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CONNECT	CONseNt methods in paediatric Emergency and urgent Care Trial
CPAS	Chemotherapy and Pharmacy Advisory Service
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trials Authorisation
CTC	Common Toxicity Criteria
CTIMP	Clinical Trial of Investigational Medicinal Product
CTIS	Clinical Trials Information System
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
CXR	Chest X-ray
CYP	Children and Young People
DDX	Doctors and Dentists Exemption
DH	Department of Health
DNA	Deoxyribonucleic Acid
DSUR	Development Safety Update Report
eCRF	electronic Case Report Form
ED	Emergency Department
eDRIS	Electronic Data Research and Innovation Service
EHR	Electronic Health Records

EMBASE	The Excerpta Medica database
EMEA	European Medicines Agency
EUCTD	European Union Clinical Trials Directive
EudraCT	European Clinical Trials Database
EVITA	Evaluation of Intravenous Therapies for Asthma
FIM	Feasibility of Intervention Measures
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GAPRUKI	General and Adolescent Paediatric Research network in the UK and Ireland
GCP	Good Clinical Practice
GDPR	General Data Protection Regulations
GMP	Good Manufacturing Practice
GP	General Practitioner
GRO	General Register Office
HB	Health Board
HCRW	Health and Care Research Wales
HDU/ICU	High Dependency/ Intensive Care Unit
HE	Health Economics
HiFlo	High flow humidified oxygen
HSCIC	Health and Social Care Information Centre
HTA	Health Technology Assessment
IAM	Intervention Appropriate Measure
IB	Investigator Brochure
IC	Informed consent
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
IU	International Unit
IV	Intravenous
LC-MS/MS	Liquid Chromatography - Tandem Mass Spectrometry
LCTC	Liverpool Clinical Trials Centre
LT	Life threatening
MA	Marketing Authorisation
MedDRA	Medical Dictionary for Regulatory Activities
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHRA	Medicine and Healthcare products Regulatory Agency

MRC	Medical Research Council
NCA	National Competent Authority
NCT	National Clinical Trial
NHS	National Health Service
NHSE	NHS England
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health and Care Research
NIMP	Non-Investigational Medicinal Product
NLI	No Local Investigator
NPSA	National Participant Safety Agency
NPT	Normalization Process Theory
NRR	National Research Register
PCT	Primary Care Trust
PERUKI	Paediatric Emergency Research in the United Kingdom & Ireland
PI	Principal Investigator
PIAG	Participant Information Advisory Group
PIC	Participant Identification Centre
PICANet	Paediatric Intensive Care Audit Network
PICU	Paediatric Intensive Care Unit
PIS	Participant Information Sheet
PLICS	Patient-Level Information and Costing Systems
PPI	Patient and Public Involvement
PROSPERO	Prospective Register of Systematic Reviews
PSS	Personal Social Services
PV	Pharmacovigilance
QA	Quality Assurance
QALY	Quality-adjusted Life Years
QC	Quality control
QL (QoL)	Quality of Life
QP	Qualified Person
R&D	Research and Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RGF	Research Governance Framework for Health and Social Care
RR	Relative risk
RSI	Reference Safety Information
RTQA	Radiotherapy Trials Quality Assurance
SABA	Short acting beta-2 adrenoceptor agonist
SAE	Serious Adverse Event

SAR	Serious Adverse Reaction
SIGN	Scottish Intercollegiate Guidelines Network
SmPC	Summary Product Characteristics
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TSF	Trial Site File
UKCRC	UK Clinical Research Collaboration

1. Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No.	Protocol version no.	Date issued	Summary of changes made since previous version

2. Synopsis

Short title	EValuation of Intravenous Therapies for Asthma trial
Acronym	EVITA
Clinical phase	Phase III
Funder and ref.	NIHR [HTA Programme], NIHR162027
Trial design	Open-label, three arm, individually randomised, parallel group superiority trial
Trial participants	Children and young people (CYP) with an exacerbation of asthma who have not responded to maximal inhaled bronchodilator therapy
Planned sample size	357
Planned number of sites	20
Inclusion criteria	1. CYP aged 2-18 years (up to and including the day prior to 19th birthday). 2. Previous clinical diagnosis of asthma or presenting with acute wheeze which the assessing healthcare professional considers to relate to underlying asthma. 3. Clinically unresponsive to maximal inhaled bronchodilator therapy (this would usually include three back-to-back doses of inhaled high dose salbutamol plus any amount of ipratropium) or is so severe (critical asthma) that IV treatment is needed immediately.
Exclusion criteria	1. Immediate need for invasive ventilatory support. 2. Co-existing long term respiratory conditions (e.g. cystic fibrosis) or requiring long term supplemental oxygen therapy. 3. Known severe renal or liver disease. 4. Uncorrected cyanotic congenital cardiac disease. 5. Known neuromuscular disease. 6. Participants where the use of intravenous (IV) aminophylline, magnesium sulfate or salbutamol would be contraindicated according to the relevant summary of product characteristics (SmPC), including known hypersensitivity or history of severe allergic reaction to any of the trial medications or their excipients. 7. Known previous randomisation into the EVITA trial. 8. Already received IV therapy for an episode of acute asthma during current hospital admission, or within the last 10 days.

	9. Currently receiving regular theophylline or other xanthine medication. 10. Currently receiving beta-blockers. 11. Involved with a trial of a medicinal product within the last three months. 12. Participants or parents/carers request not to be included in the trial.
Treatment duration	Treatment to be continued at the discretion of the treating clinician until no longer clinically indicated as assessed by the investigator.
Follow-up duration	30 days from randomisation (qualitative interview up to 45 days from randomisation)
Planned trial period	01/01/2025 until 31/12/2027
Primary objective	To determine which of IV aminophylline, magnesium sulfate or salbutamol (interventions and comparators) is most effective at treating severe acute asthma unresponsive to maximal inhaled therapy in CYP aged 2-18 years.
Primary economic objective	To determine which IV bronchodilator is most cost-effective.
Secondary objectives	Key secondary objectives are: 1. To determine which IV bronchodilator has the shortest time to discharge from hospital. 2. To determine, using qualitative interviews, questionnaires, avoidance of escalations and adverse events, which IV bronchodilator is most acceptable to patients, parents/carers and healthcare professionals.
Tertiary/Exploratory objectives	1. To determine whether the response to IV salbutamol therapy varies with the serum concentration of salbutamol immediately before IV therapy. 2. To determine if specific genetic polymorphisms can predict response to individual IV bronchodilator therapies. 3. To determine if specific baseline characteristics predict response to each of the three IV bronchodilators. a. frequency of inhaled bronchodilator therapy and systemic corticosteroid therapy pre-randomisation; b. level of maintenance asthma therapy; c. any previous severe asthma exacerbation[1] at any timepoint; d. co-existing atopic disease (e.g. eczema, allergic rhinitis, food allergy); e. eosinophil count.

	4. To determine whether season of presentation effects the outcome. 5. To determine whether inhaled and intravenous salbutamol can give rise to a lactic acidosis.
Primary outcome	Asthma severity score (ASS) two hours after randomisation.
Primary economic outcome	Incremental cost per quality-adjusted life years (QALYs) gained based on an NHS and personal social service (PSS) perspective.
Secondary outcomes	1. Length of stay in hospital (hours) 2. Number of nights in hospital 3. Acceptability of intervention measure 4. Intervention Appropriateness Measure (IAM) 5. Feasibility of Intervention Measure (FIM) 6. Escalation of therapy during the admission (e.g. additional IV bronchodilator, non-invasive or invasive ventilatory support) 7. Admission to high dependency or intensive care 8. Non-invasive ventilation 9. Invasive ventilation 10. Readmission within 30 days 11. Adverse events 12. Health utility based on responses to the CHU-9D and health services utilisation
Tertiary/Exploratory outcome	The primary care secondary outcomes will serve as outcomes for the tertiary/exploratory objectives which focus on serum salbutamol concentration, specific polymorphisms and other patient factors, and season of presentation. Blood gas results (pH, carbon dioxide, lactate) and serum potassium will serve as the outcome for the lactic acid objective.
Investigational medicinal products	1. **Magnesium sulfate**: single IV infusion of 40 mg/kg (max. 2g) over 20 minutes[2]. 2. **Salbutamol**: a single IV infusion of 15 micrograms/kg (max. 250 micrograms) over 5 to 10 minutes, then a continuous infusion of 1 microgram/kg/minute (max. 20 micrograms/minute[3]), continue as clinically indicated[2]. 3. **Aminophylline**: a single IV infusion of 5 mg/kg (max. 500 mg) over 20 minutes, then a continuous infusion of 1 mg/kg/hour (2–11 years) or 0.5 mg/kg/hour (≥12 years) and continue as clinically indicated[2].

3. Trial summary & schema

3.1 Trial schema

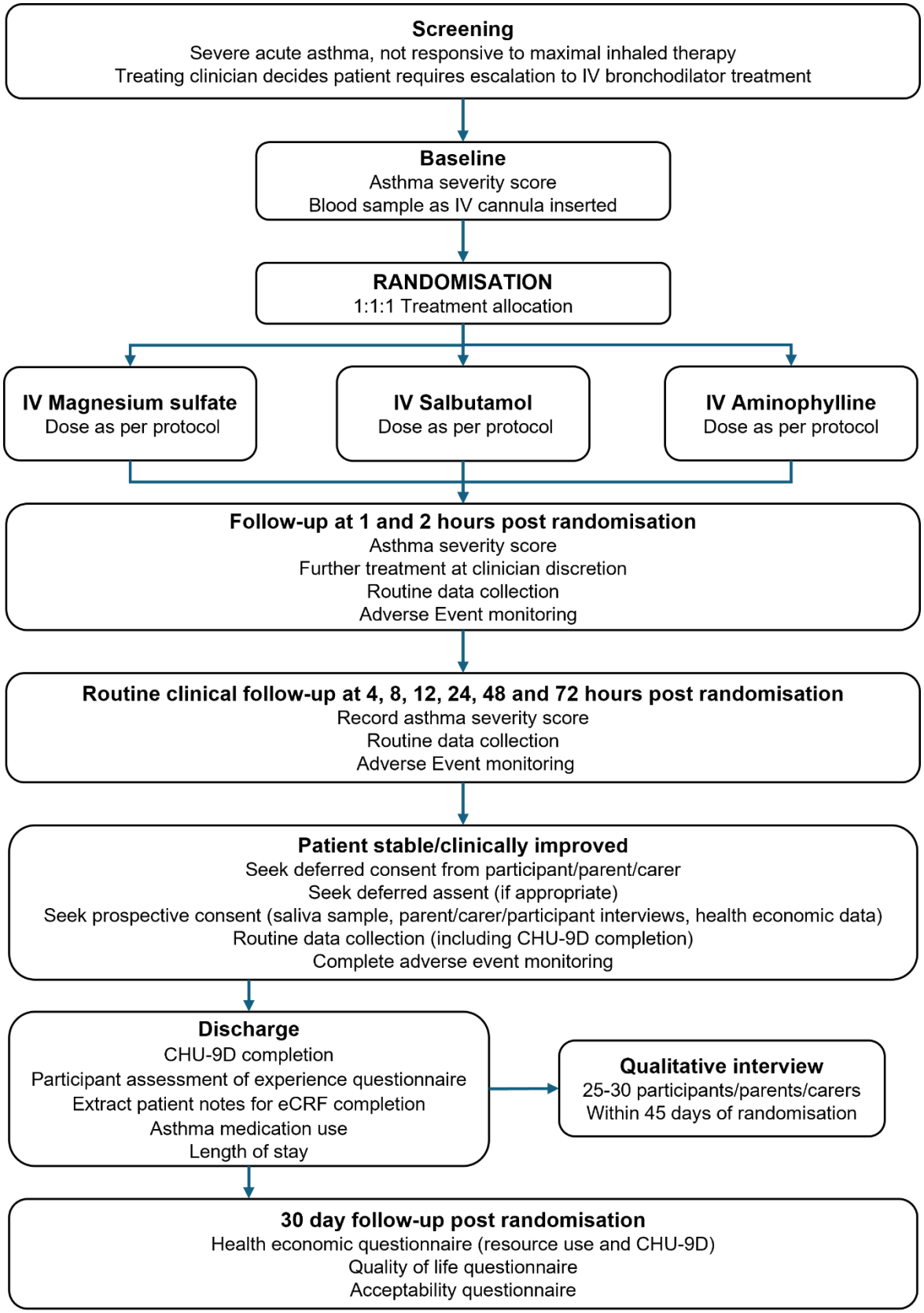

Figure 1. Overview of trial

3.2 Participant flow diagram

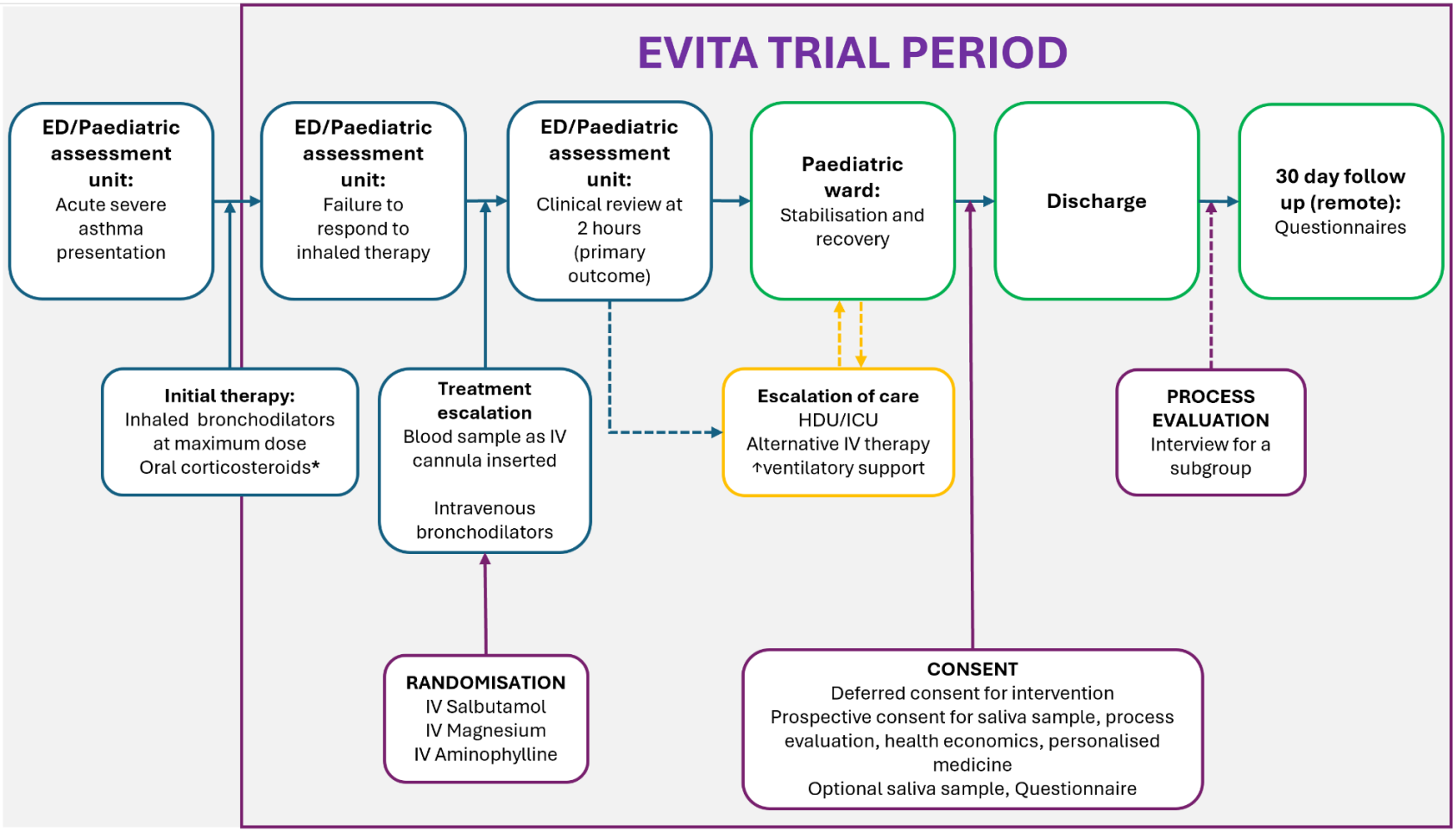

Figure 2. Participant flow diagram

*For patients who are unable to swallow or retain oral treatment, the BTS guideline recommends alternatives such as IV hydrocortisone or intramuscular methylprednisolone. Infrequently some participants may not have been treated with corticosteroids (e.g. young patients with recurrent wheeze where this is not part of the local clinical pathway).

3.3 Trial lay summary

Asthma is a common lung condition that causes breathing problems. People affected may be short of breath and have a tight chest. Asthma attacks may be triggered by infections like colds or allergies such as dust mites. Many children and young people (CYP) have severe asthma attacks which do not respond to inhaled reliever medication. Hospital treatment may be needed with medication given as an injection into a vein. Three medications are currently used in the UK: aminophylline, magnesium sulfate or salbutamol. Although all three medications are highly effective at treating asthma attacks when given as an injection, doctors are not sure which works the best. Severe asthma attacks in CYP are a common medical emergency so it is important that doctors use the most effective and most acceptable injection treatments for CYP in hospital.

The EVITA trial will compare the three medications (aminophylline, magnesium sulfate or salbutamol) given as an injection and determine which is best at treating severe asthma attacks in CYP. The trial will be led by experts, who work in children's asthma care, who will compare the medications by looking at how acceptable each treatment is to patients, their families and healthcare professionals, and which gives the best value for money to the NHS.

All trial participants will be having a severe asthma attack and not getting better with inhaled medications so will be classed as a medical emergency. For this reason, there will be no time to delay treatment by asking for consent. All eligible patients will be entered into the trial upon assessment of their condition. We will request consent for continuation in the trial from parents and then CYP, once their asthma has improved. This is called 'research with deferred consent'. Everyone taking part in the research trial will have an equal chance of receiving one of the three medications. All the participants and their trial teams will know which treatment they have been given within the trial. Overall, we aim to recruit 357 CYP (aged 2-18 years) from UK hospitals.

To see which treatment works best we will look at several results. We will see which children are getting better more quickly by using a validated asthma severity score. This is based on ratings made by doctors and nurses such as heart rate. We will measure how long CYP stay in hospital and compare the side effects of each treatment. Some patients, parents and healthcare staff will be interviewed to understand how they feel about the treatment they received. We will also collect data on the costs of treatment, to allow us to see which treatment delivers the best value for money in the NHS.

We have designed this trial with two patient and public involvement (PPI) groups that include parents and CYP: Centre for Applied Respiratory Research Innovation & Implementation (CARRii) and The Asthma + Lung UK expert patient panel. The PPI groups will be involved in our trial meetings to help develop the trial documents, make decisions on how the research is run and advise how the research results should be shared with patients and the public.

4 Background

4.1 Acute severe asthma in children and young people

Asthma is the most common long-term condition in UK CYP affecting about 1.5 million people[4]. Despite modern therapy, many CYP have asthma exacerbations which can be fatal[5,6]. Asthma

affects the whole family and in 2016 cost the NHS over a billion pounds[7]. The UK is a concerning outlier in Western Europe with 0.3 asthma deaths annually per 100,000 in young people[8,9].

An asthma exacerbation is an acute worsening of symptoms, usually characterised by shortness of breath, wheezing and chest tightness. Exacerbations are usually triggered by viruses, allergens and/or irritants[10] and asthma exacerbations are one of the key causes for admission of CYP to hospital[11]. An acute exacerbation is treated with a high dose inhaled bronchodilator and oral corticosteroids[12]. But in a fifth of presentations, these treatments fail and intravenous (IV) bronchodilator therapy is required[13]. Although children under 6 years of age may have acute wheeze without a diagnostic label of asthma, clinicians manage these children in the same way.

IV aminophylline, magnesium sulfate or salbutamol are three options that are identified for treating severe acute asthma by the UK national guideline[12]. They are recommended for the management of acute severe asthma in children and young people by the SIGN/BTS British guideline on the management of asthma[12].

However, there is no preference recommendation as comparative-effectiveness data are too limited[14]. Consequently, there is wide variation in practice and two or more are frequently prescribed. A prospective UK study found that of the CYP needing IV bronchodilators during a 10-week period in 2013, 61% received magnesium sulfate, 56% salbutamol and 47% aminophylline[15]. Patients with severe asthma require admission, often for a few days - 60% needed high dependency and 8% intensive care in the UK prospective series[15].

There are multiple ways of assessing asthma severity with different advantages and disadvantages[16]. In clinical practice, healthcare professionals focus on clinical parameters (e.g. wheeze, effort of breathing, heart and respiratory rate) and oxygen saturation in air to dictate therapy[12]. As part of the development of this protocol, a survey of 106 members of the paediatric emergency and general paediatric research networks (PERUKI and GAPRUKI respectively) was undertaken in 2023. Respondents prioritised a severity score, length of stay, quality of life and adverse effects. In our preparatory work for this trial, members of the Asthma+Lung UK expert patient group (7 adults) and CARRii PPI group felt that response to therapy and acceptability (including adverse effects) were the most important outcomes.

The Asthma Severity Score (ASS) combines wheeze, accessory muscle use and heart rate[17]. It is validated[17-19]; and applies a numerical score to routine clinical observations that reflect severity making it relatively objective, clinically relevant and easy to implement. It requires fewer contributing descriptors than equivalent scores and is known to discriminate between IV bronchodilators (Table 1)[20]. It was successfully used in the severe acute asthma MAGNETIC trial[21]. Other ways of assessing asthma focus on therapeutic needs (e.g. oxygen therapy, non-invasive ventilation) or healthcare utilisation (e.g. high dependency care, intensive care).

4.2 Summary of findings from clinical trials that are relevant to the trial

A recent overview of Cochrane reviews of acute exacerbation of childhood asthma included 13 reviews (67 trials)[22]. Methodological issues with aminophylline and salbutamol trials are limitations, with most being over 20 years old. Additionally, most studies were undertaken on paediatric wards or intensive care units; while most patients with acute severe asthma are

managed in the emergency department (ED)[23]. Only IV magnesium sulfate significantly reduced hospital stay and frequency of serious adverse events compared to standard care. Additionally, there is only one head-to-head trial[9]. It was an open label trial comparing aminophylline, magnesium sulfate and terbutaline (not salbutamol) that only enrolled 100 CYP and so was underpowered for clinical important differences. The trial demonstrated that the asthma severity score dropped more rapidly with magnesium sulfate.

Powell et al. has undertaken a series of World Health Organisation funded systematic reviews on managing paediatric severe acute asthma[14,20,24,25]. The reviews have used a standard systematic review approach and are registered with the Prospective Register of Systematic Reviews (PROSPERO). In brief, MEDLINE, EMBASE, CINAHL and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to 12th April 2023. References were searched for missing publications; www.clinicaltrials.gov and www.controlled-trials.com were also searched for unpublished ongoing clinical trials. Only randomised controlled trials were included. The results of the systematic reviews are summarised in Table 1. Most studies compared individual IV bronchodilators with a control. There were only four head-to-head comparisons for the three IV bronchodilators of interest. Severity scores were better with magnesium than aminophylline[26] and IV short acting beta-2 agonist (SABA) was better than control[20]. Aminophylline reduced duration of hospital stay compared to IV salbutamol bolus in one trial[27] and IV SABA reduced it compared to control in another[20]. Only IV SABA reduced the duration of supplementary oxygen[20]. In conclusion, these new systematic reviews demonstrate that there is some high certainty evidence for clinical benefit of individual IV bronchodilators compared to control. They also suggest that asthma severity scores and duration of hospitalisation may differentiate interventions. However, the head-to-head evidence was of low certainty, emphasising the need for a large head-to-head trial of IV aminophylline, magnesium sulfate and salbutamol[28].

Evidence on cost-effectiveness for paediatric severe acute asthma is limited to an economic evaluation alongside the MAGNETIC trial. This indicated that additional therapy with nebulised magnesium sulfate had a 75% percent probability of being cost-effective at a £1,000 per unit decrease in ASS score[29].

There are three ongoing trials assessing the effectiveness of IV bronchodilators in severe acute asthma; the first two are focused on IV magnesium[30,31], the third is comparing IV magnesium with IV aminophylline[32] (www.clinicaltrials.gov, www.controlled-trials.com and WHO International Clinical Trials Registry Platform, searched 7th April 2025).

The survey we conducted in 2023 as part of the development of this protocol, including 106 UK paediatricians from the PERUKI and GAPRUKI networks, found that 91% initially use IV magnesium sulfate to treat CYP with severe acute asthma. This is confirmed by our additional survey of 13 paediatric emergency departments with salbutamol and aminophylline being second line therapy for different units. However, 86% of paediatricians reported being willing to randomise a patient to any of the three bronchodilators.

Table 1. Summary of the Powell *et al* systematic reviews focusing on IV aminophylline, magnesium sulfate and salbutamol

	IV SABA vs control	**IV Aminophylline vs control**	**IV Magnesium vs control**	**Individual bronchodilator vs other bronchodilator**
PROSPERO	CRD42023405119[24]	CRD42023405234[24]	CRD42023405261[25]	CRD42023405226[14]
Studies included	Four RCTs, n=183. Salbutamol bolus (N=3), terbutaline infusion (N=1). Only 2 at low risk of bias.	Nine RCTs, n=464. Only 2 were at low risk of bias for all areas.	Nine RCTS, n=473. Only 2 were at low risk of bias for all areas.	31 RCTs, n=1684, only four compared two or more of the three bronchodilators. Half were at low risk of bias for all areas.
Asthma severity scores	**Greater improvement** for IV SABA but unable to meta-analyse.	No difference at 24 hours (0.13 units, 95% CI -0.79 to 1.06, I^2= 0, n= 78, N=2), high certainty of evidence.	No difference (-0.18 units, 95% CI -1.35 to 0.98, I^2 1.9%, n=115, N=2), high certainty evidence.	Kassisse 2021:[26] Magnesium associated with **better score** compared to aminophylline (3.70 units, 95% CI 2.79 to 4.61). Roberts 2003,[27] Wheeler 2005[33]: No difference between salbutamol and aminophylline (0.00 units, 95% CI -0.88 to 0.88, I^2 51%, n=73, N=2).
Duration hospital stay	**Reduced duration** for IV SABA (-23.45 hours, 95% CI -36.09 to -10.81, I^2 0%, n= 153, N=3, high certainty evidence.	No difference (-3.62 hours, 95% CI -13.05 to 5.82, I^2 31%, n= 154, N=4), moderate certainty of evidence.	No difference (-78.86 hours, 95% CI -200.37 to 42.66, I^2 99%, n=284, N=4), low certainty.	Roberts 2003[27]: Shorter duration for aminophylline compared to salbutamol bolus group (-28.10 hours, 95% CI -58.86 to 2.66). Santana 2001[34]: No difference in duration for SABA compared to magnesium (-35.28 hours, 95% CI -80.50 to 9.94, n=34).
Supplementary oxygen duration	**Reduced need** for O_2 with IV SABA (RR 0.26, 95% CI 0.11 to 0.61, I^2 0%, n=74, N=2)	No difference in duration of oxygen therapy (-1.90 hours, 95% CI, -4.37 to 0.57, n=60, n=2).	No difference in duration of O_2 (1.78 hours, 95% CI -12.75 to 9.19, I2 0%, n=94, N=2), moderate certainty.	
Mechanical ventilation or intensive care	No difference but unable to meta-analyse.		No difference in invasive mechanical ventilation (RR 0.35, 95% CI 0.11 to 1.17, I^2 0%, n=237, N=3), moderate certainty.	Kassisse 2021[26]: Aminophylline and magnesium had similar need for intensive care (RR 1.41, 95% CI 95% 0.47 to 4.26). Santana 2001[34]: No difference in invasive ventilation for SABA compared to magnesium (RR 0.2, 95% CI 0.01 to 3.88, n=34).

CI: confidence interval; I^2: heterogeneity

4.3 Summary of the known and potential risks and benefits to human participants

Intravenous aminophylline, magnesium sulfate and salbutamol have been in routine clinical use for the treatment of acute severe asthma in childhood for many years. Clinicians considering them to be effective, although the evidence (summarised above) is relatively sparce. Additionally, for all their benefits are considered to outweigh their risks.

Adverse events (AEs) associated with IV aminophylline are usually related to gastrointestinal irritation (e.g. nausea, vomiting, abdominal pain, diarrhoea, gastro-oesophageal reflux, gastrointestinal bleeding). If injection is too rapid, central nervous system and cardiovascular system compromise can be seen with hypotension, arrhythmias and convulsions. Hypersensitivity reactions, hypokalaemia, hypophosphataemia, and hyponatraemia may occur. Use of concomitant theophylline therapies (uncommon at this age) when additional aminophylline is provided could compound these potential risks; for this reason use of theophylline is an exclusion criteria.

Two Cochrane reviews evaluating intravenous magnesium sulfate for the treatment of acute asthma in children and adults noted that side effects and adverse events were inconsistently reported across published studies. The most commonly observed adverse effects were dose-related skin flushing, fatigue, nausea, and rate-related hypotension and vasodilation[35,36]. Excessive administration of IV magnesium sulfate leads to the development of hypermagnesaemia. However, the administration of magnesium sulfate as an IV bolus therapy using British National Formulary for Children (BNFc) doses makes significant hypermagnesaemia highly unlikely.

Common risks associated with IV salbutamol are tremor, headache, tachycardia, muscle cramps, hypokalaemia and palpitations. Less common risks are hyperglycaemia, cardiac arrhythmias (e.g. atrial fibrillation, supraventricular tachycardia and extrasystoles) and hypotension. Rare risks would be hypersensitivity reactions. Lactic acidosis is often cited as a risk but it is unclear whether or not this is related to IV salbutamol. A low infusion rate of 1 microgram/kg/minute (max. 20 micrograms/minute) has been chosen to minimise the risk of adverse effects.

In practice, the only adverse effects seen in clinical practice with children and young people are minor gastrointestinal irritation with IV aminophylline and tremor with IV salbutamol at higher infused rates. So the potential benefits of each of these IV bronchodilators outweigh their potential risks.

4.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period

This is a pragmatic trial aiming to compare three IV bronchodilators that are routinely used to manage children and young people with acute severe asthma. All three IMPs are products with marketing authorisations in the UK and are commonly used on-label and off-label for acute severe asthma, with doses provided for this indication within the BNFc. Therefore, the standard BNFc doses will be used[2].

4.5 Rationale for current trial/Justification of Treatment Options

IV aminophylline, magnesium sulfate or salbutamol are three options that are identified for treating severe acute asthma by the UK national guideline[12] but the current trial evidence base

is characterised by small trials meaning that it is unclear to as which agent is the most effective in this clinical situation. The Scottish Intercollegiate Guidelines Network / British Thoracic Society (SIGN/BTS) asthma guideline describes without preference the use of IV aminophylline, magnesium sulfate and salbutamol for severe acute asthma[12]. Unsurprisingly, professionals use any or a combination[15].

Furthermore, asthma outcomes have not improved since the 2014 Royal College of Physicians review into asthma deaths[37]. Both PERUKI[38] and GAPRUKI[39] in their research prioritisation exercises have identified IV treatment for acute severe asthma as a high priority for UK paediatricians.

Therefore, the EVITA trial will compare the three IV bronchodilators in CYP with severe acute asthma who are unresponsive to maximal inhaled therapy to assess their clinical relative effectiveness in a multicentre clinical trial. Cost-effectiveness and acceptability to patients, families and healthcare professionals will also be assessed to inform future evidence based clinical guidelines.

5. Trial objectives/endpoints and outcome measures

We propose to test the following objectives:

Table 2: Objectives and outcome measures

	Objectives	Outcome measures
Primary	To determine which of IV aminophylline, magnesium sulfate or salbutamol (interventions and comparators) is most effective at treating severe acute asthma unresponsive to maximal inhaled therapy in CYP aged 2-18 years.	Asthma severity score (ASS) two hours after randomisation.
Primary economic	To determine which IV bronchodilator is most cost-effective.	Incremental cost per quality-adjusted life years (QALYs) gained based on an NHS and personal social service (PSS) perspective.
Key secondary	To determine which IV bronchodilator has the shortest time to discharge from hospital.	• Length of stay in hospital (hours) • Number of nights in hospital
	To determine, using qualitative interviews, questionnaires, avoidance of escalations and adverse events, which IV bronchodilator is most acceptable to patients, parents/carers and healthcare professionals	• Acceptability of intervention measure (AIM) • Intervention Appropriateness Measure (IAM) • Feasibility of Intervention Measure (FIM) • Escalation of therapy during the admission (e.g. additional IV

		bronchodilator, non-invasive or invasive ventilatory support) • Admission to high dependency or intensive care • Non-invasive ventilation • Invasive ventilation • Readmission within 30 days • Adverse events • Health utility based on responses to the CHU-9D
Tertiary/ Exploratory	To determine whether the response to IV salbutamol therapy varies with the serum concentration of salbutamol immediately before IV therapy.	Outcomes as above.
	To determine if specific genetic polymorphisms can predict response to individual IV bronchodilator therapies.	
	To determine if specific patient baseline characteristics predict response to each of the three IV bronchodilators, e.g. a. frequency of inhaled bronchodilator therapy and systemic corticosteroid therapy pre-randomisation b. level of maintenance asthma therapy c. previous severe asthma exacerbation[1] at any timepoint d. co-existing atopic disease (e.g. eczema, allergic rhinitis, food allergy) e. eosinophil count.	
	To determine whether season of presentation effects the outcome	
	To determine whether inhaled and intravenous salbutamol	Blood gas results (pH, carbon dioxide, lactate) and serum potassium

	can give rise to a lactic acidosis.	

6. Trial design and setting

EVITA is a multicentre, open-label, phase III, three arm, individually randomised, parallel group trial. An internal pilot is included in the trial design following 9 months of recruitment. Participants will be randomised to one of three IV bronchodilators in a ratio of 1:1:1.

The trial setting is 20 acute hospital sites across all four UK countries that manage CYP with acute severe asthma. Depending on the site, this may be an emergency department or acute assessment unit. Sites will be selected to include areas where NHS Digital practice disease registers suggest that asthma is particularly prevalent and centres with populations that have previously been underrepresented in respiratory research. Selected sites will have a good track record of recruiting emergency department patients, particularly from diverse backgrounds.

6.1 Risk assessment

A Trial Risk Assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as a TYPE A, where the level of risk is no higher than the risk of standard medical care. A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 24.1).

6.1.1 Risk assessment of IV bronchodilators

In summary, aminophylline, magnesium sulfate, and salbutamol IV infusion are treatment options in standard medical care for children with acute severe asthma who have not responded to initial inhaled bronchodilators therapy and steroids. All IMPs used within this trial have marketing authorisations in the UK for children in this age group and both salbutamol and aminophylline will be used within the authorised therapeutic indications. Aminophylline and salbutamol IV infusions are authorised in the UK for the treatment of acute severe bronchospasm in children over 6 months and 12 years, respectively. The use of magnesium sulfate IV infusion for the treatment of acute severe asthma is considered off-label use (the primary indication in children is hypomagnesemia) but it has common use for acute severe asthma and forms part of national guidelines for treatment of acute severe asthma symptoms[12] with inclusion in the BNFc from 2 years of age under for this indication[2], the age range for inclusion within this trial.

The use of these three drugs for children with acute severe asthma is supported by national clinical guideline[12]. Based on supporting evidence, the Scottish Intercollegiate Guidelines Network (SIGN) and British Thoracic Society (BTS) recommend all three interventions as treatment options for children above 2 years of age who have not responded to initial inhaled bronchodilators therapy and steroids. The doses used in EVITA are in line with the recommendations of this guideline and the BNFc 2024. EVITA is a comparative clinical trial of these three drugs with collection of efficacy and safety data and additional monitoring.

Thus, all IMPs will be dispensed in accordance with a prescription, and trial specific labelling will not be required in line with a risk proportionate approach. Local stock and prescriptions will be used, and IMP storage and accountability will be in line with routine clinical practice.

7 Site and Investigator selection

This trial will be carried out at participating sites within the UK. All sites who are interested in participating in the trial will be required to complete a registration form to confirm that they have adequate resources and experience to conduct the trial.

Before any site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the EVITA Trial email account (EVITA@cardiff.ac.uk):

1. Confirmation of Capacity and Capability (C&C) from R&D department following sharing of local information pack.
2. A signed Trial Site Agreement (including MTA) (PI, sponsor and site signatures)
3. Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
4. Completed Site Delegation Log and Roles and Responsibilities document
5. Full contact details for all host care organisation personnel involved, indicating preferred contact
6. A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper
7. A set of laboratory normal ranges and laboratory certification/accreditation from the host care organisation laboratory being used for analyses
8. Returned Source Data Checklist signed by the PI
9. Pharmacy confirmation that all three IMPs are available as stock where trial participants will be treated.

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator/lead Research Nurse detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive sample equipment and a trial pack holding all the documents required to recruit into the Trial.

Occasionally during the trial, amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become

available. It is the responsibility of the CTR to ensure that they obtain local R&D approval for the new documents.

All documentation must be stored in the Investigator Site File (ISF) at the site and in the Trial Site File (TSF) at the CTR. The CTR must be notified of any changes to the trial personnel and their responsibilities during the running of the trial and the respective trial files must contain this up-to date information.

Site initiation will be by videoconference.

8 Participant selection

Participants are eligible for the trial if they meet all the following inclusion criteria and none of the exclusion criteria apply. The eligibility criteria are designed to be pragmatic so that they encompass almost every patient with asthma who healthcare professionals would treat with an IV bronchodilator.

8.1 Inclusion criteria

The participant must satisfy **all** the following criteria to be eligible for the trial:

1. CYP aged 2-18 years (up to and including the day prior to 19th birthday).
2. Previous clinical diagnosis of asthma or presenting with acute wheeze which the assessing healthcare professional considers to relate to underlying asthma.
3. Clinically unresponsive to maximal inhaled bronchodilator therapy (this would usually include three back-to-back doses of inhaled high dose salbutamol plus any amount of ipratropium) or is so severe (critical asthma) that IV treatment is needed immediately.

8.2 Exclusion criteria

The participant may not enter the trial if **any** of the following apply:

1. Immediate need for invasive ventilatory support.
2. Co-existing long term respiratory conditions (e.g. cystic fibrosis) or requiring long term supplemental oxygen therapy.
3. Known severe renal or liver disease.
4. Uncorrected cyanotic congenital cardiac disease.
5. Known significant neuromuscular disease.
6. Participants where the use of intravenous (IV) aminophylline, magnesium sulfate or salbutamol would be contraindicated according to the relevant summary of product characteristics (SmPC), including known hypersensitivity or history of severe allergic reaction to any of the trial medications or their excipients.
7. Known previous randomisation into the EVITA trial.

8. Already received IV therapy for an episode of acute asthma during current hospital admission, or within the last 10 days.

9. Currently receiving regular theophylline or other xanthine medication.

10. Currently receiving beta-blockers.

11. Involved with a trial of a medicinal product within the last three months.

12. Participants or parents/carers request not to be included in the trial.

9 Recruitment, Screening and registration

9.1 Participant identification

Participants will be identified by the treating clinical team at recruiting sites. Participants will include patients with severe acute asthma, not responsive to maximal inhaled therapy where the treating clinician decides the patient requires escalation to IV bronchodilator treatment is needed.

The eligibility checklist should be completed prior to randomisation by the investigator or clinical designee listed on the trial delegation log and recorded in the patient notes.

9.2 Screening logs

Details of all eligible but not recruited patients (without identifiable information) will be entered into the trial database with reason for non-enrolment. This will allow any biases from differential recruitment to be detected.

9.3 Recruitment rates

A total of 357 participants aged 2-18 years at an expected average rate of 1 participant per month per site, although there will likely be seasonal variation. Taking this into account in our projections, recruitment is expected to take 2 years with 6 months for set up and a further 6 months for analysis and reporting and dissemination.

9.4 Informed consent

The EVITA trial uses a deferred consent approach. This adheres to the deferred consent criteria set out by the CONseNt methods in paediatric Emergency and urgent Care Trial (CONNECT) Advisory Group[40]. Consent and assent will be sought at the earliest appropriate opportunity by an experienced delegated member of the research delivery team. This approach is now widely accepted in the context of CTIMP trials addressing treatment in emergency situations.

Informed consent will be received for participants under 16 years from a parent/legal guardian with parental responsibility, and assent received in addition from children 7 years and over where appropriate. CYP 16 years and over will be approached for consent once their condition has stabilised and they are able to give informed consent.

The participant's/parent's/legal guardian's written informed consent must be obtained using the trial Consent Form, which follows the Participant Information Sheet. As the patient will

have already received the trial intervention, consent will be for them to continue in the trial. The participant should be given sufficient time after the initial invitation to continue before being asked to sign the Consent Form. Optional consent will also be requested for genotyping and qualitative interviews so must be obtained prior to the participant undergoing these trial procedures. Consent may be taken by a delegated member of the research delivery team (research nurse, clinical research fellow, clinical team member).

Where a participant has learning disabilities, there would be an option to use the appropriate approach and information sheets for them. Additionally, we have developed a video to explain the trial which will be available for participants with learning disabilities as well as for parents/carers with reading difficulties. This approach was successfully used in the HiFlo feasibility trial[41].

It is likely that consent will be requested prior to a patient's discharge from hospital. If, in the unusual circumstance this does not happen, the patient/parent/legal guardian would be contacted within 5 working days of randomisation by a delegated member of the research team and informed of the patient's involvement and details of the trial. Written information and a consent form can then be posted with a covering letter indicating their consent for use of the data already collected and continued participation in trial follow-up. The delegated member of the research team will attempt to contact the patient/parent/legal guardian up to three times and there would be a possibility for the patient/parent/legal guardian to give verbal consent over the phone. If the patient/parent/legal guardian is not contactable, anonymised patient data will be used up to that point.

If the patient unfortunately dies before consent is sought, the site research team will obtain information from colleagues and bereavement counsellors to establish the most appropriate time and the most appropriate practitioner to notify the parents/legal representative of their child's involvement in the trial. The use of anonymous data from deceased persons is lawful and consent is not legally required from the person before they die or from a nominated representative. However, if it is not considered appropriate to notify the family prior to leaving the hospital, a personalised letter and written information about the trial would be given to the family within 4 weeks of randomisation ideally by a practitioner who knows the family including the details of the trial team if they have further questions.

A patient is only considered to be a trial participant when written informed consent has been obtained from the participant/parent/legal guardian (with the specific two exceptions in the two above paragraphs). One copy of the consent form should be given to the participant, but the original copy should be kept in the investigator site file and a further copy should be kept with participant's hospital notes.

The right of the participant to refuse to participate in the trial without giving reasons must be respected, although it can be helpful if a reason is provided so the investigator should respectfully query this. If the patient declines consent, anonymised patient data collected up to that point will be used.

After the participant has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according

to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

9.5 Registration and Randomisation

Once patients are identified and eligibility criteria have been fulfilled (full eligibility confirmed by a medically qualified person) they can be randomised via a secure (24-hour) web-based randomisation system controlled centrally by the LCTC to receive one of the following:

- Arm 1: IV aminophylline
- Arm 2: IV magnesium sulfate
- Arm 3: IV salbutamol

Following randomisation, patients will be assigned a unique trial ID

A personal login username and password, provided by the LCTC will be required to access the randomisation system. Designated research staff will be issued with their personal login and password upon completion of training in the use of the system.

The trial will be unblinded and therefore both the participant and the site research team will know the treatment allocation. The trial pharmacist, research nurse and laboratory team will be notified of the randomisation allocation and trial ID number. A copy of the Randomisation Confirmation, signed Informed Consent Form, and Eligibility Checklist should be filed within the Investigator Site File.

Registration and Randomisation

Patient Randomisation for this trial will be through the use of a web-based system:

https://redcap02.lctc.org.uk/EVITA/

Details of how to access the system will be supplied to Investigators as part of the trial set-up.

If any problem with the web-based system or it is unavailable, please contact the trial team:

evita@liverpool.ac.uk (See section 17 for more details).

In the event of a randomisation system failure, the site should contact the trial co-ordinator (Monday to Friday between 9:00 to 17:00 excluding bank holidays and University closure days) to try to resolve the problem.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Due to time constraints of managing a severe asthma attack in CYP (see section 9.1), patients will be randomised into the trial prior to consent being obtained. Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial.

If a participant provides deferred consent but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from.

These aspects could be:

- Partial withdrawal from further data collection (questionnaires, clinical assessments)
- Complete withdrawal from further data collection
- Withdrawal from samples (Blood and/or saliva)

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal. The use of the data collected prior to withdrawal of consent is based on informed consent before its withdrawal.

Furthermore, it is important to collect safety data ongoing at the time of withdrawal, especially if the participant withdraws because of a safety event.

For participants who consent and subsequently withdraw their consent for use of samples, the Withdrawal of Consent Form should be completed by the participant and signed by both the participant and the PI or a member of the trial team who has been delegated by the PI to undertake this activity. One copy of the Withdrawal of Consent Form will be given to the participant, the original copy will be kept in the ISF, and a further copy will be kept with the participant's hospital notes.

Completed participant withdrawal forms should not be sent to the CTR, since they will contain participant identifiable information. The participating site should advise the CTR of this withdrawal by completing the relevant Withdrawal form on the database.

Any queries relating to potential withdrawal of a participant should be forwarded to EVITA@cardiff.ac.uk.

10.2 Lost to follow up

Participants will be identified as lost to follow up if it is not possible to contact them directly for 30 day follow up (+ 10 days). Before then, trial data will be collected from routine clinical data. Hospital records will be checked to ensure that they have not been re-admitted with asthma in the planned follow up period.

Every effort will be made to obtain follow-up information on these patients, unless they have completely withdrawn from the trial.

11 Trial Intervention

This is an open-label comparative trial of IV aminophylline, magnesium sulfate and salbutamol.

11.1 Treatments

The investigational medicinal products (IMPs) for this trial are provided in Table 3. Participants will be randomised to one of three IV bronchodilators: aminophylline, magnesium sulfate or salbutamol. Product details are provided in their Summary of Product Characteristics (SmPCs).

Table 3: Identification of investigational medicinal products

Drug	Aminophylline	Magnesium sulfate	Salbutamol
IMP or NIMP	IMP	IMP	IMP
Description of active substance	Chemical origin	Chemical origin	Chemical origin
Mechanism of action	Relaxation of smooth muscle and relieve bronchial spasm through phosphodiesterase inhibition, adenosine receptor antagonism, and histone deacetylase activation	Blocks calcium channel of the airway, leading to bronchodilation	Acts on the beta-2 adrenoceptors of the airway, lead to bronchodilation
Pharmaceutical form	Solution for injection/infusion	Solution for injection/infusion	Solution for injection/infusion
Concentration	The use of any concentrations with a UK marketing authorisation is permitted.	The use of any concentrations with a UK marketing authorisation is permitted.	The use of any concentrations with a UK marketing authorisation is permitted.
Brand	The use of any brands with a UK marketing authorisation is permitted	The use of any brands with a UK marketing authorisation is permitted	The use of any brands with a UK marketing authorisation is permitted
Packaging	No modification or re-packaging	No modification or re-packaging	No modification or re-packaging
Labelling	No clinical trial labelling (see risk assessment)	No clinical trial labelling (see risk assessment)	No clinical trial labelling (see risk assessment)
Sourcing	Local hospital stock	Local hospital stock	Local hospital stock

IMP=investigational medicinal product; NIMP=non-investigational medicinal product

11.2 Treatment supply and storage

All IMPs will be supplied by the trial site from their local hospital stock. Temperature monitoring of IMP storage area will be in line with standard clinical practice and the IMPs should be stored as specified within their SmPC.

11.3 Treatment prescribing and dispensing

The investigator or the investigator's designee will prescribe the treatment, as per randomisation assignment, on the participant's medical records (i.e. paper or electronic prescribing systems).

11.4 Dosing schedule

The dose and dosing schedule for participants in this trial is provided in Table 4.

IMP will be administered at the trial site under medical supervision by qualified healthcare personnel. The date, time and amount of IMP administered should be clearly documented within the eCRF.

The participants' body weight should be measured to calculate the assigned treatment dose. Where this is not clinically possible, an estimated body weight can be used, and this should be clearly documented.

Table 4: Dosing information of IMPs

Drug	**Aminophylline**	**Magnesium sulfate**	**Salbutamol**
Route of administration	Intravenous	Intravenous	Intravenous
Dose and dosing schedule	5 mg/kg (max. 500 mg) over 20 minutes, followed by a continuous infusion of: 2–11 year: 1 mg/kg/hour ≥12 year: 0.5 mg/kg/hour Infusion to be continued as clinically indicated.	40 mg/kg (max. 2g) over 20 minutes	15 micrograms/kg (max. 250 micrograms) over 5 to 10 minutes, followed by a continuous infusion of: 1 microgram/kg/minute (max. 20 micrograms/minute) Infusion to be continued as clinically indicated.
Dose adjustment	Infusion rate can be reduced or stopped for the management of adverse effects or, where possible, a failure to respond at any time. If possible, any dose adjustments should be after two hours of therapy with the trial IV bronchodilator. If treatment escalation is necessary with participants randomised to salbutamol in the first 2 hours, the investigator should, if possible, increase the dose before escalating to additional treatment. The need for additional treatment is at the discretion of the treating clinician.		
Duration	Treatment to be continued at the discretion of the treating clinician until no longer clinically indicated as assessed by the investigator.		
Preparation	Refer to the UK NHS injectable medicines guide (Medusa), the IMPs SmPC and local guidance.		

11.5 Dose modification for toxicity

Therapeutic drug monitoring is recommended for patients randomised to aminophylline and this should follow local clinical practice. The BNF for children recommends that aminophylline is monitored therapeutically in terms of plasma-theophylline concentrations with a blood sample taken 4–6 hours after starting treatment[2] In most individuals, a plasma-theophylline concentration of 10–20 mg/litre (55–110 micromol/litre) is required for satisfactory bronchodilation, although a lower plasma-theophylline concentration of 5–15 mg/litre may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase at concentrations above 20 mg/litre.

Therapeutic drug monitoring is not recommended for IV magnesium sulfate nor salbutamol. At any time, infusion rate of any of the three trial interventions can be reduced or stopped for the management of adverse effects at the discretion of the investigator. The reason for any change should be documented.

11.6 Management of toxicity and hypersensitivity reactions

If signs or symptoms of an infusion-related hypersensitivity reaction are observed during the administration of the IMP, it should be immediately discontinued, and the participant treated as medically appropriate. If signs or symptoms of other infusion-related reactions (see Section 4.3) are observed, consideration should be given to reducing or stopping or reducing the infusion with appropriate monitoring.

11.7 Failure to respond to IV aminophylline, Magnesium sulfate or Salbutamol

A failure to respond to the trial IV bronchodilator may involve:

- Deterioration in clinical status, e.g. significant worsening of airway obstruction (air entry), tachycardia or oxygenation;
- No significant change in clinical status, e.g. similar airway obstruction (air entry), tachycardia and oxygenation over a period of time may require an alternative approach. Clinicians should take into account the likely time for onset of corticosteroid effect and also the anticipated time of onset of action of these bronchodilators before initiating change as there are unlikely to be immediate benefits.

Clinical management in this situation will be decided by the local clinical team. Further interventions could include increasing the dose of salbutamol, increasing the dose of aminophylline if serum concentration is low, adding an additional IV bronchodilator, supporting with high flow humidified oxygen (HiFlo) or commencing non-invasive or invasive respiratory support.

If possible, any additional therapy should be commenced after two hours of therapy with the trial IV bronchodilator. We would suggest increasing the dose of salbutamol before adding in another IV bronchodilator.

11.8 Management of overdose

Overdose, defined for the purpose of this trial as any dose above the highest dose specified in the BNFc[2] is anticipated to be low. IMP will be administered under medical supervision by qualified healthcare personnel.

In cases of suspected overdose, the investigator should:

- Provide general supportive measures directed to the observed clinical effects. Symptoms of overdose should be treated as per clinical judgement, managed according to the SmPC and local clinical practice protocols.
- Consult TOXBASE (and contact the National Poisons Information Service for further support, if indicated). Website and telephone number: https://www.toxbase.org/, 0344 892 0111
- Closely monitor the participant for any AEs and laboratory abnormalities for as long as medically indicated in routine care after the administration of the suspected overdose.
- An overdose without associated symptoms is only reported on the Overdose eCRF module. The Overdose eCRF will include questions relating to the quantity of the excess dose the duration of the overdose.
- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

The PI or other delegated site personnel should inform the appropriate trial representative immediately of the overdose, but no later than 24 hours of when he or she becomes aware of it. The designated trial representative will work with the PI to ensure that all relevant information is provided within 1 or 5 days for SAEs, and within 30 days for other overdoses.

11.9 Pre-medication

Pre-medication is not applicable to the IMPs used within this trial.

11.10 Prohibited medications and interaction with other drugs

11.10.1 Aminophylline infusion

Aminophylline should not be administered concomitantly with other xanthine drugs - current therapy with regular theophylline is an exclusion criterion for the trial. Further details can be found in the aminophylline SmPC[42].

11.10.2 Magnesium sulfate infusion

The SmPC advises to administer with caution to patients receiving digitalis glycosides. Concomitant use of calcium channel blockers such as nifedipine or nimodipine may rarely lead to a calcium ion imbalance and could result in abnormal muscle function. Further details can be found in the magnesium sulfate SmPC[43].

11.10.3 Salbutamol infusion

Salbutamol and non-selective β -blocking drugs such as propranolol, should not usually be prescribed together. Both salbutamol and corticosteroids can increase blood glucose and reduce serum potassium so levels should be monitored with concomitant administration. Individual anti-diabetic therapy may need to be adjusted. Further details can be found in the salbutamol SMPC[44].

11.11 Permitted concomitant medications

Unless specified in section 11.10, all medications can be used alongside the IMPs used within this trial.

11.11.1 Trial restrictions

There are no restrictions for this trial.

11.12 Supportive Care

Usual asthma care will be continued during the participants involvement within the trial.

11.13 Accountability procedures

Local pharmacy personnel will be responsible for ensuring that the IMPs are managed and dispensed to participants in accordance with the duly approved current protocol.

Since the IMPs used within this trial will be sourced from local hospital stocks, trial specific accountability of the IMPs is not required.

The IMPs should be destroyed if required as per local practice without Sponsor's permission.

11.14 Compliance

IMP will be administered at the trial site under medical supervision by qualified healthcare personnel according to participant's prescription.

The time of commencement/cessation of IMP will be recorded. Additionally, any dosage changes will be recorded.

12. Sample Management

12.1 Sample collection

Sites will be provided with sample collection kits to allow them to take a blood and saliva sample from each participant as part of the trial. The samples will be taken at the timepoints shown in Table 5.

Chain of custody will be monitored by CTR. It is the recruiting sites responsibility to ensure that all the samples are labelled in accordance with the trial procedures/protocol, General Data Protection Regulation 2018 and Human Tissue Act 2004.

Table 5: Sample timepoints

Timepoint **Type of sample to be taken**	**Day 0** **(pre-trial intervention)**	**Day 1-30** **(post consent)**
Blood	X	
Saliva		X

12.1.1 Blood samples

The blood sample will be taken once acute severe asthma is identified and IV access is gained prior to initiation of IV bronchodilator therapy. This sample should be collected and processed as detailed within the EVITA laboratory manual. The CTR will periodically arrange a batch collection of blood samples and organise the shipment of these to the laboratory performing the analysis. The sample will be used to assay the level of salbutamol using LC-MS/MS technique. Consent will be obtained to use the sample in the trial. If consent is not obtained, the blood sample will be destroyed

Additionally, it will be expected that a Full Blood Count will be undertaken as part of the routine clinical assessment before IV bronchodilator therapy; this will provide the blood eosinophil concentration.

12.1.2 Saliva samples

The trial DNA collection kit should be used to collect a saliva sample once deferred consent (including for genetics) is obtained. Consent for the collection of a saliva sample is an optional separate consent process to the main trial. Consent will be undertaken by each sites research nurses and will routinely take place during the acute inpatient stay once the child has been stabilised and is well enough to provide a saliva sample. Consent and saliva sample collection could be undertaken at any point during the trial follow-up process including during a research nurse home visit as required.

Participants will be advised not to eat or drink for 30 minutes prior to sample collection. Participants will be requested to spit in the container directly up to the 2ml mark. Foam swabs are included within the DNA collection kits to assist with sample collection. Prior to transport to Professor Colin Palmer (Chair of Pharmacogenomics, Pat McPherson Centre for Pharmacogenetics and Pharmacogenomics, School of Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK) in a prepaid envelope, the sample will be stored at room temperature. The saliva sample will be used for DNA extraction and genetic analysis of asthma related single nucleotide polymorphisms (including those affecting the Beta-2-adrenoreceptor). All saliva samples should be sent the address above in the prepaid envelope within 72 hours of sample collection.

13 Trial procedures

To minimise the burden of activity for clinical staff, the data collection procedures have been designed to align with routine care. Site personnel will administer treatment in accordance with the protocol and otherwise will deliver care as per usual clinical pathways. All other routine clinical data will be retrospectively collected by research nurses or designated staff from medical records. For example, heart rate, wheeze and accessory muscle use observations will be collected at 1, 2, 4, 8, 12, 24, 48 and 72 hours post randomisation.

13.1 Schedule of procedures

All screening and baseline assessments should be performed on the day that an episode of acute severe asthma is diagnosed. Trial assessments are summarised in Figure 2 and Table 6.

The schedule of trial procedures and assessments are as follows:

Screening (acute severe asthma diagnosed) – pre-stabilisation

- Participant eligibility assessment – as per inclusion and exclusion criteria
- A summary participant leaflet will be available for participants/parents/guardians in the emergency department waiting room (a full PIS will be obtainable at request).

Baseline (alongside enrolment in trial) – pre-stabilisation

- Assessment of wheeze, accessory muscle use and heart rate (components of Asthma Severity Score (ASS)), global assessment of severity* and saturation in air (stop any supplementary oxygen for 5 minutes and record lowest saturation; if saturation falls below 90%, restart the supplementary oxygen and record as <90%) which are all routine clinical assessments
- Blood sample – including Full Blood Count (routine test) and venous blood gas (routine test) and sample for salbutamol level (prior to initiation of IV bronchodilator therapy), processing, completion of sample eCRF
- Randomisation as per Section 9.5 of the protocol
- Prescription for trial (as per randomisation allocation)
- Administer trial drug
- Review/reporting of participant adverse events (AEs)

Monitoring phase (0-72 hours post randomisation) – pre/post-stabilisation

- Assessment of wheeze, accessory muscle use and heart rate (components of ASS), global assessment of severity* and saturation in air
- Review/reporting of participant AEs

The assessments above will be repeated at the following time points post randomisation:

- 1 hour (+/- 15 minutes)
- 2 hours (+/- 15 minutes)
- 4 hours (+/- 30 minutes)
- 8 hours (+/- 60 minutes)
- 12 hours (+/- 120 minutes)
- 24 hours (+/- 240 minutes)
- 48 hours (+/- 240 minutes)
- 72 hours (+/- 240 minutes)

Additionally, we will request that a venous gas is undertaken if a participant has further blood tests. It is expected that most participants will have a U&E (routine test) and probably a gas repeated (routine test) during their hospital admission.

Deferred consent period (Days 1-5 (+30 days) post randomisation) – post-stabilisation

This will be taken once the participant is stable prior to discharge.

- Full participant information sheet
- Informed consent
- Extract routine clinical data into eCRF
- CHU-9D
- Saliva sample collection and processing
- Review/reporting of participant AEs

Discharge

The following should be completed at hospital discharge:

- Participant assessment of experience questionnaire
- CHU-9D
- Extract routine clinical data into eCRF

30 day follow up post randomisation (Day 30 -4 days to +7 days)

- Resource use questionnaire and CHU-9D
- Acceptability questionnaire - Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM)
- Review/reporting of participant AEs

Optional qualitative interview (from discharge to day 45 (+7 days))

This will be completed by a subgroup of participants.

- Qualitative interview

*Global assessment of asthma severity should be assessed as per the table shown in Appendix 1.

Table 6: Schedule of enrolment, interventions and assessments

Procedures	Screening	Baseline	Monitoring phase	Deferred consent period	Discharge	Qualitative interview	30 day follow up	End of follow up	End of trial
	Acute severe asthma diagnosed	Randomisation	1, 2, 4, 8, 12, 24, 48, 72 hours post randomisation	Days 1-5 (+ 30 days)		Discharge to 45 (+7 days)	Day 30 (-4 days to +7 days)	Day 45 (-4 to +7 days)	
Participant eligibility assessment	X								
Routine clinical assessment†		X	X						
Blood sample collection*		X							
Randomisation		X							
Prescription for trial		X							
Administer trial drug		X							
Follow up data collection			X						
Follow up venous gas$			(X)						
Informed consent				X					
Extract routine data into eCRF				X	X				
Sociodemographic and medical history				X					
CHU-9D				X	X		X		
Resource use questionnaire							X		
Saliva sample collection				X					
Participant assessment of experience questionnaire					X				
Acceptability questionnaire#							X		
Review/reporting of participant AEs		X	X	X			X		
Qualitative interview (subgroup)						X			
Physician's withdrawal checklist								X	
PLICS data collection									X

† Including components of ASS, saturation in air, global assessment of severity. * Blood sample must be collected once acute severe asthma is identified and IV access is gained prior to initiation of IV bronchodilator therapy – venous gas and sample for salbutamol level. $ Venous gas to include pH, carbon dioxide, lactate. # Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM)

13.2 Follow-up

The end of follow up will be defined as 45 days post randomisation (-4 days to +7 days).

13.3 Optional qualitative interviews

Qualitative interviews will be carried out with 25-35 trial participants (8+ years)/parents/carers who have provided optional consent to be contacted for this component of the trial. Additionally, 25-35 healthcare professionals (e.g. ED nurses and doctors) involved in the EVITA trial will be invited to take part in a qualitative interview.

Following an invite to take part in a qualitative interview, invitees will be provided with a qualitative interview information sheet. The participant's/parent's/legal guardian's consent must be obtained using the qualitative interview consent form. Consent will be taken by a delegated member of the CTR qualitative team at the start of the qualitative interview. Participation in an interview is entirely voluntary, and consent can be declined even after providing consent on the main trial consent form. If the invitee decides not to take part, they do not have to explain their reasons, although it can be helpful if a reason is provided so the investigator should respectfully query this.

The participant remains free to withdraw their consent to participate in the research interview at any time, without giving a reason, even after providing consent.

The qualitative interviews will be organised and carried out by members of the CTR qualitative team. They will take the format of either a video or telephone call and occur in the 45 days following participant randomisation. The interviews are expected to last between 30 and 60 minutes.

14 Pharmacovigilance

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the CTR PV and Safety Specialist unless the SAE is specified as not requiring immediate reporting (see section 14.2). This includes SAEs related to IMPs.

All other AEs should be reported on the eCRF following the CRF procedure described in Section 17. Other AEs will only be reported if they are likely to be related to one of the trial IMPs. These will be unsolicited, recorded from within the clinical record identified by research staff. They will include the following events:

- Nausea, Vomiting, Abdominal pain, Diarrhoea
- Tremor
- Palpitations, Arrythmia
- Rash, Hypersensitivity
- Headache, Muscle cramps, Convulsions
- Hypokalaemia (Potassium < 3.5mmol/L), Lactic acidosis (venous or capillary lactate >2.2mmol/L or arterial >1.6 mmol/L)
- Other AE that is likely to be related to one of the IMPs

14.1 Definitions

Table 7: definitions of pharmacovigilance terms

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Adverse Reaction (AR)	Any untoward and unintended response in a clinical trial participant to an investigational medicinal product which is related to any dose administered to that participant
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***
Serious Adverse Reactions (SARs)	Any SAE occurring in a clinical trial participant for which there is a reasonable possibility that it is **related** to the IMP at any dose administered.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	A SAR, the nature and severity of which is not consistent with the Reference Safety Information (RSI) for the IMP.

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subjects death; it does not refer to an event which hypothetically might have caused death if it were more severe.

** **Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

*** **Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE 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.

14.2 Trial Specific SAE Reporting requirements

In addition to the SAE reporting requirements defined in Table 7, for the purposes of this trial the following events will also be considered SAEs and must be captured on the SAE form and reported to the CTR within 24 hours of knowledge of the event:

- Cardiac arrest
- Neurological insult
- Respiratory arrest

For the purposes of this trial the following events will not require reporting as SAEs unless they lead to cardiac arrest, neurological insult or respiratory arrest or one of the other reason listed in table 7:

- Prolongation of hospitalisation
- Common expected adverse events relating to acute severe asthma including:
    - Tachyarrhythmias
    - Severe hypokalaemia <2.5
    - Clinical deterioration leading to PICU admission

These should be completed in the participant's notes and on the relevant toxicities CRF page and forwarded to the CTR in the normal timeframes for CRFs.

Pre-existing conditions should only be reported if they met the definitions for an SAE and if the condition worsens by at least one severity grade.

14.3 Severity grading

The severity of SAEs should be graded as follows:

- **Mild:** An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe:** A significant event that prevents normal everyday activities.

14.4 Causality

Causal relationship of serious adverse events will be assessed for IMPs:

Table 8: IMPs

1. Aminophylline
2. Magnesium sulfate
3. Salbutamol

The Principal Investigator (or another delegated medically qualified doctor from the trial team) and Chief Investigator and/or Co-Leads (or another medically qualified doctor from the Trial Management Group) will assess each SAE to determine the causal relationship:

Table 9: Causality assessment

Relationship	**Description**	**Reasonable possibility that the SAE may have been caused by the IMP?**
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No

Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator and/or Co-Leads (or delegate), and in the case of disagreement both opinions will be provided.

14.5 Expectedness

The Chief Investigator and/or Co-Leads (or another delegated appropriately qualified individual) will assess each SAE to perform the assessment of expectedness.

The expectedness assessment should be made with reference to the current approved Reference Safety Information (RSI) for each IMP. Expectedness decisions must be based purely on whether the event is listed in the RSI; other factors such as the participant population and participant history should not be taken into account. Expectedness is not related to what is an anticipated event within a particular disease. SARs which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected events. Fatal and life-threatening (LT) SARs should not be considered expected (unless explicitly stated in the RSI and approved by the MHRA). For example, an event more specific or more severe than that described in the RSI is considered unexpected.

Table 10: list of sources of RSI's for each IMP that should be referenced

IMP	**RSI to be used for expectedness assessment**	**Relevant section to be used for expectedness assessment**
Aminophylline	SmPC	Section 4.8
Magnesium sulfate	SmPC	Section 4.8
Salbutamol	SmPC	Section 4.8

Reference Safety Information (RSI) on any CTR trial will be reviewed regularly according to CTR procedures.

14.6 Reporting procedures

14.6.1 Participating Site Responsibilities

The PI (or delegated medically qualified doctor from the trial team) should sign and date the SAE CRF to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own health boards or trust in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via email to the CTR within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by trial number, age and initials. The participant's name (or any other personal identifiers) should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, CTR/pharmaceutical companies may request additional information relating to any SAEs/SARs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) email address:

CTR-Safety@Cardiff.ac.uk

Serious adverse events should be reported from randomisation, throughout the treatment period up to, and including discharge from hospital. Serious adverse reactions (such as long-term side effects of trial treatment under investigation) should continue to be reported until the end of follow-up given that this will considerably in excess of five half-lives of the IMPs.

An SAE form should contain at least the minimum information:

- Full participant trial number
- An Adverse Event / Adverse Reaction
- IMP
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor registered on the delegation log)

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours.

14.6.2 The CTR responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form.

The CTR should continue reporting SAEs until the patient is discharged from hospital. Serious adverse reactions should continue to be reported until the end of follow up.

Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator and/or Co-Leads (or their delegate) for an assessment of expectedness.

Investigator reports of suspected SARs will be reviewed immediately and those that are identified as SUSARs are reported to the MHRA and Main Ethics Committee.

All SAEs and SARs will be reported to the monitoring committees (TMG and TSC/IDMC) as they occur by the relevant committee/party.

14.7 SUSAR reporting

University Hospital Southampton NHS Foundation Trust is undertaking the duties of trial Sponsor and has delegated to the CTR the responsibility for reporting SUSARs and other SARs to the regulatory authorities (NCAs and relevant ethics committees).

SUSARs which are fatal or life-threatening must be reported to the MHRA and REC within 7 calendar days of receipt at the CTR.

SUSARs that are not fatal or life-threatening must be reported to the MHRA and REC within 15 days of receipt at the CTR.

If report is incomplete then additional follow-up information should be reported within a further 8 calendar days of submitting the initial report, for all fatal and life-threatening events.

Any additional, relevant information must be reported within a further 15 days.

14.8 Safety Reports

A list of all SARs (expected and unexpected) will be reported annually to the MHRA and trial sponsor in the form of a Development Safety Update Report (DSUR). This report must be submitted within 60 days of the anniversary of the MHRA CTA approval date.

The CTR will report a list of all SARs (expected and unexpected) and any other safety recommendations and, in conjunction with LCTC, these will be distributed to all PIs annually throughout the course of the trial. This frequency may be reviewed and amended as necessary. This reporting will be done via the Investigator safety report (ISR).

14.9 Contraception and pregnancy

The life-threatening nature of acute severe asthma means that treatment should be administered as soon as possible. In routine clinical practice, pregnancy testing is not carried out prior to administration of these three interventions as the risk of treatment delay is considered greater than any possible risk to the fetus based on pregnancy risk information as detailed in the SmPC:

- Aminophylline - Theophylline crosses the placenta. It is not known whether theophyllines can cause foetal harm when administered to pregnant women. Although the safe use of theophylline during pregnancy has not been established relative to potential risk to the foetus, theophyllines have been used during pregnancy without teratogenicity or other adverse foetal effect. Given the risk of uncontrolled asthma, their safety during pregnancy when clearly needed is generally not seriously questioned. As with other drugs, aminophylline should only be used during pregnancy if considered essential by the physician.

- Magnesium - Magnesium sulfate easily crosses the placenta, and fetal serum levels will closely mirror maternal estimations. Sufficient amount of magnesium may cross the placenta in mothers treated with high doses (e.g. in pre-eclampsia) to causing hypotonia and respiratory depression in newborns. When used in pregnant women, fetal heart rate should be monitored and use within 2 hours of delivery should be avoided. Magnesium sulfate can cause skeletal adverse effects when administered continuously for more than 5 to 7 days to pregnant women. There are retrospective epidemiological studies and case reports documenting fetal adverse effects including hypocalcaemia, skeletal demineralization, osteopenia and other skeletal adverse effects with maternal administration of magnesium sulfate for more than 5 to 7 days (trial IMP not expected to be administered for more than 3 days). The clinical significance of the observed effects is unknown. If prolonged or repeated exposure to magnesium sulfate occurs during pregnancy monitoring of neonates for abnormal calcium or magnesium levels and skeletal adverse effects should be considered. Serum magnesium levels in preterm infants are higher than adult levels.

- Salbutamol - There is little published evidence of the safety of salbutamol in the early stages of human pregnancy but in animal studies there is evidence of some harmful effects on the fetus at very high dose levels. Salbutamol infusion is indicated in uncomplicated premature labour (between 22 and 37 weeks of gestation)[2]. Administration of salbutamol during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

So given the life-threatening nature of acute severe asthma and the nature of the risks associated with the trial interventions, pregnancy testing will not be performed prior to IMP administration, as per routine clinical practice.

For patients who are known to be pregnant on presentation with acute severe asthma, a decision as to whether they should be included in the EVITA trial will be made by the senior clinician. This will balance the benefit of using an IV bronchodilator to treat their exacerbation versus the potential risks of each of the trial interventions. Information on a pregnancy in a trial participant will be captured on the trial CRF.

14.9.1 Pregnancy reporting whilst participating in the trial

Should a participant be subsequently identified as being pregnant at the time of IMP exposure, information relating to the pregnancy will be collected on the eCRF. Summary data will also be reported to the Data Monitoring Committee. All pregnant female participants will be followed up until post-birth or otherwise (i.e. spontaneous termination) to allow information on the status of the mother and child to be reported to the CTR and Sponsor.

Pregnancy, or the pregnancy of a partner occurring whilst participating in the trial, is not considered an SAE, however, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs in a trial, either in a female participant this should be followed up until at least the end of pregnancy, whether that is a live birth, abortion, etc.. Without follow-up of the pregnancy, it would not be possible for the CTR to know if a congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the IMP. Information on a pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form supplied to sites by the CTR.

Sites should report pregnancy occurring within SAE reporting periods stipulated in the trial protocol. Congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTR on a trial-specific SAE form. Congenital anomalies or birth defects related to the IMP and unexpected with respect to the IMP Reference Safety Information (RSI) must be submitted by the CTR within expedited SUSAR time frames (7 or 15 days) to the MHRA, relevant REC and the drug manufacturer of the IMP (to comply with any contractual agreement).

14.10 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor, Chief Investigator and/or Co-Leads or Principal Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. Any urgent safety measure relating to this trial must be notified to the MHRA and Research Ethics Committee immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

15 Statistical considerations

15.1 Randomisation

Random allocation (1:1:1 allocation) will be implemented using a minimisation algorithm (factors: centre and age group [<6 years, ≥6 years]) incorporating a non-deterministic probabilistic element to prevent predictability of the treatment allocation.

15.2 Blinding

This is an open label trial. An open design has been chosen due to the differences between the three drugs: (a) dose capping, (b) drug preparation methods including having a limited stability once prepared, and (c) need to titrate infusion rate based on therapeutic levels. A blinded trial would make the trial too complex, increase the risk of serious medication error and be costly to deliver in a busy acute setting.

15.3 Sample size

Considering the primary outcome, asthma severity score (ASS), a sample size of 89 in each group will have 90% power to detect a mean ASS difference of 1 unit. This assumes:

- The common standard deviation is 1.8[21,27]

- Two-group t-test
- Conservative 1.7% two-sided significance level. This is based on a Bonferroni correction so that the type 1 error of 0.05 is split by the three comparisons between three IV bronchodilators.

With deferred consent we assume a 10% loss[41] giving a total trial sample size of 300 (100 participants in each treatment group) for the ASS outcome.

Considering the key secondary outcome, length of stay in hospital, a sample size of 107 in each group will have 85% power to detect a mean length of stay difference of 24 hours (based on our discussions with both PPI groups). This assumes:

- The common standard deviation is 50.730
- Two-group t-test
- Conservative 1.7% two-sided significance level as above.

With deferred consent we assume a 10% loss giving a total trial sample size of 357 (119 participants in each treatment group) for this outcome.

It is possible that one or more IV bronchodilators may have a differential impact on asthma severity and length of stay in hospital. A total of 357 (119 participants in each treatment group) will be recruited to ensure that the trial should also be powered for both these outcomes.

15.4 Termination of the trial

Progression criteria for the internal pilot phase are described in section 15.4.1. There is potential for the trial to terminate early if our funder assesses the trial as not being feasible following an assessment of progress against our targets at the end of the internal pilot with input from our TSC and IDMC.

15.4.1 Internal pilot

An internal pilot is included in the trial design following 9 months of recruitment. During the first nine months of trial recruitment from the first participant recruited (July 2025 – March 2026), 89 patients are expected to be recruited across 20 sites, which will be open at that point.

The interim analysis will be performed at the end of recruitment month 9. If there is inconsistency in the scoring of the progression criteria (Table 11) then overall the trial will be categorised according to the criterion that is furthest from achieving the progression threshold e.g. if two criteria are green but one is amber, the trial will be categorised as amber.

The response to each outcome will be discussed with the funder but in general terms:

- **RED**: Unless there are mitigating circumstances, these outcomes determine that recruitment is not feasible suggesting that the trial does not proceed.
- **AMBER**: Average recruitment rate, number of patients receiving randomised treatment, complete primary outcome data collection, the number of sites opened, and the number of patients recruited is sub-optimal. Action: review recruitment strategies,

report to the trial steering committee (TSC) and NIHR HTA and continue with a modified recruitment strategy and intensive monitoring.

- **GREEN**: Targets are reached. Action: proceed with study as planned.

As well as reviewing the stop/go criteria the Independent Data Monitoring Committee (IDMC) will check the estimate of the standard deviation of the asthma severity score that was used for the power calculation as part of the wider internal pilot.

Table 11: Internal pilot criteria

	Red	Amber	Green
Average recruitment rate/ site/ month	<0.6	0.6-1.19	1.2
Participants receive randomised treatment	<67 (<75%)	67-88 (75-99%)	89 (100%)
Complete primary outcome data	<75%	75-99%	100%
Number of sites opened	<15	15-19	20
Total number of patients (key criterion)	<67	67-88	89

15.5 Inclusion in analysis

Participants will be included in the analysis in the group to which they were randomly allocated. Safety analysis population will include participants in the treatment actually received.

16 Analysis

16.1 Main analysis

A fully documented statistical analysis plan will be written and agreed by the statistical team and Chief Investigator and Co-Leads prior to analysis of the trial data. Final analysis will take place once all participants have been followed up, and the database has been locked.

The estimand for the primary objective of the trial is:

- **Primary research question**: In CYP aged 2-18 years who present at emergency departments/acute paediatric wards with severe acute asthma requiring IV bronchodilator therapy (i.e. unresponsive to maximal inhaled therapy), what is the comparative effect of prescribing one of three different IV bronchodilators (aminophylline, magnesium sulfate or salbutamol) on asthma severity measured two-hours after randomisation?

- **Population**: CYP aged 2-18 years with asthma presenting to the emergency department/acute paediatric wards with an exacerbation that is unresponsive to three back-to-back doses of inhaled high dose salbutamol plus any amount of ipratropium.

- **Endpoint**: Asthma Severity Score at two-hours post-randomisation.

- **Treatment conditions**: IV aminophylline (bolus then infusion), IV magnesium sulfate (bolus), or IV salbutamol (bolus then infusion) using protocol doses and regardless of treatment discontinuation, switching, or concurrent treatments (treatment policy strategy)

- **Remaining intercurrent events**: Treatment discontinuation, switching, and concurrent treatments are covered by the treatment policy strategy. Mortality in this population is expected to be extremely unlikely given the eligibility criteria and the primary outcome is at two hours.
- **Population-level summary**: Mean difference in Asthma Severity Score at two-hours post-randomisation adjusted for site, age and baseline Asthma Severity Score.
- **Rationale for estimand**: To compare the strategy of initially prescribing one of aminophylline, magnesium, or salbutamol as would be observed in routine practice.

Additional estimands may be considered which employ different strategies for handling intercurrent events (e.g. hypothetical and while on treatment strategies for handling departures from randomised treatments). This will be specified in full in our statistical analysis plan.

Demographic and baseline characteristics will be summarised separately using descriptive statistics for each randomised group to allow assessment of whether balance was achieved between randomised groups. This will include sex, age, ethnicity, and other relevant characteristics. No statistical testing of demographic and baseline differences between groups will be performed.

The primary analyses will report the difference between group means (with 98.3% confidence intervals) using analysis of covariance (ANCOVA), adjusting for baseline ASS and the minimisation factors (site and age [<6, ≥6 years]) as recommended by ICH E9, this will have a greater power to detect the minimum important difference than the unpaired t-test[45].

Secondary analyses will make use of all data using a mixed model longitudinal analysis. The proposed primary effectiveness analysis will have pairwise comparisons of the asthma severity score at 2 hours between the three bronchodilators.

The primary analysis will use a two-sided p-value of 0.017 (1.7% level) to declare statistical significance and will be reported alongside the 98.3% confidence interval. Testing of the length of stay in hospital between IV bronchodilators (key secondary analysis (a)) will use an unpaired t-test. A p-value less than 0.017 will be used to determine statistical significance for each of the comparisons against the most effective IV bronchodilator, a 98.3% confidence will be used for this outcome.

All other secondary outcomes will be reported alongside the 95% confidence interval. Binary outcomes will be reported using relative risks. Continuous outcomes will be reported using a linear mixed effects method including all patients, all time-points and adjusting for the minimisation factors. Time to event outcomes will be summarised by Kaplan-Meier curves and compared overall using log-rank tests and survival regression methods.

Data will be monitored with range and consistency checks built into the database. Reasons for missing data or participant withdrawals will be collected and used to inform statistical approach to missing data.

16.1.1 Sub-group analysis

Any planned sub-group analysis will be prespecified and detailed in the SAP along with their respective hypotheses.

16.2 Qualitative analysis

The process analysis will focus on (1) acceptability to patients, parents/carers and healthcare professionals and (2) barriers and facilitators in the pathway to implementation across the NHS. This will be guided by the Consolidated Framework for Implementation Research (CFIR)[46,47] and Normalisation Process Theory (NPT)[48]. Interviews (web-based, telephone or face-to-face) will include patients (8+ years), parents/carers and healthcare professionals (e.g. ED nurses and doctors). They will occur in the 45 days after randomisation. Purposive maximum variation sampling will be used to ensure diversity (e.g. ethnicity, socioeconomics, geographically) including over-recruiting seldom-heard groups to ensure the widest range of views are included. We expect to interview 25-35 patients/parents/carers from across the trial sites and 25-35 healthcare professionals with differing levels of experience across the sites to achieve data saturation. Interviews will be recorded and transcribed verbatim. Transcripts will be de-identified and managed using qualitative coding software (NVivo) for coding and analysis. A proportion of transcripts (~10%) will be double-coded to enhance reflective discussion around theme development.

Interview analysis will employ the framework method incorporating CFIR constructs as predefined deductive codes[49]. Open coding will also be applied as necessary to accommodate data nuances and uncover themes that may not be explicitly captured by CFIR constructs. Qualitative findings will be examined using the NPT perspective aiming to pinpoint potential mechanisms through which the observed effects of the interventions become integrated into routine practice.

Qualitative findings will be discussed within the Trial Management Group and with external stakeholders. They will inform the trial dissemination and implementation strategy.

16.3 Cost effectiveness analysis

The economic evaluation aims to estimate the cost-effectiveness of IV aminophylline, magnesium sulfate and salbutamol. Whilst these medicines are relatively inexpensive, the choice of treatment may ultimately be dependent on their relative cost-effectiveness, especially if differences in their clinical benefit are marginal, or if there are clear differences in hospital length of stay. The analysis will adopt the perspective of the NHS and personal social services (PSS), over a time horizon of 1-month post randomisation.

A bespoke resource use measure will be developed from existing questionnaires catalogued in our Database of Instruments for Resource Use Measurement[50] and include items from ModRUM the generic, modular resource-use measure (registration: https://express-licences.bristol.ac.uk/product/modrum---modular-resource-use-measure)[51]. Principal items of resource use will include primary, secondary, community and social care services. Resource use questionnaires will be administered via telephone by research nurses 30 days post randomisation.

Hospital costs relating to the index hospitalisation will be determined from CRF entries (capturing dates of admission and discharge, tests and procedures, and prescribed in-patient and discharge medication) and from Patient Level Information and Costing System (PLICS) data (Table 12). PLICS provides patient-level information in the form of healthcare resource groups that include information on outpatient, inpatient (including critical care) and ED

attendances for the duration of participants' hospital stay. PLICS data will be obtained from the finance departments of each site at the end of the trial (following the last follow-up of the last patient at each site). Responsibility for the PLICS data collection and anonymisation will rest with the site research nurse who will supply their site Finance Departments with the necessary details to ensure only information on consented trial participants are provided. It is the responsibility of the site Finance Departments to provide the site research nurses with the data, and should the site research nurse so request, to ensure all patient identifying data have been replaced with the patient trial number. Pseudo-anonymised PLICS data will be transferred securely from each site to Bangor University for analysis. The CTU will provide instructions for this transfer.

Unit costs will be obtained from standard sources, including the NHS reference costs[52] for hospital costs, the Personal Social Services Research Unit's Unit Costs of Health and Social Care[53] for primary, community and social care, and the BNFc[2] for medicines. Costs will be based on the most recent at the time of analysis.

Health outcomes will be based on participants' responses to the CHU-9D questionnaire (license: https://licensing.sheffield.ac.uk/product/CHU-9D). This has evidence of validity and reliability for children as young as 2 years old[54] but is generally accepted from 7 years of age[55]. The CHU-9D will be administered by research nurses at discharge to participants who are of sufficient age and capacity to comprehend and respond. Parent/caregiver proxy responses will be used for younger age groups, and for all at baseline. The CHU-9D will be administered by telephone at the 30-day follow-up. Preference weights for the CHU-9D will be based on a UK valuation trial[55,56]. QALYs will be calculated based on the time-integral of utility values.

A full health economic analysis plan will be specified prior to data lock[56]. Patient-level cost and utilities will be analysed using regression models to improve precision and account for any baseline imbalance. The primary economic outcome will be the incremental cost per QALY gained of non-dominated (or extendedly dominated) treatments and compared with the NICE threshold of £20,000 to £30,000 per QALY.

Sensitivity analyses will be conducted, including a stochastic sensitivity analysis to estimate the incremental cost-effectiveness ratio, and to assess the probability of cost-effectiveness for given threshold values of willingness to pay. A stratified cost-effectiveness analysis will be conducted for valid subgroups – such as relating to genotype – that will be specified a priori.

Table 12: Data for health economic analysis

	Baseline	Discharge	30 days (by telephone)	End of trial
Resource use questionnaire			✓	
CHU-9D	✓[a]	✓[b]	✓[b]	
PLICS				✓

Notes: [a]Parent/guardian proxy responses for all at baseline; [b]Parent/guardian proxy responses for participants who may not have the capacity to comprehend and respond.

16.4 Tertiary/Exploratory objectives - personalised medicine analysis

A responder analysis will be undertaken to assess whether response to each of the IV bronchodilators differ between participants. Three hypotheses will be explored:

i. Serum salbutamol levels predict how individuals respond to each of the three IV bronchodilators. A blood sample taken at randomisation will be used to assay each participant's serum salbutamol concentration prior to the IV bronchodilator. It is hypothesised that those with lower serum salbutamol levels following inhaled treatment will respond better to IV salbutamol than those with greater levels. If this suggests a relationship it may indicate the need for research into point of care tests for those arriving with significant asthma, to improve choice of treatments and personalised care.

ii. Specific patient baseline characteristics may predict how individuals respond to each of the three IV bronchodilators. The specific characteristics that we will explore are:

   a. frequency of inhaled bronchodilator therapy and systemic corticosteroid therapy pre-randomisation

   b. co-existing atopic disease (eczema, allergic rhinitis, food allergy)

   c. eosinophil count

   d. level of maintenance asthma therapy

   e. previous severe exacerbations[1] of asthma

iii. The season of presentation may predict how individual respond to each of the three IV bronchodilators.

iv. Specific genetic polymorphisms may predict response to individual IV bronchodilators. There is evidence that polymorphisms in the gene encoding the beta-2 adrenoreceptor are clinically significant for response to inhaled beta-2 agonists but there is no evidence for IV treatment[57,58]. Further details can be found below in Section 18 and a genetic analysis plan will be finalised prior to the end of participant recruitment detailing the specific polymorphism and analysis plan.

v. The relationship between pre-randomisation inhaled salbutamol therapy and lactic acidosis/hyokalaemia will be assessed. The relationship between the use of each IMP and subsequent lactic acidosis/hyokalaemia will be assessed and compared.

17 Data Management

Source Data is defined as "All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents." There is only one set of source data at any time for any data element, as defined in site source data information sheet.

Source documents include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. CRF entries will be considered source data if the CRF is the site of the

original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. Sites will retain all original source data from these investigations for future reference. On all trial-specific documents, other than the signed consent form, the participant will be referred to by the trial participant ID, not by name.

17.1 Completion of CRFs

17.1.1 Electronic CRFs

Participating sites will be provided with eCRF completion guidance with instructions on how to access the system, how to complete the database forms and expected timescales for data completion, and how to respond to data queries. The trial team will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner.

17.2 Qualitative data management

All the information, including any personal information (e.g. interviewee name), will be kept confidential. Recordings will not be labelled with interviewee name. Any written report of the research will have the interviewee's name removed. Written quotes of what the interviewee says in the interview may be used word for word, but quotes will be de-identified. Interviewee names will not appear on publications. All trial related records will be stored for a minimum of 25 years. The results are likely to be published in medical journals over the next few years. The interviewee will not be personally identified in any report or publication. Full details of data management will be specified in the Qualitative Data Collection and Analysis Plan/Data Management Plan.

17.3 Data linkage

The participant's NHS number will be collected to allow linkage with national data registries such as NHS Digital, Public Health England, HCRW and the Information Services Division (part of NHS Scotland), or the electronic Data Research and Innovation Service (eDRIS). Data linkage will allow for long-term follow-up data to be collected, and it will provide a more complete profile of the participants' health and disease without increased data collection burden to the NHS.

18 Translational research or substudy

With patient consent, any remaining trial sample following the analyses below will be stored at trial approved Biobanks for a period of 25 years and used for ethically approved medical research by researchers from other NHS Trusts, universities or commercial companies. This may include researchers working outside of the United Kingdom.

18.1 DNA collection for asthma related genotyping

EVITA trial participants will be invited to provide a saliva sample for asthma related genotyping. The genetic analysis will assess whether specific asthma related single nucleotide polymorphisms predict response to individual IV bronchodilators. Subgroup analysis of specific polymorphisms may demonstrate reduced efficacy or increased harm. Should an association be demonstrated severe asthma services could electively incorporate genotyping and personalisation of IV asthma therapies for children. This will be an optional separate consent process to the main trial. Chain of custody will be monitored via the trial co-ordinating centre.

The non-invasive Isohelix® DNA collection kits GFXA-01/50 (https://isohelix.com/products/genefix-saliva-dna-rna-collector-gfxa/) or equivalent will be used for the collection of saliva for DNA extraction purpose. The kit provides a median DNA yield of about 110 micrograms. The DNA from saliva is stable in this kit for up to 5 years at room temperature. The stability is achieved with proprietary reagents that inactivate bacteria and nucleases in saliva and minimize chemical hydrolysis of DNA. The kits will be posted to the trial sites by the CTR Trial Manager. Once collected, the saliva samples will be packaged in 95kPa pressure tested transport packs for GeneFix saliva samples with secure sealing strip and absorbent pad (TPS-150), which will be placed in White Transport Boxes (MB-50) UN3373 certified - includes security seal. The packaged kits will be posted by the trial sites to Professor Colin Palmer (Chair of Pharmacogenomics, Pat McPherson Centre for Pharmacogenetics and Pharmacogenomics, School of Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK) for DNA extraction and genetic analysis using pre-paid envelopes. Prior to transport the samples can be stored at room temperature. Saliva samples should be posted in the pre-paid envelopes within 72 hours of sample collection.

The genetic samples will also be included in work with an established international consortium examining pharmacogenomics of childhood asthma (http://pica-consortium.org/).

18.2 Serum salbutamol levels

At cannulation (determined by clinical asthma severity) patients will have an additional sample of blood taken to measure the concentration of salbutamol. This blood sample should be collected and processed as detailed within the EVITA laboratory manual. The CTR will periodically arrange a batch collection of blood samples and organise the shipment of these to the laboratory performing the analysis.

The sample will be used to assay the level of salbutamol using LC-MS/MS technique. Results of this analysis will inform the tertiary/exploratory outcomes of this trial.

19 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance to the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

20 End of Trial definition

The end of the trial is defined as database lock, the point at which all data entry privileges are withdrawn from the trial database.

Sponsor must notify the MHRA and main REC of the end of a clinical trial within 90 days of its completion or within 15 days if the trial is terminated early.

21 Archiving

The trial master file (TMF) and trial TSF containing essential documents will be archived at an approved external storage facility for a minimum of 25 years. The Sponsor will be responsible for archiving the TMF and TSFs. The Principal Investigator is responsible for archival of the

ISF at site on approval from Sponsor. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

22 Regulatory Considerations

22.1 CTA

The trial is being performed under a Clinical Trials Authorisation (CTA) from the UK Competent Authority: MHRA. The CTA, the approval of the MHRA, has been obtained before the start of the trial in accordance with Part 3, Regulation 12 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031).

22.2 Ethical and governance approval

All activities will be conducted in accordance with the principle of Good Clinical Practice, the Data Protection Act 2018 and UK General Data Protection Regulation 2016.

This protocol has approval from a Research Ethics Committee (REC) that is legally "recognised" by the United Kingdom Ethics Committee Authority for review and approval.

This trial protocol has been submitted through the relevant permission system for global governance review. Since the lead site is located in England, governance review and approval will be obtained through the Health Research Authority (HRA).

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

Participating sites are required to confirm their capacity and capability to deliver the trial.

Substantial amendments to this Protocol must be approved by the MREC responsible for the trial and MHRA (where applicable), before the implementation of the amendments. Minor amendments will not require prior approval by the REC and MHRA.

If the trial is temporarily halted, it will not be recommenced without reference to the REC responsible for the trial and the MHRA.

The REC and MHRA will be notified within 90 days of trial completion. If the trial is terminated early, the REC and MHRA will be notified of this within 15 days.

A summary of the clinical trial report will be submitted to the MREC responsible for the trial and MHRA within one year of the end of trial

22.3 Data Protection

The trial team will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the General Data Protection Regulation 2016 and DPA 2018. The data custodian for this trial is the University Hospital Southampton NHS Foundation Trust as trial Sponsor. Liverpool Clinical Trials Centre and Cardiff University Centre for Trials Research are the data processors. The

Chief Investigator and co-Leads will act as the translational sample custodians for all trial samples received at University Hospital Southampton NHS Foundation Trust.

This includes collection of NHS number (or equivalent – e.g. CHI number in Scotland), name and postcode to register and trace participants with the HSCIC.

Representatives of the Sponsor or regulatory authorities will be given access to trial data and trial documents (at sites or the CTR) for monitoring or inspection purposes. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

22.4 Indemnity

The sponsor of the study is University Hospital Southampton NHS Foundation Trust. For NHS sponsored research HSG (96) 48 reference no.2 applies. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

22.5 Trial sponsorship

University Hospital Southampton NHS Foundation Trust will act as Sponsor for trial. Delegated responsibilities will be assigned to the sites taking part in this trial.

The trial is being sponsored by University Hospital Southampton NHS Foundation Trust with responsibilities delegated to the CTR. The CTR shall be responsible for ensuring that the trial is performed in accordance with the following:

- The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031) and subsequent amendments.
- Conditions and principles of Good Clinical Practice.
- Declaration of Helsinki (1996)
- UK Policy Framework for Health and Social Care Research.
- The General Data Protection Regulation 2018.
- The Human Tissue Act 2004.
- Other regulatory requirements as appropriate.

The trial will be conducted in compliance with the protocol, the EU regulation and Good Clinical Practice as required by the regulations.

The Sponsor has/will be delegating certain responsibilities to Cardiff University (CTR), the Liverpool Clinical Trials Centre (LCTC), the Chief Investigator and Co-Leads, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type.

22.6 Funding

The EVITA trial is being funded by the NIHR Health Technology Assessment (HTA) Programme (NIHR162027) and is part of the NIHR Portfolio.

23 Trial management

23.1 CTU coordination

The trial will be jointly coordinated by Cardiff University Centre for Trials Research (CTR), and the Liverpool Clinical Trials Centre (LCTC). Both are UKCRC registered Clinical Trials Units. They will conduct the project according to Standard Operating Procedures, including those for data management, serious adverse event reporting, maintaining trial documentation according to Good Clinical Practice and archiving.

Each CTU's contribution has been organised to ensure there is no overlap. The trial management, pharmacovigilance and safety aspects, quality assurance and qualitative aspects will be managed by CTR. The data management, information systems and statistical analysis will be managed by LCTC. The trial management team will be responsible for day-to-day running and coordination of the trial and will be accountable to the Chief Investigator and Co-Leads. The Chief Investigator and Co-Leads, trial management team, statistician, administrator and other directly employed staff (project team) will meet regularly and take responsibility for the day-to-day conduct of the trial. The project team will refer any key management decisions to the Trial Management Group (TMG).

23.2 TMG (Trial Management Group)

The Trial Management Group (TMG) will also be responsible for the day-to-day running of the trial and will meet monthly to discuss key management issues and monitor milestones. The TMG members will include the Chief Investigator and Co-Leads, all co-applicants and project team members, including PPI co-applicants.

The Committee's terms of reference, roles and responsibilities will be defined in a charter. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter.

23.3 TSC (Trial Steering Committee)

The TSC will provide oversight of the trial. The role of the TSC is to act on behalf of the Sponsor, to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP, and to provide advice through its independent chairperson. The TSC will review the recommendations from the IDMC and will decide on continuing or stopping the trial or modifying the protocol as required. It will meet at least once a year during the trial to provide executive oversight for the trial. The TSC will also consider each open report of the IDMC as well new information which has arisen and recommend appropriate action.

The Committee's terms of reference, roles and responsibilities will be defined in a charter. TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter.

23.4 IDMC (Independent Data Monitoring Committee)

The trial data will be reviewed by an Independent Data Monitoring Committee (IDMC), consisting of at least two Clinicians (not entering patients into the trial) and an independent Statistician. The IDMC will meet throughout the trial to review safety and other relevant trial data. The IDMC will be asked to recommend whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients. A decision to discontinue recruitment will be made only if the result is likely to convince a broad range of Clinicians including PIs in the trial and the general clinical community. The IDMC will make confidential recommendations to the Trial Steering Committee (TSC).

IDMC members will be required to sign up to the remit and conditions as set out in the DMC Charter.

24 Quality Control and Assurance

24.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the EVITA trial. Low monitoring levels will be employed and are fully documented in the trial monitoring plan.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained. Where electronic health records (EHR) are being used, trial teams and monitors should check EHR process early in trial and periodically thereafter.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI and Co-Leads, PI & local R&D.

24.2 Audits & inspections

The trial may be audited by providers of centrally sourced health systems data.

The trial is participant to inspection by MHRA as the regulatory body. The trial may also be participant to inspection and audit by University Hospital Southampton NHS Foundation Trust under their remit as Sponsor.

The CI or PI organisations/institution(s) will permit trial-related monitoring, audits, REC/ IRB review, and regulatory inspection(s), providing direct access to source data / documents.

Sites must inform the CTR of any MHRA inspections.

25 Public Involvement and Engagement

25.1 Patient and public involvement (PPI) input into the development of the trial

This trial has been designed collaboratively with two PPI groups: the Centre for Applied Respiratory Research Innovation & Implementation (CARRii) which has PPI members from across the UK, and the Asthma + Lung UK expert patient panel. Four PPI meetings informed the design of this trial: two CARRii PPI meetings (03.08.23 and 04.12.23) with six parents of

children with severe asthma, who have had a recent emergency department attendance, and one child with severe asthma; two Asthma + Lung UK expert panel meetings (13.07.23 and 11.12.23). Trial concepts and dilemmas were discussed, with PPI feedback provided on the proposed trial methodologies, e.g. open label or double-blind trials, acute consent or deferred consent processes and important outcomes to consider. Feedback from these discussions included:

- Deferred consent process: PPI members agreed with the clinical trial legislation, that from 16 years of age, young people can consent to participate in trials. PPI members confirmed that deferred consent (and assent where appropriate e.g. from age 7 years onwards) to use patients' data in the trial should be obtained once clinically stable. One PPI member stated:

  'The voice of the younger children is also so important, because they'll see it from a different point of view. But then it's how you communicate with younger children. Is it more visual rather than asking a question?'

  We will collaborate with our PPI members to review all patient facing documents to ensure they are accessible and understandable for participants.

- Effective communication strategies: PPI members suggested creating a trial website to promote engagement and dissemination. We will ensure this strategy is created collaboratively with our PPI groups.

- Considering the primary outcome: The PPI groups agreed with the decision for the team's choice of primary outcomes (asthma severity score) and secondary measures of length of hospital stay, amount of inhaler reliver, need for oxygen, admission to high dependency or intensive care, re-admission and adverse events. For hospital stay, the group discussed if ½ day shorter stay would make a difference to parents/CYP. One member stated:

  'To me half a day doesn't really do anything a day, I would say a day is a big thing like an extra night…the nights make a big difference to us as a family but daytime I don't see it as making that much of a difference.'

- Members also discussed that cost of therapy, in relation to benefit, was not a priority when considering the possible outcomes.

All of the suggestions from our PPI groups have been incorporated into the design of the trial to ensure the opinions and feedback of our PPI members have been acknowledged and acted upon.

25.2 Patient and public involvement input into the conduct of the trial

To ensure meaningful PPI within the trial, we will have a dedicated PPI team (PPI lead, supported by senior researcher, charity representative, asthma nurse and public contributors). They will support the PPI volunteers and deliver PPI activities. We will form a PPI group (including members who helped develop the application) to collaborate with us on all aspects of the research. The PPI group will be comprised of those most affected by the research, including CYP with severe asthma and their parents. We will ensure diversity and inclusivity by actively seeking participation from volunteers throughout the UK and seldom reached out

to groups (e.g. socioeconomically or ethnically marginalized). Clinical teams across the UK will identify potential PPI panel members. We will augment this by utilising Asthma + Lung UK networks plus community organisations to identify additional members. CYP will be encouraged to be PPI members and engage with training to support their interaction e.g. via International Children's Advisory Network educational materials.

We have designed a detailed PPI plan to facilitate PPI activities, as described below. To ensure we are recording all contributions made by PPI members and measuring impact, we will record all meetings and capture meeting notes. The trial will have a 'PPI impact log' noting PPI discussions and suggestions and updates/changes that are made as a result. This PPI impact log will be based on The Public Involvement Impact Assessment Framework Guidance[59]. We will report the PPI impact in all outputs and publications, following the GRIPP2 Reporting Checklist[19].

PPI colleagues will be compensated for their contributions via CARRii, in line with NIHR guidance.

Specific PPI activities will include:

- PPI group quarterly meetings: The PPI group will discuss patient and public issues, concerns and implications specific to the project. Timing will depend on the needs of the trial (about 4 meetings a year). The PPI staff will ensure that there is two-way communication between the PPI group and the research team. To ensure accessibility and increase engagement, we will use plain language and a range of communication methods.
- PPI representation on Trial Steering Committee meetings (TSC): Two PPI lead members, a parent of children with severe asthma and a young person with severe asthma supported by her mother, will attend the TSC to ensure patient voices are listened to, and acted upon, in the management of the trial.
- Reviewing trial documents: PPI members will review any patient-facing documents to ensure they are understandable and accessible for CYP living with asthma and/or their parents.
- Development of qualitative interviews/topic guides: We will work with PPI members to create, test and refine the qualitative interview guides based on their feedback.
- Interpretation of findings workshop: We will present findings to the PPI group to gain their perspective on results including interpretation through an 'end of trial workshop'.
- Dissemination of results: PPI members will have the opportunity to co-author research papers and PPI contributions will be acknowledged on all dissemination related to the project.
- Working with PPI members throughout this programme will ensure we have produced research that matters and is relevant to patients and public members.

We will also work with community organisations to gain understanding and develop tools to deliver research that is inclusive. We will link with groups (e.g. Barnado's, including the team delivering the Boloh helpline, to identify the concerns and solutions to engaging CYP from hard to reach populations in research; Runnymede Trust, with their wide experience of research into community engagement and interest in partnering with academia; Race Equality Foundation, with their experience of CYP engagement in research from different ethnicities; Council for Disabled Children, including the Making Ourselves Heard network). From these initial discussions, we will snowball to other organisations using the community organisations' suggestions.

An NIHR equality impact assessment [https://arc-em.nihr.ac.uk/arc-store-resources/equality-impact-assessment-eqia-toolkit, last accessed 6th May 2024] will be conducted as part of the PPI plan development to ensure that recruitment processes are inclusive and do not present barriers to participation or disadvantage to any groups affected by protected characteristics or other marginalising factors.

26 Publication policy

A publication plan will be written. All publications and presentations relating to the trial will be authorised by the TMG.

Data from all sites will be analysed together and published as soon as possible. Individual participating PIs may not publish data concerning their participants that are directly relevant to questions posed by the trial until the TMG has published its report. The TMG will form the basis of the writing committee and advice on the nature of publications, subject to the Sponsor's requirements.

The main trial results will be published in the name of the trial in a peer-reviewed journal on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the TMG, and this may also include high accruing clinicians and/or other people who contribute to the trial. All participating centres and clinicians will be acknowledged in this main publication together with appropriate staff from the CTR and LCTC.

All publications should include a list of participating PIs, and if there are named authors, these should include the CI and Co-Leads, Co-Investigators, Trial Manager, and Statistician involved in the trial, as agreed by the CI and Director of the CTUs. If there are no named authors, a writing committee will be identified.

27 Milestones

Table 13: Project timetable

Project month	Phase	Activities
1-6	Set-up	Finalise protocol, Ethics, HRA & MHRA submission, design data collection tools, site set up and training
7-31	Recruitment and follow up	357 participants across 20 NHS secondary care centres
7-15	Internal pilot	Monitoring to demonstrate feasibility

8-31	Process evaluation	Questionnaire and interviews to assess acceptability to patients, parents/carers and healthcare professionals and barriers and facilitators in the pathway to implementation across the NHS
8-31	Follow-up	Collection of routine hospital stay data, health economics questionnaire
30-36	Analysis and write up	Data analysis and report writing: analysis, discussion of results with PPI panel, trial steering and data monitoring committees plus drafting trial report and manuscripts.
1-36	Dissemination and implementation planning	Working with PPI panel and other key stakeholders; utilising process analysis and survey findings

28 References

1. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med.* 2009;180(1):59-99.
2. Paediatric Formulary Committee. British National Formulary for Children (BNFC) (online) London: BMJ, Pharmaceutical Press, and RCPCH Publications. https://bnfc.nice.org.uk/. Accessed 5th March 2025.
3. Walsh S, Pan S, Sheng Y, et al. Optimising intravenous salbutamol in children: a phase 2 study. *Archives of Disease in Childhood.* 2023;108(4):316-322.
4. Kallis C, Maslova E, Morgan AD, et al. Recent trends in asthma diagnosis, preschool wheeze diagnosis and asthma exacerbations in English children and adolescents: a SABINA Jr study. *Thorax.* 2023.
5. Fleming L, Murray C, Bansal AT, et al. The burden of severe asthma in childhood and adolescence: results from the paediatric U-BIOPRED cohorts. *European Respiratory Journal.* 2015;46(5):1322-1333.
6. Kurukulaaratchy RJ, Raza A, Scott M, et al. Characterisation of asthma that develops during adolescence; findings from the Isle of Wight Birth Cohort. *Respiratory medicine.* 2012;106(3):329-337.
7. Mukherjee M, Stoddart A, Gupta RP, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC medicine.* 2016;14(1):1-15.
8. Society ER. International respiratory coalition lung factors. 2023; https://international-respiratory-coalition.org/diseases/asthma/ Accessed 25th August, 2023.
9. Rakhee Shah AH, Ronny Cheung. International comparisons of health and wellbeing in adolescence. 2019; https://www.nuffieldtrust.org.uk/files/2019-02/1550657729_nt-ayph-adolescent-health-report-web.pdf. Accessed 25th August 2023.
10. Murray CS, Poletti G, Kebadze T, et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. *Thorax.* 2006;61(5):376-382.
11. Al-Mahtot M, Barwise-Munro R, Wilson P, Turner S. Changing characteristics of hospital admissions but not the children admitted—a whole population study between 2000 and 2013. *European journal of pediatrics.* 2018;177:381-388.
12. SIGN/BTS. British guideline on the management of asthma. 2019; https://www.sign.ac.uk/media/2269/sign-158-2024-update-final.pdf. Accessed 5th March 2025, 2025.
13. Sinha I LS, Amusan L, Andrews R, Afful S, Imoedemhe E, Yassin N, Bunning T, Adamson A, Stone P, Quint J, Roberts MC. . National Asthma and COPD Audit Programme: Children and young people asthma secondary care clinical audit 2019/20.

Clinical audit: Data analysis and methodology report. . 2021; https://www.nacap.org.uk/NACAP/welcome.nsf/0/91FB03D588DC19AC802586D80055CC2E/$file/CYPAA_clinical_audit_data_analysis_and_methodology_report_May_2021.pdf.

14. Ibtihal Abdelgadir KM, Ali Hamud, Aiman Zou Zou, Naim Alnasif, Adham Alhaji, Amjad Tonbari, Abdul, Kareem Pullattayil S CP. Second line treatment options (IV aminophylline, versus IV short-actingbeta2-agonist (SABA), versus IV magnesium sulphate, versus SC adrenaline) for children and adolescents with an acute severe asthma exacerbation: a systematic review and meta-analyses of randomized controlled trials (CRD42023405226). . 2023; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023405226. Accessed 8th September, 2023.
15. Morris I, Lyttle M, O'sullivan R, Sargant N, Doull IJM, Powell CVE. Which intravenous bronchodilators are being administered to children presenting with acute severe wheeze in the UK and Ireland? *Thorax.* 2015;70(1):88-91.
16. Gray CS, Powell CV, Babl FE, Dalziel SR, Craig S. Variability of outcome measures in trials of intravenous therapy in acute severe paediatric asthma: a systematic review. *Emergency Medicine Journal.* 2019;36(4):225-230.
17. Yung M, South M, Byrt T. Evaluation of an asthma severity score. *Journal of paediatrics and child health.* 1996;32(3):261-264.
18. Bishop J, Carlin J, Nolan T. Evaluation of the properties and reliability of a clinical severity scale for acute asthma in children. *Journal of clinical epidemiology.* 1992;45(1):71-76.
19. Staniszewska S, Brett J, Simera I, et al. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *bmj.* 2017;358.
20. Ibtihal Abdelgadir AH, Khalid Mudawi, Adham Alhaji, Naim Alnasif, Aiman Zou Zou, Amjad Tonbari, Abdul Kareem Pullattayil S, Colin Powell. The use of intravenous (IV) short-acting-beta2-agonist (SABA) in addition to standard first-line treatment in children and adolescents with an acute severe asthma exacerbation: a systematic review and meta-analysis of randomized controlled trials. 2023; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023405119. Accessed 28th August, 2023.
21. Powell C, Kolamunnage-Dona R, Lowe J, et al. Magnesium sulphate in acute severe asthma in children (MAGNETIC): a randomised, placebo-controlled trial. *The Lancet Respiratory Medicine.* 2013;1(4):301-308.
22. Craig SS, Dalziel SR, Powell CV, Graudins A, Babl FE, Lunny C. Interventions for escalation of therapy for acute exacerbations of asthma in children: an overview of Cochrane Reviews. *Cochrane Database of Systematic Reviews.* 2020;8:CD012977.
23. Neame M, Aragon O, Fernandes RM, Sinha I. Salbutamol or aminophylline for acute severe asthma: how to choose which one, when and why? *Archives of Disease in Childhood-Education and Practice.* 2015.
24. Khalid Mudawi AH, Colin Powell, Amjad Tonbari, Naim Alnasif, Adham Alhaji, Aiman Zou Zou, Abdul, Kareem Pullaattayil IA. The use of intravenous aminophylline in addition to standard first-line treatment in children and adolescents with an acute asthma exacerbation; a systematic review and meta-analysis of randomized controlled trials. . 2023; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023405234. Accessed 28th August 2023.
25. Ali Hamud KM, Colin Powell, Ayman Zou Zou, Naim Alnasif, Adham Alhaji, Amjad Tonbari, Abdul, Kareem PULLATTAYIL S. IA. The use of intravenous magnesium sulphate in addition to standard firstline treatment with inhaled/nebulized short-acting beta2 agonist (SABA) and systemic steroid in the management of acute asthma exacerbations: a systematic review and meta-analyses of randomized controlled trials. . 2023;

https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023405261. Accessed 28th August 2023.

26. Kassisse E, Jimenez J, Mayo N, Kassisse J. Magnesium sulfate vs aminophylline as a second line of treatment in children with severe acute asthma. Randomized clinical trial. *Andes Pediatrica : Revista Chilena de Pediatria.* 2021;92(3):367-374.
27. Roberts G, Newsom D, Gomez K, et al. Intravenous salbutamol bolus compared with an aminophylline infusion in children with severe asthma: a randomised controlled trial. *Thorax.* 2003;58(4):306-310.
28. Assessment HT. 23/43 Management of severe acute asthma in children commissioning brief. 2023; https://www.nihr.ac.uk/documents/management-of-severe-acute-asthma-in-children/32894. Accessed 15th September, 2023.
29. Petrou S, Boland A, Khan K, et al. Economic evaluation of nebulized magnesium sulphate in acute severe asthma in children. *International journal of technology assessment in health care.* 2014;30(4):354-360.
30. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier: NCT06137040, Timely Administration of IV Magnesium Sulfate in Patients With a Moderate Asthma Exacerbation. 2023 Oct 09. https://clinicaltrials.gov/study/NCT06137040. Accessed 6th March 2025.
31. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 - . Identifier: NCT06785272, Magnesium Trial in Acute Asthma in Emergency Department (MAGICIAN). 2023 Oct 09. https://www.clinicaltrials.gov/study/NCT06785272. Accessed 7th April 2025.
32. International Clinical Trials Registry Platform Search Portal (ICTRP) [Internet]. World Health Organization. 2022 May - . Idenitifer: CTRI/2023/01/049011, Intravenous Magnesium Sulphate as a second line therapy in children between 2 to 16 years admitted to PICU with acute severe asthma- A Randomised control trial. 2022 May - https://trialsearch.who.int/Trial2.aspx?TrialID=CTRI/2023/01/049011. Accessed 12th March 2025.
33. Wheeler DS, Jacobs BR, Kenreigh CA, Bean JA, Hutson TK, Brilli RJ. Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial. *Pediatric critical care medicine.* 2005;6(2):142-147.
34. Santana JC, Barreto SSM, Piva JP, Garcia PC. Randomized clinical trial of intravenous magnesium sulfate versus salbutamol in the early management of severe acute asthma in children. *Jornal de pediatria.* 2001;77:279-287.
35. Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. *Cochrane Database Syst Rev.* 2014;2014(5):Cd010909.
36. Griffiths B, Kew KM, Normansell R. Intravenous magnesium sulfate for treating children with acute asthma in the emergency department. *Paediatric Respiratory Reviews.* 2016;20:45-47.
37. Physicians RCo. *Why asthma still kills: the National Review of Asthma Deaths (NRAD) Confidential Enquiry report. .* 2014.
38. Hartshorn S, O'Sullivan R, Maconochie IK, Bevan C, Cleugh F, Lyttle MD. Establishing the research priorities of paediatric emergency medicine clinicians in the UK and Ireland. *Emergency Medicine Journal.* 2015.
39. Cathie K, Sutcliffe AG, Bandi S, Coghlan D, Turner SW, Powell C. Priorities for child health research across the UK and Ireland. *Archives of Disease in Childhood.* 2022;107(5):474-478.
40. CONNECT—Institute of Psychology Health and Society—University of Liverpool. https://www.liverpool.ac.uk/psychology-health-and-society/research/connect/. Accessed 5th March 2025.
41. H. Rojas-Anaya AK, G. Roberts, D. Roland, A. Gupta, M. Lazner, D. James, S. Fitzgerald, F. Cantle, S. Bremner, P. Seddon. High flow humidified oxygen as an early intervention in children with acute severe asthma - a feasibility randomised controlled trial. *European Respiratory Journal.* 2023;in press.

42. Pharma A. Aminophylline hydrate 25mg/ml Solution for injection SmPC. In: Datapharm (for EMC); 07 Nov 2023: https://www.medicines.org.uk/emc/product/6560/smpc. Accessed 17th April 2024.
43. Kalceks A. Magnesium Sulfate 10% w/v Solution for Injection/Infusion SmPC. In: Datapharm (for EMC); 24-Feb-2023 https://www.medicines.org.uk/emc/product/13169/smpc. Accessed 19th September 2024.
44. UK G. Ventolin Solution for Intravenous Infusion 5mg in 5ml (1mg/ml) SmPC. In: Datapharm (for EMC); 23-Oct-2023: https://www.medicines.org.uk/emc/product/853/smpc/print 1/8. Accessed 17th April 2024.
45. Borm GF, Fransen J, Lemmens WA. A simple sample size formula for analysis of covariance in randomized clinical trials. *Journal of clinical epidemiology.* 2007;60(12):1234-1238.
46. Damschroder LJ, Aron DC, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implementation science.* 2009;4(1):1-15.
47. Schroeder D, Luig T, Finch TL, Beesoon S, Campbell-Scherer DL. Understanding implementation context and social processes through integrating Normalization Process Theory (NPT) and the Consolidated Framework for Implementation Research (CFIR). *Implementation Science Communications.* 2022;3(1):13.
48. MacFarlane A, O'Reilly-de Brún M. Using a theory-driven conceptual framework in qualitative health research. *Qualitative health research.* 2012;22(5):607-618.
49. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC medical research methodology.* 2013;13(1):1-8.
50. Ridyard CH, Hughes DA, Team D. Development of a database of instruments for resource-use measurement: purpose, feasibility, and design. *Value in Health.* 2012;15(5):650-655.
51. Garfield K, Husbands S, Thorn JC, Noble S, Hollingworth W. Development of a brief, generic, modular resource-use measure (ModRUM): cognitive interviews with patients. *BMC health services research.* 2021;21:1-12.
52. Care DoHaS. NHS reference costs. 2014; https://www.gov.uk/government/collections/nhs-reference-costs. Accessed 17th December 2023.
53. Unit PSSR. Unit Costs of Health and Social Care. 2022; https://www.pssru.ac.uk/project-pages/unit-costs/. Accessed 12th Jan 2024.
54. Xiong X CN, Huang L, Chen G, Jones R, Devlin N, Mulhern B, Dalziel K. . Psychometric Properties of Child Health Utility 9D (CHU9D) Proxy Version Administered to Parents and Caregivers of Children Aged 2-4 Years Compared with Pediatric Quality of Life Inventory™ (PedsQL). *Pharmacoeconomics.* 2024;Jun;42:147-161.
55. Stevens K. Assessing the performance of a new generic measure of health-related quality of life for children and refining it for use in health state valuation. *Applied health economics and health policy.* 2011;9:157-169.
56. Lindvall K, Vaezghasemi M, Feldman I, Ivarsson A, Stevens KJ, Petersen S. Feasibility, reliability and validity of the health-related quality of life instrument Child Health Utility 9D (CHU9D) among school-aged children and adolescents in Sweden. *Health and Quality of Life Outcomes.* 2021;19(1):193.
57. Turner S, Francis B, Vijverberg S, et al. Childhood asthma exacerbations and the Arg16 β2-receptor polymorphism: a meta-analysis stratified by treatment. *Journal of Allergy and Clinical Immunology.* 2016;138(1):107-113. e105.
58. Lipworth BJ, Basu K, Donald HP, et al. Tailored second-line therapy in asthmatic children with the Arg16 genotype. *Clinical science.* 2013;124(8):521-528.

59. Popay J, Collins, M., & with the PiiAF Study Group. *The public involvement impact assessment framework guidance.* Universities of Lancaster, Liverpool and Exeter.; 2014.
60. BTS/SIGN/NICE. Acute asthma in children, SIGN 244 guidelines. 2019; https://rightdecisions.scot.nhs.uk/asthma-pathway-bts-nice-sign-sign-244/managing-acute-asthma/management-of-acute-asthma-in-children/acute-asthma-in-children/. Accessed 5th March 2025, 2025.

29 Appendices

Appendix 1

Table 15: Overall Assessment of Asthma Severity: Please use the criteria in this table to guide your overall assessment of asthma severity. Taken from NICE BTS/SIGN management of acute asthma guidelines 2024[60].

	Moderate	Acute Severe	Life-Threatening
Age 2-5 years	- SpO_2 ≥ 92% in room air - No features of acute severe asthma	- SpO_2 < 92% in room air - Too breathless to talk or feed - HR > 140/minute - RR > 40/minute - Use of accessory muscles	SpO_2 < 92% in room air plus any of the following - Silent chest - Poor respiratory effort - Agitation, confusion, cyanosis - Hypotension - Exhaustion
Age >5 years	- SpO_2 ≥ 92% in room air - No features of acute severe asthma	- SpO_2 < 92% in room air - Too breathless to talk - HR > 125/minute - RR > 30/minute - Use of accessory muscles - PEF 33-50%	SpO_2 < 92% in room air plus any of the following - Silent chest - Poor respiratory effort - Agitation, confusion, cyanosis - Hypotension - Exhaustion - PEF < 33%

HR = heart rate, PEF = peak expiratory flow, RR = respiratory rate, SpO_2 = Arterial oxygen saturation
Note: If a patient has signs or symptoms from multiple categories rate according to the most severe features.