Salbutamol for Analgesia in Renal Colic: A prospective, randomised, placebo-controlled Phase II trial (SARC)	
Version and Date of Protocol:	V2.1 15/JUL/2019
Sponsor:	University Hospitals of Derby and Burton NHS Foundation Trust
Chief Investigator:	Dr Graham Johnson
EudraCT Number:	2018-004305-11
Local Study Reference:	DHRD/2018/079
IRAS Number:	252075
ISRCTN number:	tbc
Funder(s):	NIHR – Research for Patient Benefit (RfPB)
This protocol has regard for the HRA guidance	

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host NHS Trust, regulatory authorities, and members of the Research Ethics Committee.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the CTU's SOPs, and other regulatory requirements as amended.
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 study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Protocol v2.1 15th July 2019 authorisation signatures:

For and on behalf of the Study Sponsor:

Signature: ……. Date: ……/……/……

Name (please print): ……

Position: ……

Chief Investigator:

Signature: ……. Date: ……/……/……

Name (please print): ……

Statistician:

Signature: ……. Date: ……/……/……

Name (please print): ……

Position: ……

KEY TRIAL CONTACTS

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TRIAL SUMMARY

Trial Title:	Salbutamol for analgesia in renal colic: A prospective, randomised, placebo-controlled Phase II trial	
Local Study Reference:	DHRD/2018/079	
Clinical Phase:	Phase II	
Trial Design:	Single centre, prospective randomised, placebo-controlled trial	
Trial Participants:	Consecutive adult patients presenting to the emergency department with a working diagnosis of renal colic and a requirement for intravenous analgesia.	
Planner Number of Sites:	1	
Planned Sample Size:	It is estimated that 118 patients with suspected renal colic will need to be recruited in order to enrol 106 patients with subsequently confirmed renal colic (to inform the primary outcome analysis)	
Treatment Duration:	Single dose (3-5 minute injection)	
Follow Up Duration:	24 hours or until hospital discharge, whichever takes place first	
Planned Start Date:	16th September 2019	
Planned Recruitment End Date:	31st July 2021	
Planned Study End Date:	1st August 2021	
	Objectives	**Outcome Measures**
Primary:	To explore whether salbutamol is an efficacious analgesic adjunct when added to the standard analgesic regime for patients presenting to the ED with subsequently **confirmed** renal colic.	The difference in the change in pain scores (measured on an 100mm Visual Analogue Scale [VAS]) from baseline to 30 minutes post drug administration between trial arms in patients with "Confirmed Renal Colic"
Secondary:	1. To explore whether salbutamol could be an efficacious analgesic adjunct when added to the standard analgesic regime for patients presenting to the ED with **suspected** renal colic. 2. To assess the feasibility of conducting a definitive phase III multi-centre randomised	1. The difference in the change in pain scores from baseline to 30 minutes post drug administration between trial arms in patients with "Suspected Renal Colic" 2. The difference in the change from baseline pain score to pain scores at the following time points between trial arms: 15min, 60min, 120min, 240min,

	controlled trial (RCT) of the cost and clinical effectiveness of salbutamol as an analgesic adjunct for patients with renal colic when added to the standard analgesic regime in the ED.	and then four-hourly thereafter, until 24hours post drug administration or hospital discharge (whichever happens first). 3. The difference in the change in qualitative pain description from baseline to the following time points between trial arms: 15min, 30min, 60min, 120min post drug administration. 4. Frequency and dose of morphine during the first 24h from enrolment (including prehospitally) 5. Any other analgesics required and the timing of their administration 6. Length of hospital stay 7. Presence/absence, site and size of renal calculus 8. Degree of hydronephrosis (if present) 9. Side effects of trial treatment 10. The mean and standard deviation of the primary outcome 11. Other feasibility outcomes to inform subsequent trial design
Investigational Medicinal Product(s):	Salbutamol (Ventolin®)	
Formulation, Dose, Route of Administration:	**Salbutamol formulation:** 500micrograms/ml presented as ampoules of 1ml, each containing 500 micrograms salbutamol as salbutamol sulphate BP in a sterile isotonic solution.	

	Dose: 250 micrograms salbutamol in Sodium Chloride 0.9% (5ml) or Placebo (5ml Sodium Chloride 0.9%) **Route of administration:** Slow intravenous injection over 3-5 minutes.

FUNDING AND SUPPORT IN KIND

Funder(s)	**Financial and Non-Financial Support Given**
NIHR – Research for Patient Benefit (RfPB)	£149,832

ROLES & RESPONSIBILITIES

University Hospitals of Derby and Burton NHS Foundation Trust (UHDB), as the sponsor of this trial has delegated certain duties to the Derby Clinical Trials Support Unit and the Chief Investigator in the conduct of the trial, as outlined in a tripartite Division of Responsibilities. UHDB controls the final decision regarding any aspects of the trial, as outlined within this tripartite agreement.

Patient and public (PPI) representatives have been involved in the design and final review of the protocol as well as other aspects of trial design, including reviewing documentation. They will be involved in the Trial Management Group and will attend meetings to give them an opportunity to input into the ongoing management of the trial.

Sponsor

The Sponsor, University Hospitals of Derby and Burton NHS Foundation Trust, take on overall responsibility for appropriate arrangements being in place to set up, run and report the research project. The sponsor is not providing funds for this trial but has taken on responsibility for ensuring finances are in place to support the research.

Funder

The trial is funded by the National Institute of Health Research (NIHR) Research for Patient Benefit (RfPB) programme.

Trial Management Committees

Trial Management Group

The trial management group will meet regularly (as detailed within the trial monitoring plan) to oversee the day-to-day management of the trial, including all aspects of the conduct of the trial. Any problems with trial conduct and participating centres will be raised and addressed during TMG meetings.

Trial Steering Committee

The trial steering committee will oversee and supervise the progress of the trial and ensure that it is being conducted according to ICH-GCP and the applicable regulations. The TSC is an independent body that includes majority members who are not involved with the running of the trial (known as independent members). TSC meetings will be held according to the monitoring plan and may be conducted in person, or remotely via teleconference.

Data Monitoring and Ethics Committee

The data monitoring and ethics committee will review the accruing trial data and will assess whether there are any safety issues that should be brought to the participant's attention or any reasons to terminate the trial. They will also review the scientific validity and the conduct of the trial. DMEC meetings will be held according to the monitoring plan.

Protocol Contributors

A number of protocol contributors have been involved in the development of this protocol; these include:

Chief Investigator (Graham Johnson)
Co-applicant (Andrew Tabner)
Trial Statistician (Apostolos Fakis)
Trial Pharmacist (Liz Bedford)
Data Manager (Victoria Chester)
Trial Manager (Rachelle Sherman)
Statistical Advisor (Richard Jackson)
Academic Advisor (Sue Mason)

Protocol contributors are responsible for inputting into the design of the trial, ensuring that it is designed transparently and efficiently. All have reviewed the final version of the protocol and assume responsibility for the academic and methodological rigour of the trial.

Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
DMEC	Data Monitoring and Ethics Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials
IV	Intravenous
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person

RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TMF	Trial Master File

TRIAL PROTOCOL

1. BACKGROUND

Renal colic is the pain experienced by a patient when a renal calculus (kidney stone) causes partial or complete obstruction of part of the renal outflow tract. The lifetime incidence is approximately 12% in males and 6% in females (1), with recurrence rates approaching 50% (2). The Royal Derby Hospital Emergency Department treats approximately 400 patients a year with renal colic.

The standard analgesic regimes for renal colic are often ineffective; in some studies less than half of patients achieve complete pain relief and a large proportion of patients require rescue analgesia within four hours (3).

Current analgesic regimes are also associated with significant side effects. Treatment strategies usually involve a non-steroidal anti-inflammatory drug (NSAID) and an opiate (e.g. intravenous morphine). Opiates are known to cause nausea, vomiting, drowsiness and respiratory depression (4). Oral absorption of NSAIDs in this cohort can be poor due to gastroparesis and vomiting; rectal administration is frequently felt by patients to be unpleasant.

The onset of action of the existing analgesic options is slow (4,5); NSAIDS require a period of absorption before they are effective and intravenous opioids are controlled drugs, the administration of which is often delayed by practical concerns in their dispensing and prescription.

Our patient and public involvement group have emphasised how intolerable renal colic is, how slow and inadequate the analgesic regimes can be, and how unpleasant the side effects are. They have also noted the importance of remedying these factors with future research (6).

It has been hypothesised that beta adrenoreceptor agonists may reduce the pain of renal colic (7–10). Salbutamol is a beta adrenoreceptor agonist with widespread use across the health service for multiple indications, extensive staff familiarity and a good side effect profile (11).

Beta adrenoreceptors agonists have been shown to impact on a number of factors that target the physiological causes of pain in renal colic (ureteric spasm and increased peristalsis, increased pressure at the renal pelvis and prostaglandin release with inflammation) (12). They:

- Promote ureteral relaxation (9,13–16)
- Reduce frequency of ureteral contractions (17)
- Reduce renal pelvic pressure (18)

Approximately 60% (19) of an intravenous dose of salbutamol is excreted, unchanged, in the urine; there is therefore the potential for both systemic and local stimulation of beta-adrenoreceptors to take place.

The protocol authors have completed a systematic review (20); there have been no trials of beta agonists as analgesics in renal colic and there are no registered clinical trials on this topic. However, there is extensive evidence (both in the laboratory and other clinical settings) suggesting it may be effective, and a number of authors have identified this as a promising research avenue.

There is biological plausibility and a body of evidence sufficient to suggest that this novel treatment for the pain of renal colic should be taken to a phase II clinical trial.

Medical Expulsive Therapy and time to stone passage

Many studies have investigated agents which may decrease time to stone passage; this is NOT the primary outcome of interest in this trial but is included within the secondary outcomes.

It is worth noting that the previous research in this area supports the potential efficacy of salbutamol as an analgesic adjunct in renal colic via the process of ureteral relaxation (the same process thought to speed stone passage in the aforementioned studies).

The use of alpha adrenoreceptor antagonists as medical expulsive therapy to speed stone passage is a practice previously widely recommended (21) but more recently brought into question (22). The action of alpha adrenoreceptor antagonists in the renal tract is similar to that of beta agonists; they reduce the force and frequency of ureteral contractions.

Alpha adrenoreceptor antagonists have previously been shown to reduce the number of pain episodes during the management of renal colic (21) but this has never formed the main focus of research and their use is uncommon within emergency departments in the UK; the likely reasons for this are discussed below.

Onset: The onset of action of salbutamol is measurable in minutes (11) whereas tamsulosin reaches peak levels after 6 hours and steady state after five days. Salbutamol is therefore much more appropriate as a potential analgesic for acute pain in the emergency department setting.

Familiarity: Emergency department staff administer salbutamol in inhaled, nebulised and intravenous forms on a regular basis. This means there will be fewer barriers to adoption.

Side effects: The side effects of salbutamol (fast heart rate, tremor) are relatively minor compared to those of alpha blockers (low blood pressure, fainting, nausea), even at high doses, and are likely therefore to be better tolerated by patients (11,21).

2. RATIONALE

Scientific Justification

Pain in renal colic is caused first by ureteric peristalsis, followed by ureteral spasm and then subsequent inflammation and oedema (12).

β-agonists are known to reduce ureteric peristalsis and spasm, and it is therefore hypothesised that its use will reduce the pain associated with renal colic. Additionally, salbutamol is excreted unchanged in the urine and therefore has the potential for both systemic and topical action as detailed below.

In Vitro

β_1-, β_2- and β_3-adrenoceptors are found in the smooth muscle and urothelium of the human ureter (13).

β-agonists decrease the tone of contractions of the human ureter (13).

Stimulation of β_2 receptors decreases the contraction of the human ureter (14).

β_2 receptors are present in human ureteral smooth muscle; their stimulation mediates ureteral relaxation (15).

A systematic review has identified that β adrenergic stimulation inhibits ureteral activity (16).

In Vivo

β-agonists decrease the frequency and amplitude of contractions in the canine ureter (23).

β-agonists inhibit peristalsis in the canine ureter (24).

β-agonists reduce renal pelvic pressure and ablate ureteral peristalsis (25).

Topical and systemic β-agonists decrease the frequency and amplitude of ureteral contractions in the pig ureter (17).

Human evidence

Endoluminal isoproterenol decreases renal pelvic pressure during flexible ureterorenoscopy (18,26).

Alpha blockers (which also mediate ureteral relaxation) have been shown to reduce the frequency of pain episodes in patients with renal colic, as well as reducing the need for other analgesics (21).

Potential Benefits

Patient and Public Involvement (PPI) work conducted by the research team demonstrated the clear and urgent need for faster, more effective pain relief that causes fewer side effects (6). Salbutamol has the potential to fulfil that clinical and patient need. If salbutamol is subsequently proven to be an effective analgesic in patients suffering with renal colic, the benefits are myriad:

- **Improved Analgesia:** Pain in renal colic is caused by ureteric spasm and increased peristalsis, as well as increased pressure at the renal pelvis and prostaglandin release with inflammation (12). Beta agonists relax the ureter, potentially providing physiologically targeted pain relief.

- **Reduced time to pain relief:** Salbutamol has onset of action within 5 minutes, with early peak effect (11). This is significantly quicker than all existing analgesic options, where peak effects occur between 20 and 60 minutes after administration (4,5).
- **Route of administration:** The need for parenteral administration was highlighted as a priority during the PPI work (6), due to the frequent association of nausea and vomiting with both renal colic and opiates. Salbutamol is solely administered parentally, and its aerosolised form means it can be administered prior to securing intravenous access, further reducing the time to analgesia.
- **Better side effect profile:** Salbutamol's side effect profile is well recognised and relatively narrow, especially when compared to the combined components of the existing analgesic regime. The side effects of current treatments were also highlighted by the PPI group as a notably unpleasant part of treatment and any measures which reduce these were welcomed (6).
- The use of salbutamol may reduce the need for other analgesic agents and their associated side effects.
- **Staff burden:** Salbutamol is not a controlled drug, enabling nursing staff to access and administer it more readily. This reduces nursing and physician burden whilst decreasing time to administration when compared to intravenous opiates.
- **Reduced admissions and length of stay:** Patients with uncomplicated renal colic can be discharged once their pain is controlled; persisting pain is frequently the sole reason for continuing admission. A more effective analgesic regime may result in a shorter length of stay, whilst avoiding some admissions entirely. This has clear potential cost, service and patient benefits that will be investigated in the subsequent planned phase III trial.
- It is also possible that salbutamol may positively impact the time to stone passage.
- **Home use:** Patients with known renal colic may be able to self-medicate with a salbutamol inhaler, avoiding the need for hospital attendance entirely.
- **Speed of adoption:** Staff familiarity with salbutamol and its already widespread use means that subsequent translation into clinical practice will be easier and faster than if an alternative beta agonist were studied.

Expert advice has already been sought on route of drug delivery from both a phase II trial methodologist (Richard Jackson, Liverpool CTU) and a Professor of Drug Discovery (Patrick Barton, University of Nottingham).

Intravenous salbutamol is the IMP for this phase II trial. Inhaled salbutamol is certainly a feasible option (and will likely form part of the phase III trial design) but for the purposes of this phase II trial it was felt important to maximise bioavailability and reduce confounding factors in terms of absorption in order to ensure maximal safe serum levels such that any potential efficacy signal on the primary endpoint is apparent.

This trial represents a re-purposing of an established treatment. We have therefore employed the established maximum safe and efficacious intravenous dose used for acute exacerbations of asthma; this dose is safe for patients who meet the inclusion criteria (11). A higher dose is possible but is associated with a greater frequency of side effects (11); this dose is employed in pregnant women in pre-term labour where the potential benefits outweigh the potential harms.

2.1. Assessment and Management of Risk

As per the requirements of the sponsor, a full risk assessment has been conducted identifying risks, their likelihood, impact and detectability in order to produce a risk score that will be used to

determine mitigation strategies. Such mitigation strategies will be implemented in trial documentation including the monitoring plan as well as the protocol itself.

The frequently occurring side effects of tremor and tachycardia are very well tolerated by the majority of patients and were felt by our patient group to be acceptable if salbutamol is proven to be an effective analgesic. Patients with ischaemic heart disease tolerate tachycardia less well and for this reason are excluded from this trial. Rare occurrences of myocardial ischaemia with the use of high doses of salbutamol have been identified (11). The dose being administered in this trial is the typical "loading" dose of intravenous salbutamol used when patients are having an acute, severe and/or life-threatening asthma attack. Such patients have typically already received large doses of inhaled beta-agonist in addition to this intravenous dose. It is therefore not thought that the proposed dose poses a significant risk in patients without known ischaemic heart disease.

The dose and rate of administration chosen are the same as that for the relief of severe bronchospasm; 250microcgrams diluted to a total volume of 5ml with 0.9% Sodium Chloride and given by slow intravenous injection over 3-5 minutes (11,27).

Salbutamol is known to precipitate hypokalaemia (11). Literature assessing the magnitude of this effect suggests a drop of 0.87-1.4mmol/l (28) with a bolus dose of intravenous salbutamol. However, this trial data is largely obtained in patients with underlying hyperkalaemia and it would appear that the lower the baseline serum potassium the smaller the drop seen with intravenous salbutamol. Additionally, the doses used in studies identified in the review paper referenced use a higher dose of salbutamol than this trial protocol dictates. Finally, 40% of patients identified in the review paper were non-responders to salbutamol i.e. intravenous salbutamol did not cause a fall in serum potassium. As such we feel the potential side effect of hypokalaemia secondary to a single bolus dose of intravenous salbutamol is likely to be clinically insignificant. However, we dictate that serum potassium must be ≥3.7mmol/l for a participant to be eligible for enrolment. Symptomatic hypokalaemia secondary to trial medication will be recorded as an adverse reaction.

Risks surrounding cannulation of the patient, taking of blood samples and preparation of the trial medication are covered by existing nursing staff training and procedures and provide no additional risk above normal patient care.

This trial is categorised as:

Type A = No higher than the risk of standard medical care – the trial involves the use of a medicinal product licensed in an EU member state, used for an off-label indication, supported by extensive clinical experience with the product and no reason to suspect a different safety profile in the trial population (29).

3. OBJECTIVES AND OUTCOME MEASURES/ ENDPOINTS

The trial proposes to investigate the potential efficacy of salbutamol as an analgesic adjunct in patients with confirmed renal colic and to collect feasibility data to inform the development of a subsequent phase III randomised controlled trial.

3.1. Primary Objective

To explore whether salbutamol is an efficacious analgesic adjunct when added to the standard analgesic regime for patients presenting to the ED with subsequently confirmed renal colic. The addition of salbutamol will be compared to the addition of placebo to the standard analgesic regime for patients with confirmed renal colic.

3.2. Secondary Objectives

To explore whether salbutamol could be an efficacious analgesic adjunct when added to the standard analgesic regime for patients presenting to the ED with suspected renal colic.

To assess the feasibility of conducting a definitive phase III multi-centre randomised controlled trial (RCT) of the cost and clinical effectiveness of salbutamol as an analgesic adjunct for patients with renal colic when added to the standard analgesic regime in the ED.

3.3. Primary Endpoint / Outcome

The primary outcome will be the difference in the change in pain scores (measured on an 100mm Visual Analogue Scale [VAS]) from baseline to 30 minutes post drug administration between trial arms in patients with "**Confirmed** Renal Colic".

3.4. Secondary Endpoints / Outcomes

1. The difference in the change in pain scores (measured on an 100mm Visual Analogue Scale [VAS]) from baseline to 30 minutes post drug administration between trial arms in patients with "**Suspected** Renal Colic"
2. The difference in the change from baseline pain score to pain scores at the following time points between trial arms: 15min, 60min, 120min, 240min, and then four-hourly thereafter, until 24 hours post drug administration or hospital discharge (whichever happens first) in both of the above subgroups.
3. The difference in the change in qualitative pain description from baseline pain assessment to pain assessments at the following time points between trial arms as measured using the short-form McGill Pain Questionnaire: 15min, 30min, 60min, 120min post drug administration.

4. Frequency and dose of morphine during the first 24 hours from enrolment (including prehospitally)
5. Any other analgesics required and the timing of their administration
6. Length of hospital stay
7. Presence/absence, site and size of renal calculus
8. Degree of hydronephrosis (if present) as identified on routine imaging
9. Side effects of trial treatment
10. The mean and standard deviation of the primary outcome
11. Feasibility outcomes to inform subsequent trial design, including:
    - Screening rate
    - Randomisation rate
    - Recruitment rate
    - Participant retention
    - Any identified process issues
    - Volume of missing data
    - Patient compliance with trial assessments
    - Proportion of enrolled patients with confirmed renal colic
    - Emergency department diagnosis
    - Hospital discharge diagnosis
    - Patient satisfaction with the trial medication, process and delivery within the ED, including their belief regarding arm of the trial to which they were randomised

4. TRIAL DESIGN

This Phase II randomised-controlled trial will be composed of two groups:

- Intervention group: Intravenous salbutamol + standard analgesic regime
- Placebo group: Intravenous Sodium Chloride 0.9% + standard analgesic regime

Eligible participants will be those presenting to the emergency department with symptoms suggestive of renal colic and meeting the eligibility criteria (Section 6).

5. TRIAL SETTING

This trial will take place in the emergency department of the Royal Derby Hospital, a University hospital with approximately 130,000 emergency department presentations per year, approximately 400 of whom are adults presenting with renal colic. The centre has an active emergency medicine research group (REMEDY) with experience recruiting to both commercial and non-commercial NIHR portfolio trials. The department has a senior medical clinician based within the triage area for rapid assessment and diagnosis; this enables us to develop a working diagnosis and initiate management rapidly after patient arrival in the department.

6. ELIGIBILITY CRITERIA

The trial population will consist of adults (≥18 years old) presenting to the emergency department complaining of abdominal and/or flank pain, consistent with a working diagnosis of renal colic.

Patients aged ≥50 must have the serious differential diagnosis of abdominal aortic aneurysm (AAA) excluded prior to consent in line with standard practice (30). Females of child-bearing potential must have the serious differential diagnosis of ectopic pregnancy excluded prior to consent in line with standard practice.

Potential participants will be assessed to determine the working diagnosis and immediate treatment requirements as part of routine practice. This normal treatment for patients with suspected renal colic (including standard analgesia) can be given prior to trial screening. If the working diagnosis following this assessment is felt to be renal colic, the patient will be screened for trial eligibility by one of the GCP-trained clinicians working within the department.

6.1. Inclusion Criteria

The trial population will consist of consecutive adults presenting to the Emergency Department in whom ALL of the following apply:

1. Subjects capable of giving informed consent
2. Age ≥18
3. Working diagnosis of renal colic, as suggested by severe flank/unilateral abdominal pain, +/- radiating to suprapubic/groin area
4. Experiencing severe pain with a requirement for intravenous analgesia

6.2. Exclusion Criteria

The participant will not enter the trial if ANY of the following apply:

1. Abdominal aortic aneurysm not yet excluded **and** participant aged ≥50 (30)
2. Ectopic pregnancy not yet excluded in a female of child-bearing potential.
3. Currently actively taking part in another CTIMP

4. Previous participant in this trial
5. Unable to understand verbal and/or written information in English
6. Known allergy to salbutamol (11)
7. Evidence of sepsis or clinical suspicion of urinary tract infection
8. Serum potassium <3.7mmol/l as measured on "point-of-care" venous blood gas
9. Concomitant use of: **any** beta blockers (11) (including beta-blocker containing eye drops (31)); prolonged release opiates; long-acting β-agonists
10. Use of short-acting β2-agonists within the 6 hours preceding presentation to the emergency department
11. Current arrhythmia (defined as non-sinus rhythm)
12. History of any of:
    - ischaemic heart disease
    - arrhythmogenic heart disease
    - valvular heart disease
    - unilateral kidney
13. Any other contraindication to the use of salbutamol

7. TRIAL PROCEDURES

A schedule of assessments can be found in Section 7.7.

7.1. Recruitment

7.1.1. Patient Identification

Patients arriving into the emergency department (ED) will be identified as potentially eligible for the trial by the clinical team and undergo routine assessment to determine working diagnosis. Treatment requirements should continue, and standard treatment may be given as per local guidelines prior to recruitment onto the trial. If the patient appears to meet the eligibility criteria (Section 6), they will be provided with information about the trial.

Advertising materials such as posters are provided to increase awareness of the trial to support recruitment and patient information.

7.1.2. Screening

Eligibility will be reviewed against the inclusion and exclusion criteria as detailed in Section 6 by a member of staff with appropriate trial training. **Where further tests are required to be performed to assess eligibility, informed consent must be taken prior to these taking place (i.e. patients that do not have a bedside potassium measurement or an ECG performed as part of their routine clinical care).**

All participants considered as potentially eligible for the trial will be recorded on the screening log with reasons for non-participation identified (in order to contribute towards secondary outcomes).

7.2. Consent

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial.

The Principal Investigator (PI) retains overall responsibility for the informed consent of participants and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent according to the REC-approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

Patients will be provided with an information sheet and provided adequate time to review the information and ask any questions they may have, including discussions with the research team, non-research staff members as well as family and friends. Their normal treatment (standard analgesic regime) may continue independently of this decision-making time and trial screening.

Patients who are unable to consent for themselves for suitability for the trial will not be approached as obtaining patient reported outcome measures will not be practical. Written material will not be provided in various languages for the purpose of this Phase II trial. This trial utilises questionnaire surveys that have not been validated in different languages. There is also a qualitative element to the trial where lack of required language skill may prove to be difficult. Recruitment into the trial is time-sensitive which must be considered when considering the availability of translation services.

The PI is responsible for ensuring that all subjects are protected and participate voluntarily, free from coercion or undue influence. Patients may refuse to participate without giving reason, however where possible, reasons for non-participation will be noted on the screening log.

7.3. Standard Analgesic Treatment

Analgesia, aside from the trial treatment, will be managed according to the local guidelines for patients presenting with acute suspected renal colic.

7.4. The Randomisation Scheme

Randomisation will be based on a computer-generated randomisation list, created using random permuted blocks of randomly varying size and implemented using a “scratch card” randomisation system. The randomisation list will be prepared using NQuery Advisor software by an unblinded statistician. Allocation will be in the ratio 1:1 without any stratification factors.
Participants will be randomly allocated to one of two trial groups:

- **Intervention group:** Single dose of 250 micrograms salbutamol in 5ml sodium chloride via slow intravenous injection over 3-5 minutes

- **Placebo group:** Single dose of 5 ml Sodium Chloride 0.9% via slow intravenous injection over 3-5 minutes

7.4.1. Method of Implementing the Allocation Sequence

Randomisation will be carried out using scratch cards with the allocation concealed by silver scratch-off stickers. The scratch cards will be filed in a card dispenser (or "card shoe") to allow an unblinded staff member to draw the next card in the correct randomisation order and reduce the chance of re-ordering. The allocation is revealed by scratching off the silver area on the scratch card.

7.5. Blinding

The individuals and roles that should be blinded to treatment allocation are detailed in the Randomisation Schedule.

In order to maintain the blind for treatment administration, both trial treatments will be presented as identical syringes containing 5ml of a colourless solution labelled with a pre-printed trial label. This will be prepared by unblinded staff delegated responsibility for randomising patients and preparing trial medication.

No staff member with knowledge of the treatment allocation, as indicated in the Randomisation Schedule, will have any involvement in collecting trial data or administering trial treatment.

Any accidental unblinding of staff or participants should be recorded as a non-compliance.

Pre-trial testing of both the randomisation and blinding procedures will be performed to ensure the effectiveness of the proposed methodology and will be documented in the risk assessment of the trial.

7.6. Unblinding

Unblinding of participants should only occur for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary to know which treatment the patient is receiving before they can be treated. All instances of unplanned patient unblinding should be clearly documented in the participant's medical notes (together with the reasons for doing so) and recorded in the investigator site file. Details regarding the unblinding of participants must be forwarded to the Chief Investigator and the Sponsor (via the Derby CTSU Trial Manager) without revealing the allocation.

7.6.1 Emergency unblinding

The procedure for emergency unblinding can be found in the investigator site file. Responsibility for the emergency unblinding of any participant on the trial resides with the investigator. If emergency unblinding is required for clinical reasons, this can be initiated by any treating healthcare professional. They will not be required to discuss unblinding with anyone in the research team if they feel that unblinding is necessary. The sponsor is not required to be involved in the decision to unblind a patient in an emergency situation.

Once treatment allocation details are known, the treating health care professional will continue to provide ongoing clinical care as appropriate. The unblinding, together with reasons for doing so, will be documented in the participant's medical notes.

The randomisation list for the trial must be held securely within the pharmacy department, in a controlled area, separate to the investigator site file and easily accessible by those authorised to reveal treatment allocation at the site.

In the event that the unblinding process cannot occur (e.g. out of hours) the requester should assume that the patient has received IMP and treat according to symptoms/physiology; there is no reversal, antidote or specific treatment for the sequelae of salbutamol use that cannot be managed appropriately using this approach.

7.6.2 Unblinding for a potential SUSAR

In the event of a suspected SUSAR that has not required emergency unblinding for clinical reasons, the Sponsor will take appropriate action and seek to reveal the treatment allocation of the individual participant concerned in accordance with regulatory requirements (see Section 9.4).

7.6.3 Planned unblinding

Final unblinding of the data will occur following final database lock. Interim unblinding of the data will be performed by the unblinded statistician in order to prepare reports for the Data Monitoring and Ethics Committee (DMEC).

7.7. Trial Assessments

Following informed consent, the following assessments should be conducted at the time points outlined in Table 1 and continue until 24 hours post-trial medication administration or hospital discharge (whichever happens first).

Procedures			Administration of trial medication	Time from start of trial drug administration (mins)				Follow Up (hours)					
	Screening	Baseline*		15	30	60	120	4	8	12	16	20	24
Eligibility assessment	X	X											
Demographics	X												
Informed consent	X												
ECG		X											
Blood gas measurement (K^+)		X											
Randomisation		X											
o Respiratory rate o Oxygen saturations o Blood pressure o Heart rate		X		X	X	X	X						
VAS Pain Score		X		X	X	X	X	X	X	X	X	X	X
McGill Questionnaire		X		X	X	X	X						
Adverse event assessments				X	X	X	X	X	X	X	X	X	X
Satisfaction Questionnaire							X						
OPTIMISED SWAT Questionnaire							X						
Protocol Non-Compliances	X	X		X	X	X	X	X	X	X	X	X	X

Table 1: Schedule of Assessments for the SARC trial

*All baseline assessments should take place **immediately prior** to administration of trial treatment

7.8. Baseline Assessments

The following measurements should be undertaken **immediately prior** to administration of the trial treatment:

- Baseline pain assessment using a Visual Analogue Scale (VAS) and McGill Pain Questionnaire (Section 7.8.1)
- Respiratory rate (RR)
- Oxygen saturations (SaO_2)
- Blood pressure (BP)
- Heart rate (HR)

7.8.1. Pain Scores

All pain score measurements for the trial will take place using a Visual Analogue Scale [VAS] 0-100mm (apart from the pre-enrolment score to ensure eligibility, which will be a NAS as per routine practice). Patients should record their own pain scores on a VAS sheet. The Visual Analogue Scale will be a 100mm line with cues at either end (0 = no pain, 100mm = worst pain) and patients will be asked to mark their current pain score with a cross at each time point listed below.

The qualitative assessment of participants' pain will be obtained using the short-form McGill Pain Questionnaire.

7.9. Administration of Treatment

Treatment must be administered by staff blinded to treatment allocation and recorded on the prescription chart using the pre-printed label provided. The participant will receive either:

- **Intervention group:** Single dose of 250 micrograms salbutamol in 5ml via slow intravenous injection over 3-5 minutes, followed by a 5ml flush of Sodium Chloride 0.9%

  Or

- **Placebo group:** Single dose of 5 ml Sodium Chloride 0.9% via slow intravenous injection over 3-5 minutes, followed by a 5ml flush of Sodium Chloride 0.9%.

Details for the drawing up and administration of the trial medication are available in the pharmacy manual.

7.10. Follow-up Assessments

Follow up assessments must be undertaken by staff blinded to the treatment allocation at the time points indicated in Table 1 until either 24 hours after administration of trial medication or discharge from the hospital (whichever is sooner). Participants should be monitored in the Emergency Department for at least 120 minutes following trial drug administration.

Patients will record their own pain scores on a VAS sheet, whilst the research team will record trial-specific observations on a separate eCRF.

If patients report a significant deterioration in their pain levels in the 30 minutes following administration of trial medication then further analgesia may be administered at the clinician's discretion; a suspected exacerbation of pain due to trial treatment should be recorded as an adverse reaction, with any required treatment recorded as concomitant medication.

At 120 minutes following treatment administration or upon emergency department discharge (whichever comes first) the patient will be asked to complete a satisfaction questionnaire regarding pain relief and their experience of the trial in the emergency department. Presence/absence of renal calculus will be determined by appropriate imaging (CT renal tract or XR KUB); this takes place in the course of normal treatment and should take place within 24 hours of admission in routine practice. Results of the imaging will be reviewed at the same time that discharge diagnosis is identified.

As data will be collected from assessments conducted during the participants' inpatient stay it is unlikely that any will be deemed "lost to follow up". In cases where the ongoing collection of data becomes impossible, for example should the patient require further treatment that takes them away from the team, every effort will be made to collect data and reduce missing data. If this is unachievable, the participant will be considered "lost to follow-up".

The patient's active participation in the trial will end at 24 hours from treatment administration or at discharge from the hospital (if this is earlier than 24hours).

7.10.1. Qualitative Assessments – Nested Studies

A "Study within a Trial (SWAT)" will be undertaken to assess the impact of different participant information sheets on recruitment rates; more information is provided in **Appendix 3**. Patients identified as eligible to take part in the main trial will be provided with either PIS A (optimised format, an A4 booklet) or PIS B (conventional format). This will be determined randomly and patients will not be made aware of the different formats available.

Participants should also be asked to complete the optional "OPTIMISED Decision-Making Questionnaire" at the 120min follow-up that will assess patient satisfaction with the participant information sheet they were given.

7.11. Withdrawal Criteria

Participants may withdraw consent to participate in the trial at any time; this will be explained to them at the time of consent. It will also be explained that their rights to access, change or remove their data once collected will be limited due to the requirements of the trial.

Participants will be withdrawn from the trial under any of the following circumstances:

- Withdrawal of participant's consent

- Violation of inclusion / exclusion criteria identified prior to trial medication administration.

Given the single administration of trial medication and the short duration of its action, there are no foreseen situations where an individual participant would need to be withdrawn from the study for safety reasons after administration of the trial medication. Side effects of trial treatment are included within the secondary outcomes.

In the unlikely event that participants withdraw prior to completion of the primary outcome then it is planned that trial recruitment will continue until the target sample size is reached.

Patients withdrawn prior to trial medication administration will continue with standard care. If participants withdraw their consent to further trial assessments then these will not take place but any previously collected data will be used in the analysis.

7.12. End of Trial

The end of trial will be defined as the final assessment of the last participant. The MHRA and REC will be notified within 90 days of the end of trial. The clinical trial report will be written within 12 months of the end of trial.

8. TRIAL MEDICATION

There is one Investigational Medical Product (IMP), Salbutamol, and the placebo, Sodium Chloride 0.9%.

8.1. IMP: Salbutamol

Licensed drug name: Ventolin® Injection 500 micrograms (0.5mg) in 1ml (Salbutamol) © Glaxo Wellcome UK Ltd trading as GlaxoSmithKline UK

Marketing Authorisation Number: PL 10949/0084

The IMP will be diluted to a concentration of 50 micrograms per ml with Sodium Chloride 0.9% injection prior to administration.

8.2. Legal Status of the Drug

Salbutamol (Ventolin®) injection is a licensed product and is indicated in adults and adolescents for the relief of severe bronchospasm. For the purpose of the trial, Salbutamol (Ventolin®) is being used out of its product license for a new indication.

8.3. Summary of Product Characteristics (SmPC)

The summary of Product Characteristics (SmPC) for Salbutamol (Ventolin) Injection 500micrograms in 1ml can be accessed on www.medicines.org.uk.

All SmPCs, including current and superseded, must be filed in the TMF and ISF.

8.4. Placebo: Sodium Chloride 0.9%

The Sodium Chloride 0.9% Injection will be the product currently purchased by the Pharmacy Department, University Hospitals of Derby and Burton NHS Foundation Trust (Site: Royal Derby Hospital). The brand used may change if the Trust's contracts change but the product will always have a UK Marketing Authorisation.

8.5. Drug Storage and Supply

Detailed information regarding drug storage, shipment, receipt, distribution, return and destruction of IMP is detailed in the pharmacy manual.

Trial medication will be obtained from normal hospital pharmacy supplies, ordered and received in accordance with Pharmacy standard operating procedures.

Medication issued for use in the trial will be supplied in the original manufacturer's packaging. The outer packaging will be labelled in accordance with Annex 13 of the Rules and Guidance for Pharmaceutical Manufacturers 2007 to indicate that they are for use in the trial.

Accurate records for medication dispensed and returned must be maintained and a record available for inspection.

- Salbutamol (Ventolin) injection should be stored below 30°C and the ampoule kept in the outer container in order to protect from light.

- Sodium chloride 0.9% ampoules should be stored below 25°C and kept within the outer container.

8.6. Preparation and Labelling of Investigational Medicinal Product

In order to reduce the risk of unblinding members of the research team, the allocated treatment will be drawn up for injection by an appropriately trained member of staff who is not directly involved in the trial and works in a different clinical area. Once prepared, the trial medication will be provided to the trial team in a labelled syringe containing 5ml of a clear, colourless solution. This is then administered by slow intravenous injection over 3-5 minutes immediately after preparation in accordance with the prescription.

Drug accountability will be recorded on the reverse of the scratch card indicating the participant's treatment allocation and will not be revealed to anyone except those involved in the injection preparation and designated pharmacy staff (Section 7.4.1).

8.7. Dosage Schedules

The patient will receive only one slow intravenous injection over 3-5 minutes (either intervention or placebo according to the treatment allocation that they receive).

8.8. Dosage Modifications

No dosage modifications are permitted.

Individual stopping criteria: If a participant develops clinical evidence of a significant adverse reaction during the course of treatment administration then administration can be stopped at the direction of the treating clinician.

If a product recall should occur, the medication will be quarantined and the trial will temporarily halt recruitment until either the matter is resolved or alternative drugs are sourced.

8.9. Known Drug Reactions and Interaction with Therapies

Drug interactions are stated in the exclusion criteria (Section 6.2) and the SmPC.

8.10. Concomitant Medication

All concomitant medication, including over the counter or prescription medication, vitamins, and/or herbal supplements taken by the participant during their time on the study will be recorded. This includes concomitant medications prescribed and administered at the discretion of the patient's clinical team. Any associated adverse events should be recorded as directed in Section 9.

Concomitant medications not permitted to be taken during the patient's participation on this trial (unless for the management of a clinical emergency e.g acute asthma, tachyarrhythmia) include:

- **Any** beta blockers (11) (including beta blocker-containing eye drops (31));
- Short and long-acting β-agonists

8.11. Trial Restrictions

There are no restrictions related to involvement in the trial that are not covered by the exclusion criteria.

8.12. Assessment of Compliance

Participants are administered medication by slow intravenous injection. A record of administration

must be kept in the medical notes, available for inspection on request; it will also be recorded in the eCRF.

8.13. Name and Description of Each Non-Investigational Medicinal Product (NIMP)

There are no Non-Investigational Medicinal Products used for this trial.

9. PHARMACOVIGILANCE

9.1. Definitions

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

9.2. Operational Definitions for (S)AEs

The use of Salbutamol is outside of its licensed indication, but with a well-known safety profile and no reason to suspect a change in the safety profile for the population of patients included in the trial. For this trial, it is expected that all AEs that show a potential causal relationship with the IMP (known as ARs) are recorded. Other AEs of unexpected severity (in the opinion of the investigator), or which meet the criteria for an SAE should also be recorded. The investigator must seek further information on such adverse events, record details in the patient's medical notes and on the eCRF. They should be recorded using the CTCAE term provided in the NCI CTCAE v5.0. Severity should be assessed using the NCI CTCAE v5.0 grading as per Section 9.5.1. The clinical course of each event should be followed until resolution or stabilisation.

9.2.1. Exceptions to (S)AE or (S)AR reporting:

Events that are recognised and expected complications of renal colic are **not** required to be reported as adverse events unless they are of an unexpected severity (i.e. require an intervention not usually required in the management of renal colic and its complications), are thought to be related to the IMP (and are therefore ARs) or meet the definition of serious.

The following circumstances are usually not considered SAEs:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- Treatment which was elective or pre-planned for a pre-existing condition not associated with any deterioration in condition.
- Any admission to hospital or other institution for general care where there was no deterioration in condition.
- Treatment of an emergency on an outpatient basis for an event **not** fulfilling any of the definitions of serious as given above and not resulting in hospital admission.

9.3. Recording and Reporting AEs and ARs

All AE/ARs and SAE/SARs not considered exempt as per Section 9.2.1 must be recorded from the time of trial medication administration until the end of the participant's last data collection point and assessed as per Section 9.5. Due to the fast–acting nature and short half-life of Salbutamol, active monitoring for AEs and ARs is not required after 2 hours post administration. Following this, investigators are still required to record any ARs or SARs they become aware of.

9.4. Recording and Reporting SAEs and SUSARs

All SAEs/SARs must be recorded by the investigator using the Derby CTSU SAE reporting form and emailed to Derby CTSU within 24 hours of the research team becoming aware of the event; even if not all information is available at the time (further information should be provided on the Derby CTSU SAE Follow Up Report Form).

Any change of condition or other follow-up information should be sent to the Derby CTSU as soon as it is available, or at least within 24 hours of the information becoming available. Events will be followed up until the event has been resolved or a final outcome has been reached.

Derby CTSU contact information:
Email: dhft.randdsae@nhs.net **Hand delivery address**: Room 5033, Medical School, Royal Derby Hospital) **Telephone**: 01332 724639 or 01332 789339 (must be followed up with a written report).

For each SAE/SAR the following information will be collected:

- Full details of the event, including a diagnosis
- MedDRA coding (system organ class and preferred term)
- Duration (start and end dates)
- Seriousness criteria
- Outcome.
- Action taken.
- Causality (i.e. related to IMP)
- Expectedness

Each SAE that is assigned as both suspected to be related to IMP treatment and unexpected will be initially classified as a SUSAR and reported to the Sponsor who will take necessary steps to reveal the treatment allocation of the individual participant concerned and report to the MHRA if required within the required expedited reporting timescales.

Safety information will be reviewed for ongoing assessment of the risk/ benefit during Data Monitoring and Ethics Committee (DMEC) meetings.

9.5. Assessment of AEs and SAEs

9.5.1. Severity

Assessment of severity should be guided by the NCI CTCAE v5.0. The investigator should determine the severity of the AE;

- Grade 1 / Mild: no interference with daily activities.
- Grade 2 / Moderate: moderate interference with daily activities.
- Grade 3 / Severe: considerable interference with daily activities (e.g. inability to work).
- Grade 4: Life-threatening consequences; urgent intervention indicated

NOTE: to avoid confusion or misunderstanding the term “severe” is used to describe the intensity of the event, which may be of relatively minor medical significance, and is NOT the same as “serious” which is described in the safety definitions.

9.5.2. Causality

Clinical judgment should be used to determine the relationship between the IMP and the occurrence of each AE. As a double-blind trial, the Investigator should evaluate the causality and expectedness of AEs as though the participant was receiving the active medication.

- Not-related: There is no evidence of a causal relationship between the event and IMP.
- Related: There is evidence of a causal relationship between the event and IMP i.e. a relationship to the IMP cannot be completely ruled out.

Assessment of causality must be made by a medically qualified doctor (usually the principal investigator). If a doctor is unavailable initial reports should be submitted to Derby CTSU without the causality assessment but they must be followed up with a medical assessment as soon as possible.

9.5.3. Expectedness (SARs only)

The assessment of expectedness is only required if the event is deemed to be an SAR.

- Expected: Reaction previously identified and described in the reference safety information (RSI) and/or protocol.
- Unexpected: Reaction not previously described in the protocol or RSI.

The expectedness assessment is delegated to the CI and is recorded on the CRF and the DCTSU SAE Reporting Form. The Reference Safety Information (RSI) for this trial is Section 4.8 of the current approved version of the Salbutamol (Ventolin) Injection 500micrograms in 1ml SmPC. The RSI is used for pharmacovigilance purposes to assess the causality and expectedness of events and will be checked by the Sponsor for changes at least annually on the anniversary of the CTA.

9.6. Overdose

All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and CRFs. Overdoses should be reported to the Derby CTSU as a non-compliance as described in Section 13.4. If the overdose results in an AE or SAE it must be reported according to the Derby CTSU procedure described above.

9.7. Reporting Urgent Safety Measures

If any urgent safety measure is taken the research team should inform the Derby CTSU within 24 hours using the Derby CTSU safety incident reporting form. The Derby CTSU will inform the MHRA, REC and participating sites of the measures taken and the circumstances giving rise to those measures within 3 days on implementation of the urgent safety measure.

9.8. Development Safety Update Reports

The Derby CTSU will provide (in collaboration with the CI) DSURs once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and Sponsor.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

10. DATA HANDLING

10.1. Data Collection Tools and Source Document Identification

An electronic software platform will be used for trial data capture. Data capture will be via a web-based, fully validated system, compliant with 21 CRF Part 11; Electronic records; Electronic signatures and EU Commission Directive 2005/28/EC with comprehensive audit trials. DCTSU will be responsible for database build and system validation. Data will be hosted externally according to General Data Protection Regulation guidance.

10.2. Source Data

Source data will consist of paper and electronic medical records depending on the data being collected. Patient reported outcomes (specifically the McGill Questionnaire, Patient Satisfaction and VAS) will be recorded directly onto paper which will serve as the source data prior to being transcribed onto the eCRF. There may be some instances where the data is transcribed directly onto the eCRF and this will be determined with the PI prior to the start of the trial at the site.

Source data should be kept in line with the record retention information (as per Section 10.5) and according to the investigator site's archiving procedures.

10.3. Data Handling and Record Keeping

The investigator and trial team will ensure that the participant's identity is protected at every stage of their participation within the trial, according to the Caldicott principles. If any patient information needs to be sent to a third party the trial team will adhere to maintaining pseudo-anonymous participant parameters in correspondence.

The trial database will be designed to capture the clinical data in accordance with the best principles of clinical data management and the relevant SOPs on Clinical Data Management System Specification and Validation, Data Capture, Instrument Design and Database Development developed by the Derby CTSU.

Access to the trial database will be restricted by role-based permission to authorised trial personnel. Users will be suitably trained on the system prior to being granted access. Individual user accounts will be password protected and will not be shared between members of the trial team.

Data will be entered into the eCRF using worksheets & source documents at the site. Post data entry, validation checks will be performed on the data to ensure accuracy and consistency according to the data validation plan. All data queries generated as a result of these checks will be available for resolution by the site online. After data entry is complete, all data queries have been resolved and medical coding is completed, the database will be locked and released for statistical analysis.

All clinical data will be collected, stored, processed and archived in accordance with the Data Management Plan for this trial and in line with the relevant SOPs on Data Entry, Data Quality Assessment, Data Validation, Database Lock and Data Transfer and Archiving developed by the Derby CTSU and any relevant legislation.

Access will be granted to authorised representatives from the sponsor, trial team and the regulatory authorities to permit trial-related monitoring, audits and inspections. The purpose of these inspections is to verify and corroborate the data collected on the case report forms. In order to do this direct access to medical or clinic records is necessary. The CI / PI must inform the Sponsor if they are notified of a forthcoming audit by the IEC/IRB or regulatory authorities.

The Principal Investigator will ensure that the following information is contained in the medical or clinic records of the participant and that the entries are signed and dated:

- Sufficient data to allow verification of the entry criteria in terms of past and present medical and medication histories;
- The day the participant entered the trial describing the trial number, the treatment being evaluated, the unique number assigned to the participant and a statement that informed consent was obtained;
- Each subsequent trial visit including any concerns about adverse events and their resolution.
- Any deviation from protocol procedures and subsequent impact on endpoint data validity
- All concomitant medication taken by the participant, including start and stop dates;
- The date when the participant finished the trial, the reason for termination and the participant's general condition at trial completion.

10.4. Access to Data

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

10.5. Archiving

At the end of the trial, following completion of the end of trial report, Derby CTSU will securely archive all centrally held trial related documentation for a minimum of 15 years. At the end of the defined archive period arrangements for confidential destruction will be made. It is the responsibility of each PI to ensure that data and all essential documents relating to the trial are retained securely for a minimum of 15 years after the end of trial, and in accordance with national legislation.

Derby CTSU will notify sites when trial documentation held at sites may be archived, and then destroyed. All archived documents must continue to be available for inspection by appropriate authorities upon request.

11. STATISTICS AND DATA ANALYSIS

The statistical analysis will be undertaken by the trial statistician. The trial statistician will draft the Statistical Analysis Plan (SAP) according to *CTU-SOP-019 Statistical Analysis Plan*, which will be reviewed by the Trial Management Group (TMG), the Trial Steering Committee (TSC), and the Data Monitoring and Ethics Committee (DMEC). The finalised SAP will be approved and signed by the CI and the trial statistician.

11.1. Sample Size Calculation

This is a phase II trial to demonstrate some efficacy signal on the primary outcome. The sample size estimation has therefore been estimated based on the "probability of benefit" approach using the Mann-Whitney U test with the R Software (32).

Two studies (33,34) have defined the minimum clinically significant difference between consecutive ratings of pain to be 13mm in emergency department patients. Assuming that a difference of 13mm between groups in the change in pain score from baseline is clinically important (standard deviation of 20mm – the maximum reported deviation of VAS pain at 30 minutes in a Cochrane Review (3), then at 5% significance level with 90% power, 53 patients with **confirmed** renal colic should be recruited per arm.

The standard deviation of the primary outcome in this trial will be used to inform power calculations for the subsequent definitive trial.

11.2. Planned Recruitment Rate

Four hundred and forty-seven patients were discharged from the Royal Derby Hospital Emergency Department between 17/11/2016 and 16/11/2017 with a final diagnosis of "Renal Colic" (approximately 37 patients per month).

Approximately 10% of these participants will subsequently be found not to have a renal calculus (local audit data and previous research (35)). Therefore approximately 34 patients per month will have a confirmed diagnosis of renal colic.

We estimate a recruitment rate of between 18% and 30% of eligible patients. This figure is derived from current department recruitment to a comparable CTIMP (ISRCTN 34153772), another trial in an ED setting (36), and discussion with the PPI group.

Assuming a minimum recruitment rate of 18%, we estimate that 106 patients with **confirmed** renal colic could be recruited in 22 months. This allows for a slow start in recruitment (3 months to reach

20% recruitment rate) and recruitment plateau during the last five months (10% recruitment rate). This requires recruitment of approximately 118 patients with **suspected** renal colic.

11.3. Statistical Analysis

11.3.1. Summary of Baseline Data and Flow of Patients

Descriptive statistics will be presented to summarise the distribution of baseline variables across each of the randomisation groups. The continuous baseline variables (age and weight) will be reported with medians & Interquartile Ranges (IQR). The categorical variables (gender) will be reported with frequencies & percentages.

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be produced, showing the frequency of patients/participants:

- Potentially eligible
- Assessed for eligibility or found eligible,
- Given consent,
- Excluded before consent (and the frequency of each reason for exclusion),
- Randomised,
- Allocated to each randomisation group,
- That received each allocated intervention,
- That did not receive each allocated intervention,
- Lost to follow-up (and the frequency of each reason for loss to follow-up) for each randomisation group,
- Analysed for each randomisation group,
- Analysed for each sub-group,
- Not analysed (and the frequency of each reason for not being analysed) for each randomisation group /sub-group.

11.3.2. Primary Outcome Analysis

The primary outcome of the change in pain scores (measured with VAS) from baseline to 30 minutes in patients with "**Confirmed** Renal Colic" will be compared between the two trial arms using Mann U Whitney test. Further analysis of the primary endpoint will be carried out using an Analysis of Covariance (ANCOVA) approach, analysing the pain scores at 30 minutes and including the baseline pain scores as a covariate, along with any other clinical/demographic covariates of import. Results of the primary endpoint will be reported as the mean change in pain score for each treatment arm along with associated 95% confidence intervals.

11.3.3. Secondary Outcome Analysis

Pain Scores

The secondary outcome of the change in pain scores (measured with VAS) from baseline to 30 minutes in patients with "**Suspected** Renal Colic" will be compared between the two trial arms using Mann U Whitney test. The change in pain scores (measured with VAS) from baseline to 15, 60, 120, 240 minutes, and four-hourly thereafter in patients with "**Confirmed** Renal Colic" and with "**Suspected** Renal Colic" will be compared between the two trial arms at each time point using Mann U Whitney test, and across all time points using repeated measures ANCOVA including the baseline pain scores as a covariate, along with any other clinical/demographic covariates of import.

The change in pain scores (measured with McGill Pain Questionnaire) from baseline to 15, 30, 60, and 120 minutes in patients with "**Confirmed** Renal Colic" and with "**Suspected** Renal Colic" will be compared between the two trial arms at each time point using Mann U Whitney test, and across all time points using repeated measures ANCOVA including the baseline pain scores as a covariate, along with any other clinical/demographic covariates of import.

Clinical Outcomes

Secondary continuous outcomes (length of stay, degree of hydronephrosis,) will be compared between the two treatment groups using Mann U Whitney. Secondary categorical outcomes (frequency and dose of morphine, other analgesics required, and presence, site and size of renal calculus) will be compared between the two treatment groups using Chi-squared test.

Feasibility Outcomes

Descriptive statistics will be presented to summarise the feasibility outcomes across each of the randomisation groups, where relevant. The continuous feasibility outcomes will be reported with medians & Interquartile Ranges (IQR), while the categorical feasibility outcomes will be reported with frequencies & percentages.

Patient Satisfaction Questionnaire

Frequencies and percentages will be used to report the responses in the patient satisfaction questionnaire by treatment group and will be compared using a Chi-Square test.

Toxicity

The number and percentage of patients reporting a SAE or SUSAR will be summarised by treatment group and compared using a Chi-Square test.

11.4. Subgroup Analyses

The entire trial population ("**Suspected** Renal Colic" – see below) likely represents the population that would be administered salbutamol in working practice should it prove an effective analgesic; clinicians do not wait for definitive investigations prior to providing appropriate analgesia.

- **Suspected** Renal Colic: The entire enrolled trial population satisfying the inclusion / exclusion criteria.

- **Confirmed** Renal Colic: A sub-group of the trial population, defined as either:

Patients with a renal calculus on the side of their abdominal/flank pain as proven by imaging during the trial admission to hospital, AND a discharging diagnosis consistent with renal colic

Or

*Patients with a history of a renal calculus as proven by previous imaging **AND** a working ED diagnosis of renal colic **AND** (where relevant) a surgical/urology discharging diagnosis consistent with renal colic*

Or

Patients who pass a stone (visually confirmed by either patient or staff member) whilst in the ED.

- **Other Diagnoses**: A sub-group of the trial population, defined as:

*All trial participants **NOT** meeting the definition of "Confirmed Renal Colic".*

Sub-group analyses including all patients randomised in the trial with **suspected** renal colic and those with "**other diagnosis**" will be undertaken for the primary outcome using Mann U Whitney test.

11.5. Adjusted analyses

Further analysis of pain scores over time will be examined using linear mixed models including patient ID as a random effect to ensure both within patient and between patient levels of variability are estimated. Normality of model residuals, where assumed, will be assessed using the Shapiro-Wilks test and appropriate data transformations applied where necessary.

11.6. Interim analysis and criteria for the premature termination of the trial

The sponsor and Funder reserve the right to discontinue this trial at any time for ethical, safety or any other administrative reason. If this occurs the Sponsor shall justify its decision in writing and will promptly inform any relevant parties (i.e. investigators, participating sites, REC, regulatory bodies).

The Sponsor and Funder shall take advice from the Trial Steering Committee as appropriate in making this decision. An independent Data Monitoring and Ethics Committee shall monitor accumulating data and oversee safety issues. The reporting requirements and frequency of reports will be defined in the TSC and DMEC Charters.

The DMEC will advise the TSC if, in its view, there are any ethical or safety issues that may necessitate closure of the trial. These issues include (but are not limited to):

- Prevalence of excess side effects, SARs or SUSARs in the intervention group deemed unacceptable as defined by the DMEC

11.7. Analysis Groups

The primary analysis of the primary endpoint will be carried out within the "**Confirmed** Renal Colic" group on the full data set, which will be defined on the intention to treat principle retaining patients in their initially randomised groups irrespective of any protocol violations. Analyses of the "**Suspected** Renal Colic" and the "**Other Diagnosis"** groups for all secondary endpoints will be done on the intention to treat principle.

Secondary analysis of the primary endpoint will be carried out within the "**Confirmed** Renal Colic" and "**Suspected** Renal Colic" groups on the per protocol principles including patients who received the treatment medication they have been randomised to.

Analysis of harms (adverse events) will be restricted to participants who received the allocated trial medication, so that absence or occurrence of harm is not attributed to a treatment that was never received.

11.8. Procedure(s) to Account for Missing or Spurious Data

Missing data are expected to be small and final analyses are planned to be carried out on a complete case basis; any participant in whom the imaging necessary to obtain specific secondary outcome data (e.g. degree of hydronephrosis) is not performed will be excluded from that portion of the data analysis.

If there is missing data in the primary endpoint, then multiple imputation using chained equations will also be applied. If substantial missing data (>10%) are observed in either a secondary trial outcome or key prognostic covariate, then multiple imputation using chained equations will be applied.

11.9. Other Statistical Considerations

Analysis of the primary outcome will be assessed using 2-sided 0.05 level, as is consistent with the type I alpha level used in the trial design.

12. MONITORING, AUDIT & INSPECTION

The Investigator(s) must ensure that source documents and other documentation for this trial are made available to trial monitors, the REC or regulatory authority inspectors. Authorised representatives of the Sponsor and competent authority may visit the participating sites to conduct audits/ inspections.

Monitoring and source data verification will be conducted by the Derby CTSU according to the trial monitoring plan. The extent and nature of monitoring will be determined by the trial objectives, purpose, design, complexity, blinding, number of patients and sites, and endpoints.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Peer review

This trial has been peer reviewed as part of the NIHR Research for Patient Benefit (RfPB) application process.

13.2. Public and Patient Involvement

Patients with experience of renal colic contributed towards the development of the proposal, gave feedback on the proposed design, medication and route of administration of the IMP.

Possible side effects of the trial medication were discussed (e.g. palpitations, tremor, muscle cramps); these were felt by the group to be acceptable in return for improved analgesia.

The group acknowledged that, if taking part in the trial, they may be randomised to the placebo group. They felt this would be acceptable to patients providing that the rationale for placebo-controlled trials was explained during the consent process.

A PPI representative was a co-applicant on the funding application and several members of the local patient discussion group agreed to remain involved in the research project after the initial meeting. They have undertaken a number of activities related to the project to date, including developing the plain English summary and participant information leaflet. They will also be part of the Trial Steering Committee and Trial Management Group.

The Derby Patient and Public Involvement Group are supporting research in the emergency department. They will be supported and mentored in their trial activities by more experienced PPI representatives from the Sheffield Emergency Care Forum and by other research team members.

The PPI representatives will help design a poster to be displayed in the triage area of the emergency department to aid recruitment and will aid with dissemination of the research to members of the public. Specifically, they will assist with preparing written material explaining the results of the trial (e.g. a "lay leaflet"), ensuring that dissemination is effective not only in the medical literature but also to patient groups.

13.3. Research Ethics Committee (REC) & Regulatory Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) and the Medicines for Human Use (Clinical Trials) Regulations 2004 (and subsequent amendments).

The protocol and all related documentation (e.g. informed consent form, participant information sheet, questionnaires) have been reviewed and received approval by a Research Ethics Committee

(REC). The trial has been classified as a clinical trial of an investigational product (CTIMP) and has received a clinical trial authorisation (CTA) from the UK competent authority, the Medicines and Healthcare Regulatory Agency (MHRA).

The investigator will not begin any participant activities until all approvals have been obtained and documented. All documentation and correspondence must be retained in the trial master file and investigator site file. Substantial amendments that require HRA, REC and MHRA (where applicable) review will not be implemented until the HRA, REC (and MHRA) grants a favourable opinion (with the exception of those necessary to reduce immediate risk to participants).

It is the responsibility of the Derby CTSU to ensure that an annual progress report (APR) is submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, annually until the trial is declared ended. The Derby CTSU is also responsible for notifying the REC and MHRA of the end of trial (Section 7.12) within 90 days, however if the trial ends prematurely, the notification must be submitted within 15 days. Within one year of the end of trial, the Sponsor will submit a final report with the results, including any publications/abstracts to the REC.

Before any site can enroll a patient into the trial confirmation of capacity must be sought from the site's research and development (R&D) department. In addition, for any amendment that will potentially affect the site's permission, the research team must confirm with the site's R&D department that permission is ongoing.

13.4. Protocol Compliance

The investigator is responsible for ensuring that the trial is conducted in accordance with the procedures described in this protocol. Prospective, planned deviations and/or waivers to the protocol are not acceptable. Accidental protocol deviations may happen and as such these must be reported according to the Derby CTSU SOP. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action, and could potentially be classified as a serious breach.

13.5. Notification of Serious Breaches to GCP and/or the Protocol

A "serious breach" is a departure from the protocol, Sponsor procedures (i.e. SOPs), or regulatory requirements which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the trial; or
(b) The scientific value of the trial.

If a serious breach is identified the investigator should notify the Derby CTSU immediately (i.e. within 1 working day) using the MHRA 'notification of serious breaches of GCP or the trial protocol' form. The report will be reviewed by the Derby CTSU and CI, and where appropriate, the Derby CTSU will notify the MHRA and REC within 7 calendar days of being made aware of the breach.

13.6. Data Protection and Patient Confidentiality

The trial will be conducted in accordance with the Data Protection Act 2018, and other applicable legislation, including but not limited to the EU General Data Protection Regulation. The investigator must ensure that participant's anonymity is maintained throughout the trial and following completion of the trial. Participants will be identified on all trial specific documents (except for the screening log, informed consent form and enrolment log) only by the participants trial-specific identifier. This identifier will be recorded on all trial documents and the database. The investigator site file will hold an identification log detailing the trial specific identifier alongside the names of all participants enrolled in the trial.

All documents will be stored securely with access restricted to trial staff and authorised personnel.

Dr Graham Johnson, as the Chief Investigator, will act as the custodian of the data generated in the trial.

13.7. Financial and Other Competing Interests for the Chief Investigator, Principal Investigators at Each Site and Committee Members for the Overall Trial Management

At the time of protocol writing, there are no known financial or other competing interests of the Chief Investigator or their team.

The membership of the Trial Steering Committee and Data Monitoring and Ethics Committee will be asked to review the specific charter for their committee, which requests that they declare any competing interests. Such interests may include (but are not limited to):

- Ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial
- Commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company
- Any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

13.8. Indemnity

As UHDB is acting as the research Sponsor for this trial, NHS indemnity applies. NHS indemnity provides cover for legal liabilities where the NHS has a duty of care. Non-negligent harm is not covered by the NHS indemnity scheme. UHDB, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

13.9. Amendments

Changes to the protocol will be documented in written protocol amendments; the Derby CTSU is responsible for deciding if an amendment should be deemed substantial or non-substantial. Substantial amendments will be submitted to the relevant regulatory bodies (MHRA, REC, HRA) for review and approval. The amendments will only be implemented after approval and a favourable opinion has been obtained. Non-substantial amendments will be submitted to the HRA for their approval/ acknowledgment. Amendments will not be implemented until all relevant approvals are in place.

13.10. Post-Trial Care

As the trial involves administration of IMP as a single-dose, there is no scope for extended access to the treatment beyond the trial therefore continued care is not planned.

13.11. Access to Final Trial Dataset

As an Investigator-led trial, access to the final trial dataset will be restricted to the CI, the trial statistician and the appropriate members of Derby Clinical Trials Support Unit and the Sponsor. External investigators will be required to submit a formal request to the Trial Management Group for access to data.

14. DISSEMINATION POLICY

14.1. Dissemination Policy

Upon completion of the trial, an End of Trial report will be generated and submitted to REC within 12 months of the end of trial. As the funder for the trial, the NIHR will also be provided with a report of the trial, per their requirements.

As sponsor of the trial University Hospitals of Derby and Burton NHS Foundation Trust, will own all data arising from the analysis.

The results of this trial will be submitted to peer-reviewed journals for publication as soon as data analysis is completed. Participants will not be identified in any publications. As described in Section 13.2, the PPI representatives involved in the trial will support the dissemination of the information into the public domain and to the participants involved in the trial, in an appropriate manner.

Conference proceedings: the findings will be presented at national and international emergency medicine and urology conferences e.g. the Royal College of Emergency Medicine Annual Scientific Conference and Clinical Studies Group meetings, and the British Association of Urological Surgeons Endourology meeting.

Online: the findings will be presented in online fora including podcasts and blogs e.g. RCEMLearning FOAM Network.

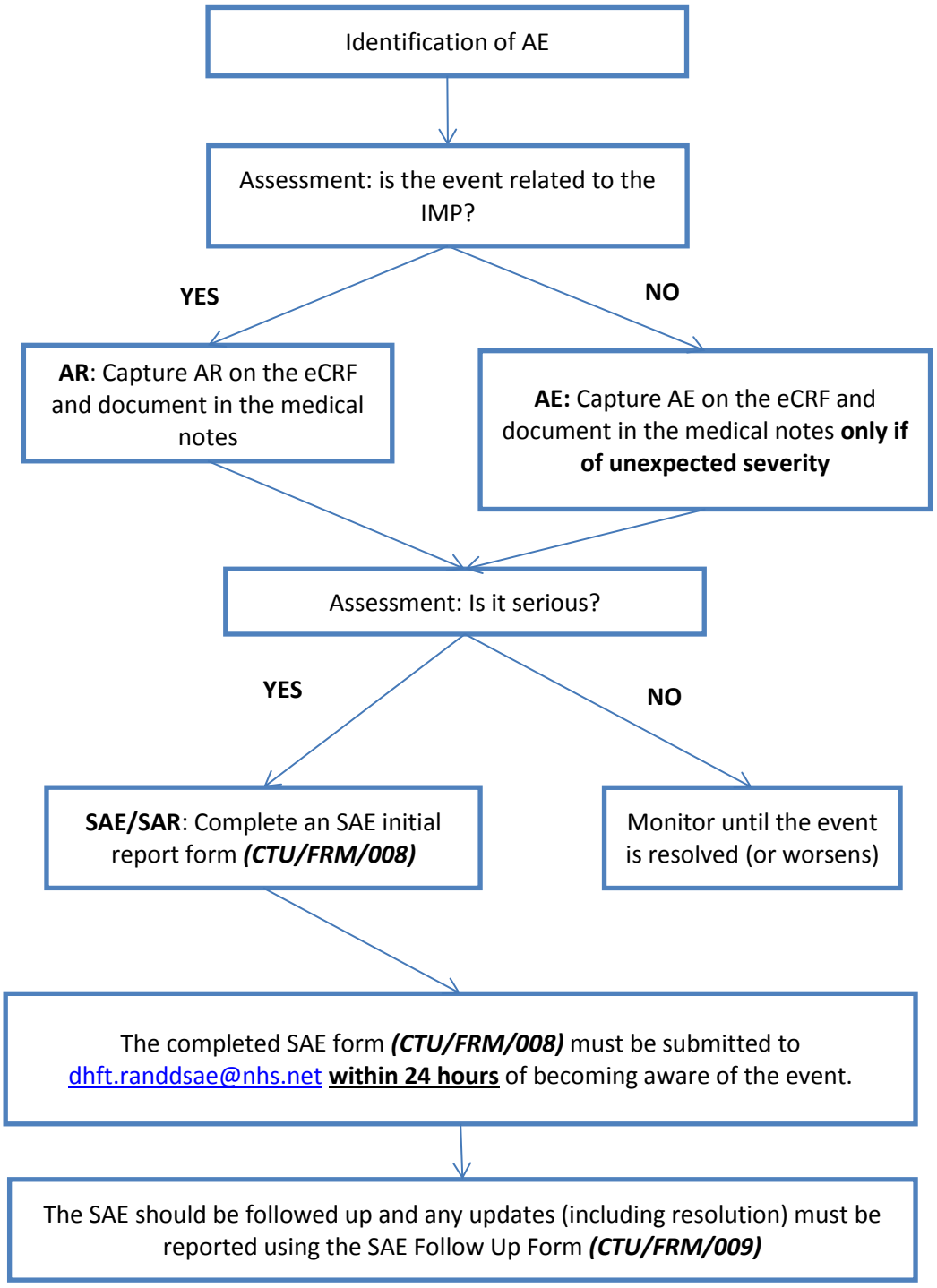
Social media: findings will be disseminated and publicised through links with organisations with a large social media presence.

14.2. Authorship Eligibility Guidelines and any Intended Use of Professional Writers

Authorship will be coordinated and led by the CI and Co-Investigators. Acknowledgement of UHDB as the Sponsor for the project will be made where appropriate.

15. APPENDICES

15.1. Appendix 1 – Safety Reporting Flow Chart



15.2. Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2.0	27/JUN/2019	Graham Johnson, Andrew Tabner, Rachelle Sherman, Apostolos Fakis	Response to MHRA Grounds for Non-Acceptance: • Additional evidence provided in the Rationale section (Section2). • Clarification of the prohibited concomitant medications – all beta blockers are prohibited (Section 6.2 and Section 8.10) • Further detail on the procedure for emergency unblinding. • Individual stopping criteria clarified in Section 7.11 and Section 8.8. • Detail on stopping guidelines in Section 11.6
	2.1	15/JUL/2019	Graham Johnson, Rachelle Sherman	Clarification of exclusion criteria 11 required as a condition of REC favourable opinion.

Detail all protocol amendments. Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.

15.3. Appendix 3 – Study Within A Trial (SWAT)

SWAT TITLE:	**dOes ParTicipant InforMatIon ShEet Design affect the recruitment rate into an interventional trial? A Study Within A Trial (OPTIMISED)**
SWAT Registration	This SWAT is registered as SWAT 32 on the MRC SWAT repository

Background and Rationale

Failure to recruit to time and target is a problem faced by many trials, including randomised controlled intervention trials. For studies to be considered a definitive trial, able to adequately explore a hypothesis, they must have an appropriate sample size; if too few participants are recruited, the chances of finding statistically significant results are lower and the study may fail to meet its objectives, posing the ethical issue that participants are taking part in a study that may have no tangible impact on healthcare (Sully *et al.*, 2013). Problems in recruiting to studies can extend their duration making them more expensive or requiring agreement of collaborators to continue to work on the project with little or no additional funding.

There are many barriers to recruitment, not only from the perspective of the potential participant, but also for the clinician looking to involve patients in a study (38). Long and complex participant information sheets may effect a patient's decision to enter a trial, either based on a lack of understanding (39), or a lack of willingness to fully read the additional information alongside non-study information provided to the patient at the same time. This is particularly relevant in emergency settings, where decisions are time-sensitive and patients cannot be given as long to consider participation, compared to non-emergency settings where patients may take information away with them.

The information provided to participants plays an important role as a point of reference for them (40,41) therefore any decision to improve, or reduce the length of information provided should consider this, especially for trials that involve more complex interventions. There should be a balance between providing enough information to patients to inform their decisions whilst avoiding the use of long and complex sentences that might negatively impact on their decision to enrol (39).

A recent Cochrane review of studies testing recruitment and retentions interventions found that some were more effective than others, with studies evaluating the use of user-tested participant information leaflets showing that there was little or no difference to recruitment (42). Despite this, modification of participant information is still considered a priority for improving recruitment and retention into clinical trials (43,44). Such studies are embedded within larger trials (otherwise referred to as SWATs – "Study within a Trial") and it is the focus of the MRC Start project and PROMETHEUS research group to increase the evidence base concerning recruitment to trials by conducting multiple SWATs that will contribute towards a meta-analysis (43,45) and future systematic reviews.

SWAT Objectives

The primary objective for this SWAT is to explore whether improving the readability of a participant information sheet (PIS) has an effect on the recruitment rate into an interventional trial.
The secondary objective of this SWAT will be to assess the impact, or "value", of the PIS in the decision making of the patient.

Outcomes

The primary outcome will be the proportion of patients who consent to take part in the interventional trial (known as the host study). Secondary outcomes will be qualitative measures, whereby consenting participants will provide feedback about the PIS they were provided. A questionnaire provided by Peter Knapp used in the "TRECA" study (a study of digital, multimedia resources used in recruitment to trials with children and adolescents) will be used to inform the development of a similar, decision making questionnaire to assess the impact or value of the PIS in the decision making of the patient.

Study Design & Setting

This study will be a randomised study within a trial (SWAT) embedded within a host clinical trial of an investigational medicinal product (CTIMP). The study population will be the patients identified as eligible for the host study and approached by the local clinical team for inclusion. After approximately 6 months of recruitment, there will be a data cut to allow for an interim analysis which will be used for the write up for an MSc in Clinical and Health Sciences being undertaken by the Clinical Trial Manager, Rachelle Sherman. At this point, results will be shared with the SARC Trial Management Group (and Trial Steering Committee if appropriate) in case the outcome impacts the ongoing running of the trial. For example, if one PIS appears to significantly increase recruitment it might be considered necessary to remove randomisation and move forward with this one, as it would be unethical to continue to randomise.

Participants will be randomised to receive either the optimised PIS (PIS A) or conventional (PIS B).
The optimised PIS (PIS A) will be designed with the following factors in mind:

- Improved readability by reducing the number of words per sentence, using familiar words and phrases, a columnar layout and clear headings (46)
- Templates used by other research groups including (39,47)
- The guidance provided by the EC on the readability of patient information leaflets for medicines (48)

The resulting optimised PIS will be reviewed by the Patient and Public Involvement (PPI) representatives involved in the host study, who will also review the conventional PIS. The PPI representatives will be informed of the intended SWAT and will be encouraged to comment on the design of the SWAT during the development of the host study.

The conventional PIS will be designed based on the template and guidance provided by the HRA (49) and will be subject to the expectations of the REC and HRA for approval, which includes adequate use of lay language and inclusion of appropriate information as deemed necessary for the study. The conventional PIS will be designed by a member of the Derby CTSU not involved in the development of the optimised PIS and the Chief Investigator for the host study as normal, before the development of the optimised PIS. This is to reduce the chance of unintentionally making the conventional PIS less readable than the optimised PIS due to prior knowledge of the design of the optimised PIS.

Patients considered eligible for the host study will first be provided with a summary patient information sheet to introduce them to the study, before then being provided with either the optimised PIS or the conventional PIS along. They will not be informed of the fact that they had been randomised to receive different information sheets, an approach deemed acceptable in other similar trials (47). Randomisation to the SWAT will be conducted using a randomisation list created by an online randomisation system (50) and the site staff will be provided with information packs in a given numerical order determined by this list. Each information pack envelope will be given a form of identification which will then be recorded on the host study's screening log. The screening log will be anonymised and used to provide the information needed to determine the recruitment rate according to information received, for the primary analysis.
Patients who agree to take part in the study will then be asked to complete a questionnaire designed to assess the impact of the PIS on the patient's decision making to enter the trial. This will be provided to them at the 2 hour follow up visit.

The proportion of patients who consented to the host study will be compared between the two groups – those who received the conventional PIS and those who received the optimised PIS – using either an independent Chi-squared test or Fisher's exact test for categorical data.
The data to inform the secondary objectives will be composed of as questionnaire responses that are a mixture of closed questions and a Likert scale to provide scores to the questions asked, designed to provide feedback on the PIS design, feasibility and general provision of information.

Sample size calculation

The sample size calculations for the SARC trial have been outlined in the main trial protocol. As is usual with a SWAT, we did not undertake a formal power calculation to determine the sample size (51), since the sample size is constrained by the number of patients being approached in the SARC host trial. The sample size will therefore be the total number of patients invited into the SARC trial during the SWAT recruitment period. Based on response rates achieved in existing emergency trials, we estimate we will need to invite approximately 236 patients in order to recruit 118 to the host trial, representing a recruitment rate of approximately 50%.
The sample size for the secondary outcome measure, the decision-making questionnaire, will be smaller as this will consist of a cohort of patients who consent to the trial and who agree to complete the questionnaire (a maximum of 118).

Statistical analyses

Analyses will be conducted on an intention to treat basis, including all randomised participants on the basis of the PIS groups to which they were randomised. Analysis will be conducted using 2 sided significance tests at the 5% significance level. For analysis of the primary outcome, Chi-squared test and logistic regression will be used to produce odds ratios and their associated 95% confidence intervals and p-values.

Dissemination

The results of the SWAT will be shared with the Prometheus group of trial methodologists and contribute towards an increasing evidence base for recruitment intervention strategies. The study will be presented at appropriate trial methodology conferences, including the UK Trial Manager's Network Annual Meeting as well as being submitted for publication in an appropriate methodology journal, for example *Trials.* At the very least, if no significant difference is seen between the two groups for the primary analysis, the secondary objectives might inform the choice of PIS style for future studies ran by the researchers and sponsor of the host study.

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