Evaluating the clinical and cost-effectiveness of Sodium Bicarbonate administration for critically ill patients with Acute Kidney Injury and metabolic acidosis

STUDY SHORT TITLE

Multicentre evaluation **O**f **S**odium bicarbonate in **A**cute kidney **I**njury in **C**ritical **C**are (**MOSAICC**)

This protocol has regard for the HRA guidance.

FUNDED BY

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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 Sponsor's (and any other relevant) 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 trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

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.....

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Assistant Director of Research & Development

Chief Investigator:

Signature: Date:

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Name:

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Consultant in Intensive Care

Statistician:

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SUMMARY

Scientific Title	Evaluating the clinical and cost-effectiveness of Sodium Bicarbonate administration for critically ill patients with Acute Kidney Injury and metabolic acidosis
Public Title	**MOSAICC** – **M**ulticentre evaluation **O**f **S**odium bicarbonate in **A**cute kidney **I**njury in **C**ritical **C**are
Primary registry and trial identifying number	ISRCTN14027629
EudraCT	2021-002587-44
Funding	National Institute for Health Research (NIHR) – Health Technology Assessment (HTA) Programme
Sponsor	University Hospitals of Derby and Burton NHS Foundation Trust
Contact for public queries	Ms Irene Chang Tel: 020 7269 9277 Email: MOSAICC@icnarc.org
Contact for scientific queries	Professor Lui Forni Tel: 014 8357 1122 Email: luiforni@nhs.net
Countries of recruitment	United Kingdom
Health conditions studied	Metabolic acidosis and acute kidney injury (AKI)
Intervention	Intravenous (IV) 8.4% weight by volume (w/v) sodium bicarbonate vs. No IV sodium bicarbonate
Trial Design	Pragmatic, multi-centre, open, data-enabled randomised clinical trial (RCT) with internal pilot phase and integrated economic evaluation Interventional Allocation: Randomised Blinding: Open, not blinded Primary purpose: Prevention
Inclusion and Exclusion Criteria	Sexes eligible for study: Male and female Accepts healthy volunteers: No Inclusion criteria: 1. Adult (aged ≥18 years) 2. Metabolic acidosis (defined by arterial blood gas values of pH <7.25, $PaCO_2$ <6.5 kPa and bicarbonate ≤20 mmol/L) 3. AKI – categorised as stage 2 or 3 of the Kidney Disease Improving: Global Outcomes (KDIGO) classification, defined as any one of the following three criteria: • Serum creatinine ≥2.0 times baseline* or • Serum creatinine ≥354 µmol/L, AND either a rise of ≥27 µmol/L within 48 hours or serum creatinine ≥1.5 times baseline* or • Urine output of <0.5 ml/kg/h for ≥12 hours

	*For baseline serum creatinine value: • If available, then use pre-hospitalisation value within 365 days of the current hospital admission date. • If there are multiple pre-hospitalisation values, then use the one closest to the date of the current hospital admission. • If a pre-hospitalisation value from the 365 days prior to admission date is not available and there are multiple serum creatinine values from the current hospitalisation, then use the lowest one from the current hospitalisation. • If no baseline serum creatinine value is available, then estimate it using the provided calculator. Exclusion criteria: 1. Respiratory acidosis (acute or chronic) 2. Clinical decision already in place to start patient on kidney replacement therapy (KRT) 3. Deemed unsuitable for KRT 4. Acute diarrhoea, including high output stoma/ileostomy 5. Percutaneous biliary drainage 6. Documented Stage 4 chronic kidney disease (CKD) [eGFR <30ml/min/1.73m^2] or end stage kidney disease (ESKD) on dialysis 7. Known renal tubular acidosis 8. Diabetic ketoacidosis 9. High anion gap acid poisoning (e.g. polyethylene glycol (PEG), aspirin, methanol) 10. Known to be pregnant 11. Symptomatic hypocalcaemia (Ionised calcium <1.05 mmol/L) † 12. Hypernatraemia (Plasma sodium >150 mmol/L) † 13. Severe hypokalaemia (Potassium <3.0 mmol/L) † 14. Solid organ transplant 15. Death perceived as imminent 16. Known hypersensitivity to sodium bicarbonate or to any of the excipients listed in section 6.1 of the SmPC † Exclusion criteria 11-13 are dynamic, and if corrected, patient may be reconsidered for the trial.
Date of first enrolment	Anticipated 1 September 2021
Target Sample Size	2,250
Intervention period	From randomisation until discharge from critical care, initiation of KRT or 90 days, whichever comes first. Participants will be continually monitored and if a participant's pH drops <7.3, at any point during this period, then sodium bicarbonate treatment will continue according to the dosage schedule.
Follow up duration	12 months
Planned Trial Period	46 months
Primary outcome	All-cause mortality at 90 days following randomisation

Secondary outcomes	- Mortality at critical care unit discharge, 28 days and one year; - Receipt and duration of respiratory, renal, and advanced cardiovascular organ support in critical care; - Duration of critical care unit and acute hospital stay; - On-going requirement for KRT at 90 days and one year
Economic outcomes	Primary economic evaluation outcome: - Incremental costs, QALYs and net monetary benefit at 90 days following randomisation (cost-effectiveness) Secondary economic evaluation outcomes: - Health-related quality of life at 90 days and one year; - Resource use and costs at 90-days and one year; and - Estimated lifetime incremental cost-effectiveness
Investigational Medicinal Product	Sodium bicarbonate 8.4% w/v, intravenous infusion
Formulation, Dose, Route of Administration	Starting dose is 50 ml administered over 30-60 minutes, with repeated doses depending on subsequent pH readings and clinical status (including haemodynamic monitoring heart rate, blood pressure), as well as blood gas analysis (including pCO_2 HCO_3 and electrolytes) up to a maximum of 500 ml per 24 hours.

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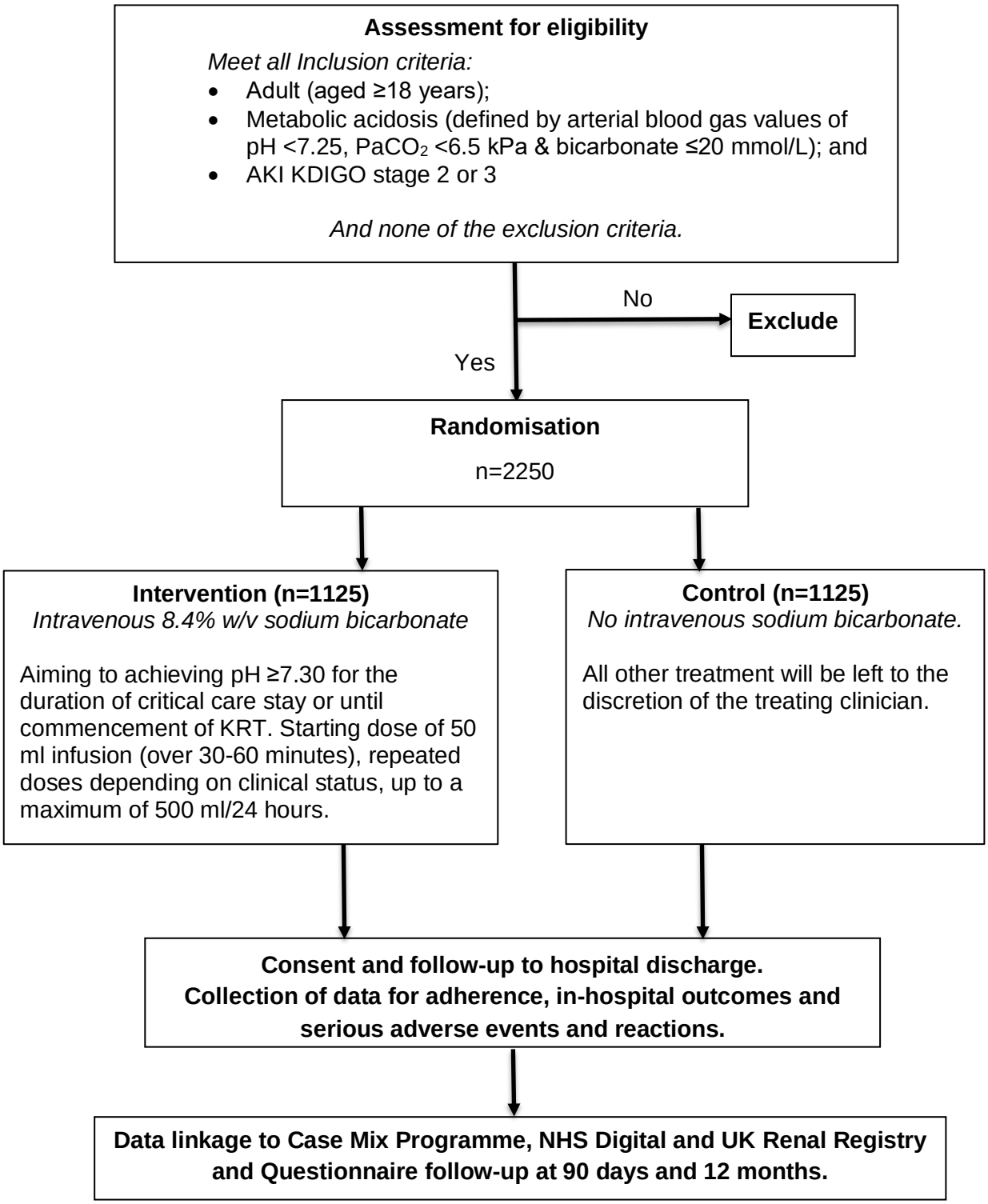
ABBREVIATIONS

ABG	Arterial blood gas
AE	Adverse Event
AKIN	Acute Kidney Injury Network
AR	Adverse Reaction
CCMDS	Critical Care Minimum Dataset
CEA	Cost-effectiveness analysis
CKD	Chronic kidney disease
CI	Chief Investigator
CMP	Case Mix Programme
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMEC	Data Monitoring and Ethics Committee
DSUR	Development Safety Update Report
eGFR	Estimated Glomerular Filtration Rate
ESKD	End stage kidney disease
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GLMM	Generalised linear mixed model
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
ICNARC	Intensive Care National Audit & Research Centre
IMP	Investigational Medicinal Product
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
IV	Intravenous
KDIGO	Kidney Disease Improving: Global Outcomes
KRT	Kidney replacement therapy
LSHTM	London School of Hygiene & Tropical Medicine
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
PEG	Polyethylene glycol
PI	Principal Investigator
PIS	Participant Information Sheet

PPI	Patient and Public Involvement
QALY	Quality-adjusted life year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL FLOW CHART



1 BACKGROUND

1.1 Acute kidney injury and metabolic acidosis

Around 184,000 critically ill adults are admitted to critical care each year in the UK. Around half have a sudden worsening in kidney function that happens as part of their illness defined as acute kidney injury (AKI). This rapid decline in kidney function frequently causes more acid to build up in the blood (a process known as acidosis) which can cause further harm.

Critically ill patients with acidosis (commonly defined as a pH <7.25 with $PaCO_2$ <6.5 kPa and bicarbonate ≤20 mmol/L) in the context of also having AKI have a very poor prognosis, with a 90-day mortality of 59% (Case Mix Programme – national clinical audit of adult critical care, 2018). In these patients, kidney replacement therapy (KRT) is the most commonly used treatment.

Another option is to treat the acidosis directly by administering "buffer" solutions (e.g. sodium bicarbonate), with the aim of raising extracellular pH to restore cardiovascular function and oxygen delivery to tissues.[1] This has the potential to both increase survival and avoid KRT, which is invasive, expensive and resource-intensive.

1.2 Sodium bicarbonate

A recent randomised controlled trial (RCT) evaluating the use of sodium bicarbonate in critically ill patients with acidosis found a significant reduction in 28-day mortality (46% sodium bicarbonate vs. 63% control) and use of KRT in a pre-specified subgroup of patients with AKI (n=182).[2] However, such sub-group analyses must be treated with caution, and the authors rightly called for a larger RCT to address this question.

While there are evidence-based recommendations for the use of sodium bicarbonate in other populations, such as for patients with chronic kidney disease (CKD) and end stage renal disease, possible side effects, such as rebound alkalosis, cardiac suppression, potential intracellular acidification due to the accumulation of carbon dioxide and risk of hypocalcaemia, have been identified.[3, 4]

Currently, there is uncertainty among critical care clinicians as to whether sodium bicarbonate should be used for routine treatment of acidosis in patients with AKI. A survey of UK critical care units indicated substantial variation in practice, with 23% of clinicians reporting some use of sodium bicarbonate for patients with moderate acidosis (pH 7.20–7.30), 34% for severe acidosis (pH 7.10–7.20), 21% for very severe acidosis (pH < 7.10) and 22% reporting no use at all. These results are consistent with a similar survey conducted in the US.[1] There is currently little high-quality evidence for the use of sodium bicarbonate in patients with acidosis and AKI which is likely to lead to varied use in critical care units worldwide.

The Multicentre evaluation Of Sodium bicarbonate in Acute kidney Injury in Critical Care (MOSAICC) RCT will address the clinically important question of whether in critically ill adults with metabolic acidosis and AKI, is treatment with IV 8.4% weight by volume (w/v) sodium bicarbonate superior to no IV sodium bicarbonate in terms of all-cause mortality at 90 days (clinical effectiveness) and incremental costs, quality-adjusted life years (QALYs) and net monetary benefit at 90 days (cost-effectiveness). This evaluation will have a large and immediate impact on clinical practice and on patient outcomes in the NHS and worldwide.

1.3 Review of existing evidence

In 2012, a Cochrane Review on the use of sodium bicarbonate in AKI, identified 25 unique reports, however, no RCTs met the eligibility criteria for inclusion.[5] This review has been updated and deemed stable (June 2017), with no eligible studies identified for inclusion. The authors concluded that the use of sodium bicarbonate for treating AKI cannot be refuted or recommended, and 'that there is an urgent need for well conducted RCTs in this area'.

A recent scoping and systematic review included 12 studies assessing biochemical and physiological effects of sodium bicarbonate in patients with acidosis in an acute care setting.[6] IV sodium bicarbonate increased blood pH, base excess, serum bicarbonate (HCO_3), sodium and $PaCO_2$, and decreased the anion gap and potassium. However, only two trials assessed its clinical efficacy[2, 7], with only one reporting clinical outcomes.[2]

To date, the only large scale RCT to evaluate sodium bicarbonate in critically ill patients with acidosis was BICAR-ICU, conducted in 26 sites in France.[2] It randomised 400 patients with severe acidosis (pH ≤7.20, $PaCO_2$ ≤45 mmHg and sodium bicarbonate ≤20 mmol/L) to receive 4.2% IV sodium bicarbonate or usual care (control). They reported a non-significant reduction in the primary outcome of a composite of mortality at day 28 or organ failure at day 7 in patients receiving sodium bicarbonate (absolute difference -5.5% 95% CI -15.2% to 4.2%). However, in a pre-specified subgroup of patients with AKI (n=182) defined by Acute Kidney Injury Network (AKIN) stage 2 or 3 criteria, the authors reported significant reductions in the primary outcome (absolute reduction -12.3% 95% CI -26.0% to -0.1%), 28-day mortality (-17.7% 95% CI -33.0% to -2.3%; OR = 0.49, 95%CI: 0.27 to 0.88), time to initiation of KRT (10.5 hours 95% CI 4.0 to 18.5) and use of KRT (-22.2% 95% CI -36.0% to -8.5%).[2] Whilst the treatment effect observed within this subgroup was strong, interpretation of this trial's results must be treated with caution due to the small sample size of the AKI subgroup and high risk of type I error.

A recent analysis of the Medical Information Mart for Intensive Care (MIMIC)-III database further indicates a possible benefit of sodium bicarbonate amongst critically ill patients with acidosis and AKI.[8] The authors investigated the effectiveness of sodium bicarbonate infusion in septic patients with acidosis. Again, no significant effect on the primary outcome of hospital mortality in the overall population (hazard ratio (HR): 1.04; 95% CI 0.86 to 1.26; p = 0.67) was reported, however, consistent with the results of the BICAR-ICU trial, a significant reduction in mortality was observed in a sub-group of patients with acidosis (pH <7.2) and AKI defined as AKIN stage 2 or 3 (HR 0.74; 95% CI 0.51 to 0.86; p = 0.021). Again, their conclusions highlight the paucity of evidence and called for large scale RCTs to confirm these results.

To date, despite numerous calls for appropriately designed studies,[2, 5, 8] there have been no RCTs primarily assessing the effects of sodium bicarbonate in critically ill patients with severe acidosis and AKI being treated in critical care. We are aware of only one on-going trial, which commenced in October 2019 (NCT04010630), and is investigating the effect of 4.2% sodium bicarbonate in patients with acidosis (pH ≤7.2) and AKI - KDIGO (Kidney Disease Improving: Global Outcomes) stage 2 or 3 on 90-day mortality. This trial, however, is currently taking place in a single centre in France and with a total sample size of 640 patients, is unlikely to provide definitive and generalisable results for critically ill patients treated in the NHS.

2 RATIONALE

The importance of this research, for critically ill patients in the NHS and globally, hinges both on the prevalence of AKI which is associated with an increased risk of mortality, prolonged critical care unit and hospital length of stay, and development of CKD[9-11], and the high mortality rate of patients with metabolic acidosis in the context of AKI. In the Case Mix Programme for the period of 1 April 2017 to 31 March 2018, 148,817 patients were admitted to the 197 adult general critical care units. Of these admissions, 97,426 (57%) had AKI - KDIGO (Kidney Disease Improving: Global Outcomes) stage 2 or 3 with a hospital mortality rate of 26% (23,950/92,623 patients). When patients were acidotic as well as having AKI, 56% died before hospital discharge rising to 59% by 90 days. In addition, 50% of patients with acidosis and AKI received KRT in the critical care unit, with an average duration of 4.7 days.

This research also has important implications for the NHS, centring on the enormous burden of AKI, which costs the NHS an estimated £1-3 Billion each year.[12] In contrast, sodium bicarbonate is

a relatively cheap and readily available drug (£11.41 / 200ml bottle of 8.4% sodium bicarbonate for infusion).

MOSAICC will be the first large scale RCT to evaluate the use of sodium bicarbonate for treating acidosis in patients with AKI and provide a definitive and generalisable answer to its clinical and cost-effectiveness. Understanding the role of a relatively cheap, widely available intervention will have important treatment implications globally, beyond the UK critical care community.

3 AIMS, OBJECTIVES AND OUTCOME MEASURES

3.1 Aim

The aim of the MOSAICC trial is to evaluate the clinical and cost-effectiveness of IV sodium bicarbonate (8.4% w/v) in critically ill adults with acidosis (pH <7.25, $PaCO_2$ <6.5 kPa and bicarbonate ≤20 mmol/L) and severe AKI (KDIGO stage 2 or 3).

The research question is: in critically ill adults with metabolic acidosis and acute kidney injury (AKI) **[Population]**, is treatment with intravenous (IV) 8.4% sodium bicarbonate **[Intervention]** superior to no IV sodium bicarbonate **[Comparator]** in terms of all-cause mortality at 90 days (clinical effectiveness) and incremental costs, quality-adjusted life years (QALYs) and net monetary benefit at 90 days (cost-effectiveness) **[Outcome]**?

3.2 Objective and outcomes

To evaluate whether treatment with IV sodium bicarbonate (8.4% w/v) is superior to no IV sodium bicarbonate for:

Primary outcome – clinical effectiveness: All-cause mortality at 90 days following randomisation.

Primary outcome – cost-effectiveness: Incremental costs, QALYs and net monetary benefit at 90-days following randomisation.

Secondary outcomes:

- mortality at critical care unit discharge, 28-days and one year;
- receipt and duration of respiratory, renal, and advanced cardiovascular organ support, defined according to the Critical Care Minimum Dataset (CCMDS), during the critical care stay;
- duration of critical care unit and acute hospital stay;
- on-going requirement for KRT at 90 days and one year;
- HRQoL at 90-days and one year (assessed using the EQ-5D-5L questionnaire);
- resource use and costs at 90-days and one year; and
- estimated lifetime incremental cost-effectiveness.

3.3 Internal pilot

The internal pilot phase will run for 12 months from the start of recruitment. The objectives of the internal pilot will be to assess whether there has been successful site set-up, screening and recruitment, and adherence to the protocol in both intervention and comparator groups. The same processes as the main RCT will be used throughout the internal pilot phase, with all patients recruited in the 12-month period included in the final analysis. We will use a traffic light system[13] to assess progression from the internal pilot phase to full trial using the following criteria:

	Red	Amber	Green
Number of sites open to recruitment	<30	30-59	60
Recruitment rate relative to anticipated (1.3 per site per month)	<50%	50-99%	100%
Proportion of participants receiving randomly allocated treatment	<75% of participants	75-99% of participants	100% of participants

If all the green criteria are met, the study will progress from the internal pilot to the full trial unchanged. If any of the amber criteria are met, we will take remedial action and the study will be amended to address the issues raised. If any of the red criteria are met, the study will stop.

4 METHODS

4.1 Design

MOSAICC is a pragmatic multi-centre, open, data-enabled randomised clinical trial (RCT) with internal pilot phase and integrated economic evaluation.

4.2 Setting

60 adult NHS critical care units (defined as intensive care and combined intensive care/high dependency units) in the United Kingdom and participating in the national Case Mix Programme.

4.2.1 Site requirements

- Active participation in the Case Mix Programme.
- Routine stock of 8.4% w/v sodium bicarbonate for infusion.
- Compliance with all responsibilities as stated in the MOSAICC Clinical Trial Site Agreement.
- Compliance with all requirements of the trial protocol.
- Compliance with the UK Policy Framework for Health and Social Care Research and International Conference on Harmonization Guidelines on Good Clinical Practice (ICH-GCP).

4.2.2 Site responsibilities

- Identify a Principal Investigator (PI) to lead the MOSAICC trial locally.
- Identify a MOSAICC research nurse responsible for day-to-day local trial coordination.
- Agree to incorporate MOSAICC into routine critical care clinical practice, highlighting the importance of systematic screening for potential eligible patients and prompt randomisation.
- Agree to adhere to individual participant randomisation allocations and ensure adherence with the trial protocol.
- Agree to aim to randomise all eligible patients and to maintain a Screening Log.
- Agree to data collection requirements.

4.2.3 Site initiation and activation

The following must be in place prior to a site being activated for recruitment:

- A completed site initiation visit (held in person or virtually).
- All relevant institutional approvals (e.g. local confirmation of capacity and capability).
- A fully signed MOSAICC Clinical Trial Site Agreement.
- A completed Delegation Log.

Once the ICNARC Clinical Trials Unit (CTU) have confirmed that all necessary documentation is in place, a site activation e-mail will be issued to the PIs, at which point, the site may start to screen for eligible patients. Once the site has been activated, the PI is responsible for ensuring:

- adherence with the most recent approved version of the trial protocol;
- training of relevant site staff in accordance with the trial protocol and Good Clinical Practice (GCP) requirements;
- appropriate means to identify and randomise eligible patients into the trial;
- timely data collection, entry and validation; and
- prompt notification of all serious adverse events (SAEs) and Serious Adverse Reactions (SARS).

All local staff (i.e. PI, local investigators, research teams) involved in the conduct of the trial must be trained to carry out their assigned roles. Site research staff should be signed off by the PI on the Delegation Log, once trained, and the Delegation Log copied and sent to the ICNARC CTU whenever changes are made.

4.3 Population

Adults admitted to critical care units in England and Wales fulfilling the below eligibility criteria, at any point during the critical care unit stay:

4.3.1 Inclusion criteria

1. Adult (aged ≥18 years);
2. Metabolic acidosis (defined by arterial blood gas values of pH <7.25, $PaCO_2$ <6.5 kPa and bicarbonate ≤20 mmol/L); and
3. AKI – KDIGO stage 2 or 3, defined as **<u>any one</u>** of the following three criteria:
   - Serum creatinine ≥2.0 times baseline*
     or
   - Serum creatinine ≥354 µmol/L, AND either a rise of ≥27 µmol/L within 48 hours or serum creatinine ≥1.5 times baseline*
     or
   - Urine output of <0.5 ml/kg/h for ≥12 hours

* For baseline serum creatinine value:

- If available, then use pre-hospitalisation value within 365 days of the current hospital admission date.
- If there are multiple pre-hospitalisation values, then use the one closest to the date of the current hospital admission.
- If a pre-hospitalisation value from the 365 days prior to admission date is not available and there are multiple serum creatinine values from the current hospitalisation, then use the lowest one from the current hospitalisation.
- If no baseline serum creatinine value is available, then estimate it using the provided calculator.

4.3.2 Exclusion criteria

1. Respiratory acidosis (acute or chronic)
2. Clinical decision already in place to start patient on kidney replacement therapy (KRT)
3. Deemed unsuitable for KRT
4. Acute diarrhoea, including high output stoma/ileostomy
5. Percutaneous biliary drainage
6. Documented Stage 4 chronic kidney disease (CKD) [eGFR <30ml/min/1.73m^2] or end stage kidney disease (ESKD) on dialysis
7. Known renal tubular acidosis
8. Diabetic ketoacidosis
9. High anion gap acid poisoning (e.g. polyethylene glycol (PEG), aspirin, methanol)
10. Known to be pregnant
11. Symptomatic hypocalcaemia (Ionised calcium <1.05 mmol/L) †
12. Hypernatraemia (Plasma sodium >150 mmol/L) †
13. Severe hypokalaemia (Potassium <3.0 mmol/L) †
14. Solid organ transplant
15. Death perceived as imminent
16. Known hypersensitivity to sodium bicarbonate or to any of the excipients (see section 6.1 of the SmPC)

† Exclusion criteria 11-13 are dynamic, and if corrected, patient may be reconsidered for the trial.

4.3.3 Co-enrolment

Co-enrolment will be permitted with observational studies (including those collecting samples) without prior agreement needed.

The Trial Management Group will consider co-enrolment with other interventional studies where there is no possible conflict with the MOSAICC Trial objectives. We will follow previous experience and existing guidelines from the UK Critical Care Research Group regarding co-enrolment to other clinical trials to maximise patient involvement in research.[14] Co-enrolment agreements will be put in place on a case-by-case basis.

4.3.4 Screening

Potentially eligible patients admitted or accepted for admission to the participating ICU will be screened against the inclusion/exclusion criteria by the local clinical team, supported by the site research team. Eligibility can be confirmed by a medical practitioner or a nurse, where delegated by the PI.

Screening Logs will record enrolled patients, reasons for exclusion and the reason eligible patients are not enrolled.

4.4 Recruitment and consent

4.4.1 Randomisation

Participants will be randomised 1:1 to receive IV 8.4% w/v sodium bicarbonate infusion (intervention) or no IV sodium bicarbonate (comparator) with randomised permuted blocks of variable block sizes, stratified by site.

A central web-based randomisation/treatment allocation system will be used. The service will be available 24 hours a day, seven days a week. The research/clinical team will randomise and co-

ordinate the treatments. Sodium bicarbonate will be available on the critical care unit and, following prescription, will be administered by one of the clinical team caring for the patient.

Following randomisation into MOSAICC, each participant will be assigned a unique MOSAICC Trial Number and a CRF will be completed by the local team (see section 4.7.4)

4.4.1.1 Blinding

MOSAICC is an open trial. With frequent blood gas measurements required as part of routine critical care practice, it is impossible to blind the effects of intravenous administration of sodium bicarbonate.

4.4.2 Consent procedures

Patients eligible for MOSAICC become so during a period of critical illness when they may be lacking mental capacity and/or the ability to communicate effectively. Moreover, the emergency clinical situation can cause profound distress for relatives, raising ethical concerns both about the burden of trying to understand the trial and the ability of a Personal Legal Representative (i.e. relative or close friend) to provide an opinion about trial participation during a time of great distress. For these reasons, attempts to obtain either prior informed consent from the patient, or the prior opinion of a Personal Legal Representative, are inappropriate.

MOSAICC will adopt a research without prior consent model (also referred to as 'deferred consent'), whereby eligible patients will be randomised prior to deferred consent to continue from a Personal (family member/close friend) or Professional (independent clinician) Legal Representative and/or deferred consent from the patient themselves. This is an accepted consent model in adult emergency and critical care research where participants are likely to lack capacity and minimises the distress and burden on families.[15] This consent model will be covered by an Emergency Waiver of Consent under the Medicines for Human Use (Clinical Trials) Regulations 2004 (approved by the North West – Greater Manchester Central Research Ethics Committee (reference: 21/NW/0228)).

The PI retains overall responsibility for the informed consent of participants at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details of above should be provided for the delegated individual.

In the rare situation where a patient has been deemed by the treating clinical team to have full capacity and is able to give informed consent at the point of meeting the eligibility criteria, they will be approached directly prior to randomisation for full written informed consent, or verbal or other non-written (e.g. through blinking or hand movement) consent to take part in MOSAICC. If they provide verbal or other non-written consent, they will then be followed up for full written informed consent, in line with the procedures outlined in section 4.4.2.1. If such a participant who gave prospective verbal/non-written consent subsequently lost mental capacity, the opinion of a Personal or Professional Legal Representative should be sought to advise on their continuation in the trial (see sections 4.4.2.2 and 4.4.2.3).

4.4.2.1 Patient informed deferred consent

Following randomisation, patients will be approached by a delegated member of the site research team once deemed to have full capacity to provide informed deferred consent. It is anticipated that this first approach will occur within 24-48 hours of regaining capacity, however this will depend on the patient's condition and will be left to the discretion of the clinical team. A Participant Information Sheet (PIS) will be given to the patient. The PIS will provide information about the background/rationale for the trial, what participation means for the patient (e.g. data collection,

follow-up questionnaires), confidentiality and data protection and the future availability of the trial results. Patients will be given time to read the PIS and have an opportunity to ask any questions they may have about participation in MOSAICC.

A Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; participation is voluntary and can be withdrawn at any time without consequence. The Consent Form will also cover consent for access to medical records for on-going data collection and follow-up.

After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. If the patient is unable to physically sign the Consent Form (e.g. due to weakness, reduced dexterity), an independent witness (i.e. someone not involved in the trial) can sign on their behalf.

In the situation where a patient is approached in hospital but wishes to have more time to consider participation, they can request to be approached via the method detailed in section 4.4.2.4.

4.4.2.2 Personal Legal Representative consent

It will sometimes not be possible to involve trial participants in the consenting process early on. Instead, consent will be obtained from patients once they have stabilised and are deemed to have capacity.

In the interim, once notified of the enrolment of a patient into MOSAICC, a delegated member of the site research team will approach the Personal Legal Representative (in person or via telephone) as soon as appropriate and practically possible to discuss the trial and seek their opinion as to the patients' likely wishes and feelings regarding participating in the trial. Ideally, this approach would take place within 24-48 hours of randomisation, but once the patient's medical situation is no longer an emergency. The Personal Legal Representative will be a person not connected with the conduct of the trial who is: suitable to act as the legal representative by virtue of their relationship with the adult, and available and willing to do so.

Where approached in person, the Personal Legal Representative will be provided with a Personal Legal Representative Information Sheet, containing all of the information provided on the PIS, supplemented with information on why the Personal Legal Representative has been approached at this stage. Personal Legal Representatives will be given time to read the Personal Legal Representative Information Sheet and have an opportunity to ask any questions they may have about the patients' participation in the MOSAICC.

A Personal Legal Representative Consent Form will be provided indicating that: the information given, orally and in writing, has been read and understood; the patients' participation is voluntary and can be withdrawn at any time without consequence; and that, in the Personal Legal Representative's opinion, the patient would not object to taking part in the trial.

After verifying that the Personal Legal Representative Information Sheet and Consent Form are understood, the person seeking opinion will invite the Personal Legal Representative to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the Personal Legal Representative, a copy placed in the patient's medical notes and the original kept in the Investigator Site File.

If a Personal Legal Representative advises that, in their opinion, the patient would not choose to participate in the trial, then the trial treatment will be stopped (if ongoing) and the Personal Legal Representative asked whether, in their opinion, the patient would be willing to continue with ongoing data collection.

Where a Personal Legal Representative is unable to visit the patient in hospital (e.g. due to infection control measures), this consultation may take place over the telephone. The consultation

should be conducted by an experienced member of the site research team with knowledge of intensive care. The telephone consultation should be witnessed by another member of staff. The Personal Legal Representative Information Sheet may be sent to the Personal Legal Representative by email or by post. The outcome of the consultation will be documented and signed by person seeking opinion on the Personal Legal Representative Telephone Consent Form, countersigned by the witness.

Upon patient recovery, the patient will be approached directly for informed deferred consent (see section 4.4.2.1). The patient's decision will be final, and will supersede the Personal Legal Representative, where there is disagreement.

4.4.2.3 Professional Legal Representative consent

In the situation where the patient has died, a Professional Legal Representative will be appointed. The Professional Legal Representative may be an independent doctor (i.e. not involved in the trial) or a person nominated by the NHS Hospital Trust. Consent on behalf of the patient from the Professional Legal Representative will be sought in the same manner as for the Personal Legal Representative.

A Professional Legal Representative will also be approached in the rare situations where no Personal Legal Representative is available (or one is available, but does not wish to be consulted). Upon patient recovery, the patient will be approached directly for informed deferred consent (see section 4.4.2.1). The patient's decision will be final, and will supersede the Professional Legal Representative, where there is disagreement.

4.4.2.4 Discharge prior to consent being confirmed

In the situation where the patient is discharged from hospital prior to confirming their consent decision, an experienced member of the site research team with knowledge of intensive care will attempt a phone call to the patient within 14 working days of ultimate hospital discharge to: inform them of their involvement in MOSAICC; provide information about the trial; and seek their consent. The telephone consultation should be witnessed by another member of staff. The Patient Information Sheet may be sent to the patient by email or by post. The outcome of the telephone call will be documented and signed by the person seeking consent on the Telephone Consent Form, countersigned by the witness.

If there is no response to at least three telephone call attempts, or, where no telephone number for the patient is documented, then the patient will be approached by post. The patient will be sent a covering letter, personalised by the most appropriate clinical/research team member, and a copy of the PIS and Postal Consent Form. The letter will direct the patient to the PIS for detailed information on the trial and provide contact details for if the patient wishes to discuss the trial further. In addition, the letter will confirm that if no Consent Form is received within four weeks of the letter being sent, then the participant's data will be included in the trial unless they notify the site research team otherwise.

Both methods described above will provide patients with the opportunity to opt out of on-going data collection or follow-up questionnaires. A decision to opt out during the telephone call will be documented by the person seeking consent on the Telephone Consent Form. For the postal approach, the patient can actively opt out by returning the Postal Consent Form or using the telephone contact details provided on the PIS, at any point during the trial.

If the participant is transferred to another hospital participating in MOSAICC before the consent procedures are complete, then the local research team will contact the research team at the receiving hospital to handover the consenting procedures.

4.5 Trial interventions

4.5.1 Intervention – Sodium Bicarbonate 8.4% w/v for intravenous administration

Participants randomised to the intervention group will receive sodium bicarbonate 8.4% w/v for intravenous (IV) administration aiming to restore pH to ≥7.30.

4.5.1.1 Regulatory status

In the UK, IV sodium bicarbonate 8.4% w/v has marketing authorisation (MA) held by Macarthys Laboratories Ltd. and will be used in its marketed presentation and packaging bearing the MA number: PL 01883/0023.

4.5.1.2 Dosage schedule

50 ml of IV 8.4% w/v sodium bicarbonate administered over 30-60 minutes. Arterial blood gas (ABG) analysis should be performed 1-2 hours after each infusion.

Participants should be assessed for response to treatment and repeated doses should be administered depending on subsequent pH readings and clinical status (including haemodynamic monitoring heart rate, blood pressure), as well as blood gas analysis (including pCO_2 HCO_3 and electrolytes) up to a maximum of 500 ml per 24-hour period (see *MOSAICC Intervention flow diagram*).

4.5.1.3 Intervention period

The intervention period will continue until discharge from critical care, initiation of KRT or 90 days, whichever comes first. As such, participants will be continually monitored (as per MOSAICC Intervention flow diagram) and if a participant's pH drops <7.3, at any point during this period, then sodium bicarbonate treatment will continue according to the dosage schedule.

4.5.1.4 Concomitant medication, known drug reactions and interaction with other therapies

Renal clearance of medications will be changed as a result of the participants having AKI, therefore, all drug doses should be checked by a pharmacist. Participants receiving corticosteroids, antibiotics, tetracyclines, potassium supplements and/or any medicinal products mentioned in section 4.5 of the SmPC should be closely monitored.

4.5.1.5 Drug storage and supply

The study drug will come from routine hospital stock and will be sourced locally by and stored at each research site according to accredited standards for routine pharmacy practice. As this is an open trial which does not involve the use of placebo or dummy infusions, no special measures are needed in terms of packaging or supply beyond those routinely required.

4.5.1.6 Preparation and labelling

IV 8.4% w/v sodium bicarbonate will be readily available on the ICU. Trial-specific labelling is not required as the IMP has a marketing authorisation in the UK, is being used within the terms of its marketing authorisation and is dispensed to a trial participant in accordance with a prescription given by an authorised healthcare professional.

4.5.1.7 Summary of Product Characteristics (SmPC)

A copy of the SmPC will be filed in the Trial Master File (TMF) and Investigator Site Files (ISF).

4.5.2 Control – no IV sodium bicarbonate

Participants randomised to the control group will not receive IV sodium bicarbonate.

4.5.3 Co-interventions

Patients in whom a decision has already been made to initiate KRT at time of screening are not eligible to participate in this trial.

Once eligible patients have been randomised, indications to commence KRT may subsequently develop and in these situations KRT may be initiated at the discretion of the treating clinician.

As a guide, KRT can be considered where at least two of the following criteria are present:

1. urine output <0.3mL/kg/h for at least 24 hours;
2. arterial pH <7.25 despite adequate volume resuscitation or in the intervention arm an arterial pH <7.25 after adequate administration of sodium bicarbonate (defined as sodium bicarbonate treatment for 24 hours and administration of the maximum 500 ml/24 hours));
3. hyperkalaemia (serum potassium >6.5 mmol/L);
4. fluid overload intractable to diuretics.

Reasons for commencing KRT will be recorded on the CRF. In both groups, all other care will be provided by the discretion of the treating clinical team according to local routine practice.

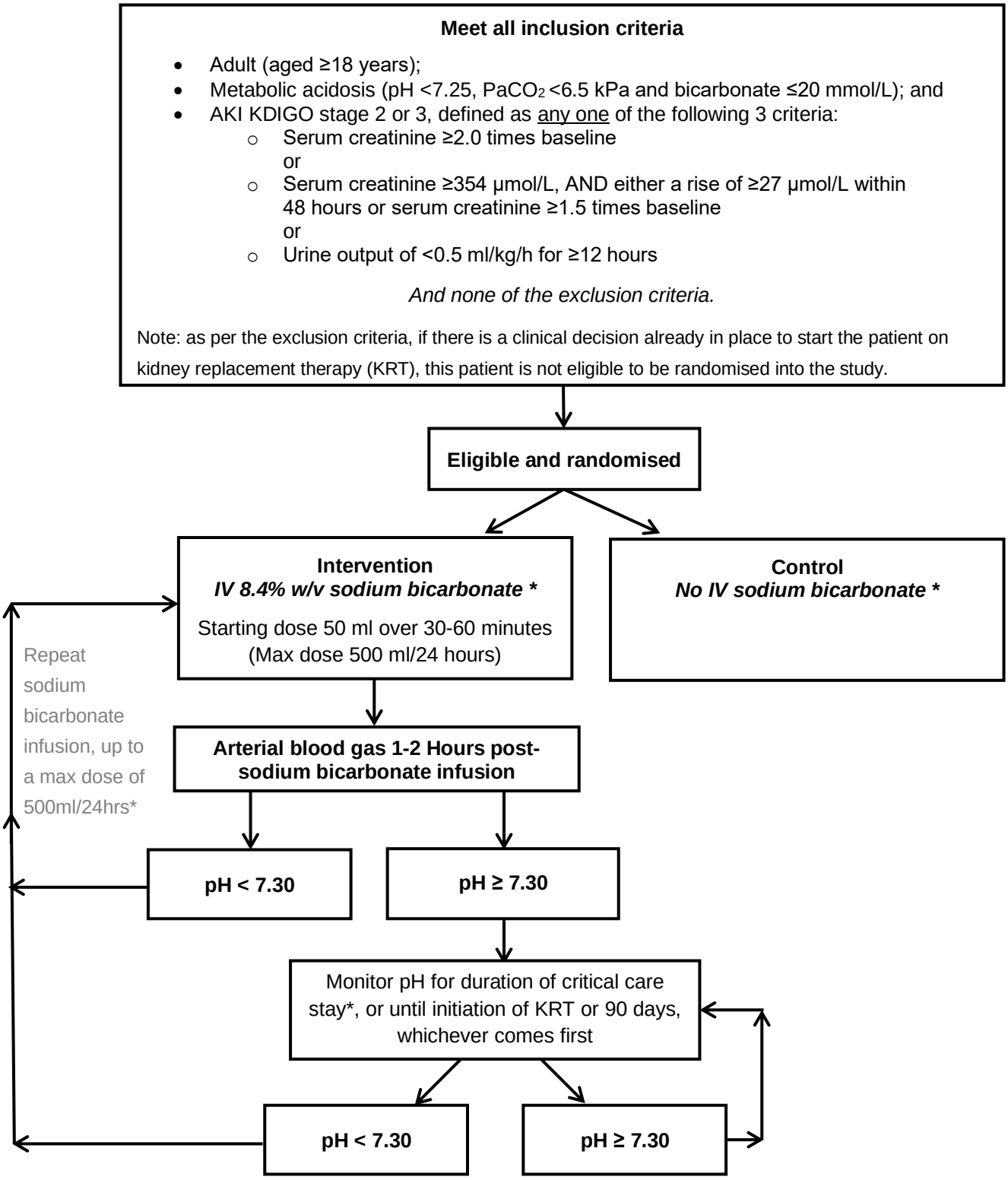
4.5.4 Monitoring adherence to interventions

In the intervention group, adherence to the protocol will be defined as receipt of IV sodium bicarbonate when pH <7.30 until critical care unit discharge or commencement of KRT. Protocol adherence in the control group will be defined by the absence of IV sodium bicarbonate.

During site set-up and recruitment, sites will receive standardised training materials, including an enhanced site training and education website that explicitly cover the current evidence base, the rationale for the study, and treatment protocols in both groups.

During the study, sites will be provided with individual site reports displaying their adherence data and highlighting areas for improvement. Protocol adherence will also be monitored as part of the central monitoring plan. Non-adherence will trigger a query to the participating site who will be required to provide justification.

MOSAICC Intervention flow diagram



* After randomisation, indications to commence KRT may subsequently develop and in these situations KRT may be initiated at the discretion of the treating clinician. As a guide, KRT may be considered where at least two of the following criteria are present:

1. urine output <0.3mL/kg/h for at least 24 hours;
2. arterial pH <7.25 despite adequate volume resuscitation, or in the intervention group an arterial pH <7.25 after adequate administration of sodium bicarbonate (defined as sodium bicarbonate treatment for 24 hours and administration of the maximum 500ml/24hours, as per algorithm above);
3. hyperkalaemia (serum potassium >6.5 mmol/L);
4. fluid overload intractable to diuretics.

4.6 Withdrawal procedures

4.6.1 Withdrawal from randomised therapy

Any physician involved in the usual care of patients may withdraw patients from randomised treatment using their clinical judgement. This might occur due to the occurrence of an AE or the onset of symptoms that limit tolerability. All reasons for withdrawal will be noted in the participant's CRF and medical notes.

4.6.2 Refusal or withdrawals of consent

If a patient declines informed deferred consent, or a legal representative advises that they believe the patient would not choose to participate in the trial, and, if a patient or their legal representative (Personal or Professional) withdraws consent at any time during the trial - this decision will be respected and will be abided by.

All data up to the point of this decision will be retained in the trial unless the patient or legal representative requests otherwise. Where possible, patients and legal representatives will be asked if they are happy for data to continue to be collected from the medical records for the trial, emphasising that this will not require any further contact with the patient/legal representative.

4.7 Assessment and management of risk

The MHRA has categorised MOSAICC as: Type A = No higher than the risk of standard medical care.

This assessment is based on the fact that the risk to the participant is no greater than routine, standard medical care that they would receive if they were not enrolled into this trial. Categorisation of the risk was determined using the Marketing Authorisation of the IMP being investigated and that its use is well established in clinical practice in critical care units in the UK (see Section 4.5.1.1). The IMP under investigation is licensed in the UK.

4.8 Pharmacovigilance and safety reporting

As per 4.2, participants will be critically ill and being treated in a critical care unit (defined as intensive care unit or a combined intensive care/high dependency unit) therefore general safety monitoring is as per standard of care for the setting.

4.8.1 Definitions

Adverse Event (AE) reporting will follow the Health Research Authority guidelines on safety reporting for clinical trials of investigational medicinal products (CTIMPs). The following definitions have been adapted from the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK), for trials with an investigational medicinal product:

Adverse Event (AE)

An untoward medical occurrence in a participant participating in a trial and/or to whom an investigational medicinal product has been administered, which is 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.

Serious Adverse Event (SAE)

Any adverse event that:

- results in death;
- is life-threatening;
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly or birth defect.

“Life-threatening” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

“Hospitalisation” refers to inpatient, regardless of length of stay. This includes admission for continued observation. Any admission for pre-existing conditions that have not worsened, or elective procedures, do not constitute an SAE.

Important adverse events that are not immediately life-threatening, do not result in death or hospitalisation but may jeopardise the subject or require intervention to prevent one or any of the other outcomes listed in the definition above should also be considered as serious.

Serious Adverse Reaction (SAR)

An adverse reaction that is classed as serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be related to the treatment, based on the information in the SmPC.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information in the SmPC.

4.8.2 Assessment of AEs and SAEs

The PI, or other medically qualified investigator as listed on the Delegation Log, should make an assessment of severity, relatedness and expectedness, categorised as follows:

4.8.2.1 Severity

- **None**: indicates no event or complication
- **Mild**: complications result in only temporary harm and do not require clinical treatment
- **Moderate**: complications require clinical treatment but do not result in prolongation of hospital stay. Does not usually result in permanent harm and where this does occur the harm does not cause functional limitations to the patient
- **Severe**: complications require clinical treatment and results in prolongation of hospital stay and/or permanent functional limitation
- **Life-threatening:** complications that may lead to death
- **Fatal:** where the participant died as a direct result of the complication/adverse event.

An event assessed as 'Severe', 'Life-threatening' or 'Fatal' will be considered an SAE, SAR or SUSAR.

4.8.2.2 Relatedness

- **None**: there is no evidence of any relationship to the trial treatment
- **Unlikely**: there is little evidence to suggest a relationship to the trial treatment, and there is another reasonable explanation of the event
- **Possibly**: there is some evidence to suggest a relationship to the trial treatment, although the influence of other factors may have contributed to the event
- **Probably**: there is probable evidence to suggest a relationship to the trial treatment, and the influence of other factors is unlikely
- **Definitely**: there is clear evidence to suggest a relationship to the trial treatment, and other possible contributing factors can be ruled out.

All AEs/SAEs judged as having a reasonable suspected causal relationship (e.g. possibly, probably, definitely) to the study drug will be considered as ARs/SARs.

4.8.2.3 Expectedness

- **Expected**: the event is consistent with the information in section 4.8 in the SmPC.
- **Unexpected**: the event is not consistent with the information in section 4.8 in the SmPC.

4.8.3 Recording and reporting

Occurrences of the specified, expected (S)AEs/ARs (Appendix 2) will be recorded and reported for all randomised patients from the time of randomisation until critical care unit discharge or 90 days (whichever comes first). If a participant is readmitted to the critical care unit within the 90 days, safety monitoring will be recommenced.

All other (S)ARs will be recorded and reported from the time of first dose of sodium bicarbonate until 24 hours after the final dose.

Considering that all eligible patients are critically ill and at increased risk of experiencing multiple adverse events due to the complexity and severity of their condition[16] – occurrences of non-specified, unexpected AEs will only be reported if they are assessed to be serious (i.e. not events that are part of the natural history of the primary disease process or expected complications of critical illness).

The following event(s) will not be reported as SAEs:

- Death (Collected as a study outcome. Note that death itself should not be reported as an SAE, but the suspected cause of death should be assessed for severity, relatedness and expectedness as detailed above)
- Commencement of kidney replacement therapy (Collected as a study outcome.)
- Any events that are part of the natural history of the primary disease process or expected complications of critical illness, and unrelated to any clinical trial procedures

All SAEs (other than those defined in the protocol as not requiring reporting), SARS and SUSARs must be recorded in the patients' medical notes and reported to ICNARC CTU within 24 hours of observing or learning of the SAE/SAR/SUSAR(s). This involves completing and uploading the MOSAICC SAE Report Form to the secure electronic data entry system, and notifying ICNARC CTU of this upload by e-mailing MOSAICC@icnarc.org. Staff should not wait until all information about the event is available before sending SAE notification. Information not available at the time of the initial report must be documented and submitted as it becomes available.

The process for recording and reporting adverse events and serious adverse events is summarised in Figure 1.

On receipt of an SAE/SAR/SUSAR report, a member of the ICNARC CTU will first evaluate the report for completeness and internal consistency. Then, a clinical member of the MOSAICC Trial Management Group (TMG) will evaluate the event for severity, relatedness and expectedness to determine whether or not the case qualifies for expedited reporting to the MHRA, REC and other competent authorities.

Fatal or life threatening SUSARs must be reported within 7 days and non-fatal and non-life threatening SUSARs within 15 days of first being aware of the SUSAR.

All other non-specified AEs that occur between randomisation and 90 days post-randomisation (or ICU discharge, if sooner) must be recorded in the participant's medical notes.

The ICNARC CTU will provide safety information to the Data Monitoring and Ethics Committee (DMEC) on a basis deemed appropriate by the DMEC.

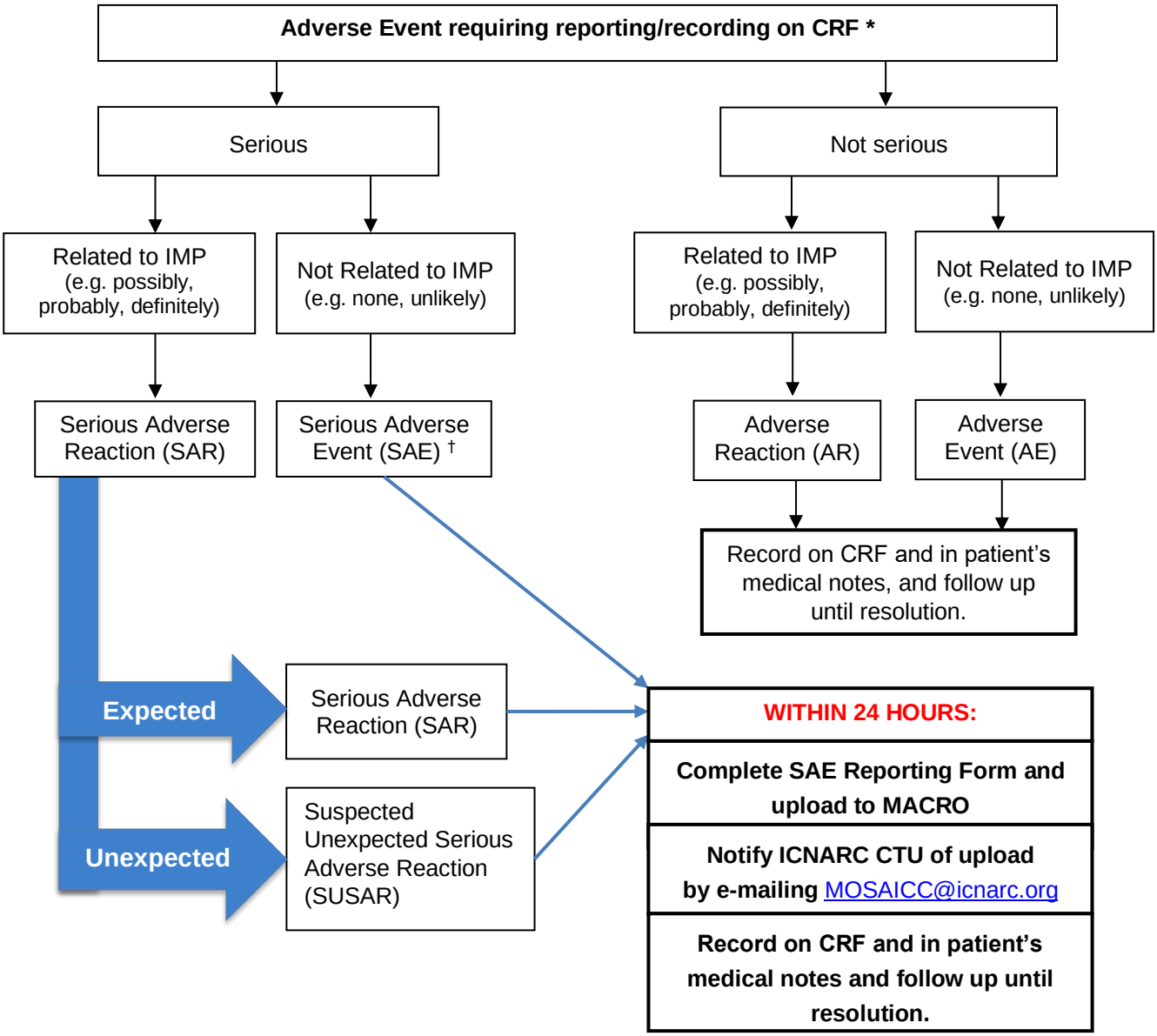
4.8.4 Follow-up after adverse event

After initially recording an AE or recording and reporting an SAE/SAR, the Investigator is required to follow each participant until resolution. Follow up information on an SAE/SAR should be reported to the ICNARC CTU using the MOSAICC SAE Report Form. AEs and SAEs should be followed up until resolution or death of the trial subject.

4.8.5 Reporting to REC and MHRA

Annual study progress reports and Developmental Safety Update Reports will be submitted to the REC and MHRA, respectively. These reports will be submitted yearly on the anniversary of REC favourable opinion and Clinical Trial Authorisation approval.

Figure 1. Safety reporting



* AEs requiring recording/reporting are specified in 4.8.3 and Appendix 2 of the protocol. Those not requiring recording/reporting will need to be documented in the patient's medical notes and followed up until resolution.

† If there is any uncertainty about whether the SAE is associated with trial treatment, then it should be reported.

4.9 Data collection

4.9.1 CMP data

To maximise efficiency, trial data collection will be nested within the Case Mix Programme 'Research Platform', enabling data collection to be incorporated within the routine Case Mix Programme data collection processes, streamlining data linkage. Data from the Case Mix Programme to be used in MOSAICC will include:

- baseline demographics and risk factors;
- secondary outcomes of critical care unit and acute hospital mortality, organ support (calendar days of organ support in critical care for the CCMDS), duration of critical care and acute hospital stay; and
- critical care costs, based on Health Care Resource Groups, from the index admission and any subsequent critical care readmissions.

4.9.2 Other routine data sources

All patients recruited to the trial will be asked to provide consent for data linkage with other routine data sources. Data from other routine sources will include:

- date of death for deaths occurring after discharge from acute hospital, by data linkage with civil registrations mortality data held by NHS Digital, until longest available follow-up (e.g. patients recruited in the first month of the trial will be able to be followed-up for survival until 24 months); and
- hospital costs for subsequent hospitalisations, by data linkage to Hospital Episode Statistics held by NHS Digital and Patient Episodes Data for Wales held by Digital Health and Care Wales.
- on-going requirement for KRT at 90 days and one year, by data linkage with the UK Renal Registry.

4.9.3 Additional data collection

Additional data items collected at each site specifically for the trial will be limited to:

- confirmation of eligibility criteria and patient/legal representative consent;
- patient and personal legal representative contact details for questionnaire follow-up at 90 days and one year;
- data to monitor adherence with the intervention;
- data related to commencement of KRT; and
- adverse event reporting.

4.10 Questionnaire follow-up

Each participant will be followed up with a questionnaire up to a maximum of one year.

Survival status at 90 days and one year following randomisation will be obtained via data linkage with nationally held routine data. At each time point, survivors will be sent (via email or post as per their indicated preference at the time of consent) a questionnaire by the ICNARC CTU containing the EuroQol EQ-5D-5L and health services questionnaires. These questionnaires are designed to take no longer than 15 minutes to complete and if completing a postal questionnaire, patients will be provided with a pen and stamp-addressed envelope for ease of return.

Non-responders will be telephoned three weeks after the questionnaire was posted and asked to check whether they have received the questionnaire. If preferable for the patient, they will be offered the option of either being sent another copy of the questionnaire, completing the

questionnaire over the telephone with a trained member of the MOSAICC Trial team, or to receive the questionnaire in a preferred alternative format (e.g. e-mail).

If a patient is an in-patient at a participating site at either of the follow-up time-points, the site research team will be asked to approach the patient and conduct the questionnaire with them in hospital, if willing and if their condition permits.

If a patient is on their initial acute hospital admission at either of the follow-up time points, they will not be asked to complete the health services questionnaire, as this contains only questions that are relevant following discharge from acute hospital.

4.11 Data management

All participant data collected will be entered onto a secure electronic data entry system. The option of entry first onto paper CRFs will be available. The site PIs will oversee and be responsible for data collection, quality and recording. Collection of data can be delegated (as per the Delegation Log) by the site PIs to qualified members of the research team.

Data entered onto the secure electronic data entry system will undergo validation checks for completeness, accuracy and consistency of data. Queries on incomplete, inaccurate or inconsistent data will be sent to the local research team at participating sites for resolution.

Security of the electronic data entry system is maintained through user names and individual permissions approved centrally by the ICNARC CTU. Central back-up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act. ICNARC is registered under the Data Protection Act (Registration number: Z6289325).

5 STATISTICS AND DATA ANALYSIS

5.1 Sample size

To achieve 90% power to detect a clinically meaningful absolute reduction in 90-day mortality of 7% ($p<0.05$) from 59% to 52% (a conservative estimate of half the treatment effect (OR 0.75) observed in the AKIN 2-3 subgroup from the BICAR-ICU Trial[2]), and allowing for 6% withdrawal/refusal of deferred consent (based on figures from the 65 trial), we will recruit a total sample size of 2250 patients.

Based on 2018 CMP data, 6139 patients meeting the proposed inclusion criteria (during the first 24 hours of admission) were treated in participating critical care units. Assuming the proportions of eligible patients recruited on previous similar RCTs and a recruitment rate of approximately 1.3 patients per site per month will allow recruitment of the full sample within 34 months from 60 critical care units, allowing for a staggered opening of sites opening over a six-month period.

5.2 Statistical analysis

5.2.1 Internal pilot analysis

Data will be analysed at the end of the internal pilot trial stage. The analysis will take place in month 14 of the trial to allow data to be collected and entered to assess all progression criteria. If all the green criteria are met, the trial will progress from the internal pilot to the full trial unchanged. If any of the amber criteria are met, the trial will be amended to address the issues raised. If any of the red criteria are met, the trial will stop.

The final decision on progression from the pilot stage to the full trial will be made by the NIHR HTA programme after recommendation by the TSC.

5.2.2 Clinical effectiveness analysis

All analyses will be described in a statistical analysis plan, a priori, before the investigators are unblinded to any study outcomes. All analyses will follow the intention to treat principle. The intention to treat population will include all patients randomised to the trial according to the group to which they were allocated, other than if a patient or their legal representative requests removal of all data from the trial (see 4.6.2). Baseline patient characteristics will be compared between the two groups to observe balance and the success of randomisation. These comparisons will not be subject to statistical testing. The delivery of the intervention will be described in detail. Results will be reported in accordance with the CONSORT statement. Missing data (including missing outcomes) will be multiply imputed using chained equations, including treatment allocation, covariates and outcomes in all imputation models.

Analysis of the primary outcome (90-day mortality) will be adjusted for site (as stratification variable) and additional baseline covariates. An analysis adjusted only for site will also be conducted to aid interpretation. Treatment effects will be estimated using generalised linear mixed models (GLMMs), including a random effect of site, with the binomial family and identity link to estimate absolute risk reduction and the Poisson family and log link to estimate relative risk. Adjustment for baseline covariates can increase the precision of the estimate of treatment effect, and therefore the power of the study, and adjust for any chance imbalance between the treatment groups. The covariates for inclusion in the adjusted analysis will be selected a priori based on established relationship with outcome for critically ill patients, and not because of observed imbalance, significance in univariable analyses or by stepwise selection method.

Analyses of secondary outcomes will use similar GLMMs with the binomial/Poisson family for binary outcomes (mortality at critical care unit discharge and 28-days; receipt of respiratory, renal and cardiovascular support; on-going requirement for KRT) and normal family for continuous outcomes (duration of organ support; health-related quality of life). Analyses of duration of critical care unit and acute hospital stay will be performed by Wilcoxon rank-sum tests, stratified by survival status. Survival will be presented as Kaplan-Meier plots and analysed by Cox proportional hazards models with shared frailty at the site level.

Subgroup analyses will test for an interaction between treatment group and subgroup (for a limited number of subgroups specified a priori) in the adjusted GLMM for the primary outcome on the relative risk scale. One of the key subgroups will include severity of the acidosis.

5.2.3 Interim analysis

A single interim analysis of the primary outcome will be carried out after the recruitment and follow-up of 1125 patients using a Peto-Haybittle stopping rule ($P<0.001$) to recommend early termination due to either effectiveness or harm. Further interim analyses will be performed if requested by the DMEC.

5.2.4 Health economic evaluation

A full cost-effectiveness analysis (CEA) will be undertaken by LSHTM to assess the relative cost-effectiveness of the use of the intervention (use of bicarbonate to treat acidosis) versus usual care (not using bicarbonate to treat acidosis). The CEA will take a health and personal health services perspective. Patient-level resource use data from the critical care and hospital stay will be taken from the case report form and linked to routine data from the CMP. Information on subsequent hospital and emergency department admissions, and KRT usage will be obtained from linkage with Hospital Episodes Statistics and the UK Renal Registry, respectively. Use of primary care and community health services will be assessed by follow-up patient questionnaires. Patient-level

resource use data will be combined with appropriate unit costs from the NHS payment by results database and Personal Social Services Research Unit to calculate total costs per patient for up to 90 days since randomisation.

The CEA will follow the intention-to-treat principle and report the mean (95% confidence interval) incremental costs, QALYs and net monetary benefit at 90 days since randomisation. The CEA will use multilevel linear regression models that allow for clustering of patients at site. The analysis will adjust for key baseline covariates at both patient and site level. The CEA will also report incremental cost-effectiveness at one year and estimate lifetime cost-effectiveness.

6 MONITORING AND AUDITING

6.1 Central monitoring

The ICNARC CTU will communicate regularly with sites via email, telephone, teleconferences and newsletters. This will include central review of consent forms and essential documents. Data will be actively and regularly reviewed centrally and local PIs will be contacted regularly to ensure adherence and the quality of the data.

6.2 Site monitoring

The on-site monitoring plan will follow a risk-based strategy. The timing and frequency of visits will be based on a risk assessment, including an assessment of each site's performance (including protocol adherence) and local research team (e.g. experience of conducting RCTs). It is anticipated that 25% of sites will be visited at least once during the recruitment period to monitor and discuss adherence to the trial protocol and standard operating procedures. Following all site visits, a report will be sent to the site summarising the visit, documents reviewed and the findings. Information learned from the site visits will be used to refine the study procedures, as requires, ensuring clarity and consistency across sites.

7 TRIAL CLOSURE

7.1 End of trial

The recruitment period will be stopped after 34 months or if the trial is stopped for another reason by the steering committee, funding body or regulatory body.

The end of the trial is defined as last patient, last follow-up, so one year after the last patient is randomised. The sponsor/ICNARC CTU will notify the REC and MHRA of the end of the trial within 90 days of the end of the study.

7.2 Archiving trial documents

At the end of the trial, the ICNARC CTU will securely archive all necessary centrally held trial-related documents for 10 years, in accordance with Regulation 31A of the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006. Arrangements for confidential destruction of all documents will then be made.

The site PI will be responsible for archiving all trial-related documents (including CRFs and other essential documents) held at the participating site for a minimum of 10 years after the end of the study. Essential documents are those which enable both the conduct of the study and the quality of

the data produced to be evaluated and to show whether the site complied with the principles of ICH-GCP and other applicable regulatory requirements. Guidance on archiving will be provided to sites in a study-specific SOP.

All archived documents, held centrally and locally, should be available for inspection by appropriate authorities upon request.

8 TRIAL MANAGEMENT AND OVERSIGHT

The Lead Investigators (Professor Lui Forni and Professor Nicholas Selby) will take overall responsibility for the delivery of MOSAICC and oversee progress against timelines/milestones.

8.1 Good research practice

MOSAICC will be managed by the ICNARC CTU according to the Medical Research Council's Good Research Practice: Principles and Guidelines[17], based on the principles of the International Conference on Harmonization guidelines on Good Clinical Practice[18] and the UK Policy Framework for Health and Social Care Research[19]. ICNARC policies and procedures are based on these guidelines, which are adhered to for all research activities at ICNARC. In addition, ICNARC has contractual confidentiality agreements with all members of staff and policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

8.2 Trial Management Group (TMG)

The TMG comprises the MOSAICC Investigators (see *MOSAICC Investigators, page 5*) and will be led by Lead Investigators (Professor Lui Forni and Professor Nick Selby). Meeting of the TMG will be held quarterly, or more frequently during key stages of the trial, to ensure the progress of the study against milestones and to ensure effective communication across the team.

The day-to-day trial team will be led by the Trial Manager (Ms Irene Chang) and comprise the Lead Investigators (Professor Lui Forni and Professor Nick Selby), Clinical Trials Unit co-investigators (Professor Kathy Rowan, Professor David Harrison, Dr Doug Gould, Dr James Doidge), alongside the Trial Statistician, Research Assistant and Data Manager. The day-to-day trial team will meet regularly to discuss and monitor progress.

8.3 Trial Steering Committee (TSC)

A TSC will be established in line with the latest NIHR HTA guidelines (i.e. consist of 75% independent members – including the Chair). The TSC will be responsible for overall supervision on behalf of the Sponsor and Funder and will ensure that the trial is conducted in accordance with the rigorous standards set out in the UK Policy Framework for Health and Social Care Research and the Guidelines for Good Clinical Practice.

The TSC will comprise one of the Chief Investigator(s), a senior representative from the ICNARC CTU and independent members (including independent PPI representatives). Representatives from the Sponsor and Funder will be invited to observe TSC meetings which will be scheduled to take place at the following time points: (1) prior to the start of the trial; (2) following the internal pilot stage; (3-5) during the trial recruitment period; and (6) at the end of primary analysis.

8.4 Data Monitoring and Ethics Committee (DMEC)

An independent DMEC will be set up to monitor recruitment and retention, protocol adherence (including adherence to treatment protocols) and patient safety, and will review the interim analysis. Meetings will take place immediately prior to TSC meetings.

9 ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Ethical compliance

The trial will require a favourable opinion from an NHS Research Ethics Committee. Following confirmation of funding and following preparation of the protocol and related trial documents (information sheets, consent forms, etc.), an application for Health Research Authority (HRA) Approval (which includes review by the NHS Research Ethics Committee and assessment of regulatory compliance, following the latest guidance from the HRA) will be made immediately.

9.2 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and the study has received favourable REC opinion. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place.

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (Research and Innovation [R&I] departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

9.4 Public and Patient Involvement

One co-investigator is a PPI representative who has actively contributed to the trial design and procedures, including the use of deferred consent. In addition, independent PPI representative(s) will be sought for membership of the TSC and they will help with the dissemination of the study findings.

9.5 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a subject if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time and must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. 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.

10 DISSEMINATION

The results of MOSAICC will be disseminated actively and extensively. This will cover both progress during the trial period and the results at the end of the study. Outputs will include, but will not be limited to, the following areas:

- meeting and conference presentations (international and national) of study progress and results;
- publication of study (1) protocol (2) statistical analysis plan (3) primary results, and (4) longer-term outcomes, including economic evaluation; and
- incorporation into clinical guidelines
- lay summary of results sent to trial participants (via email or post as per their indicated preference for the follow-up questionnaire); the summary will also be available on the study website

These separate outputs will be targeted at relevant stakeholders in formats suitable for the target audience to ensure that the potential benefit and impact of MOSAICC are maximised.

11 SPONSORSHIP AND FUNDING

11.1 Sponsorship and indemnity

University Hospitals of Derby and Burton NHS Foundation Trust are the sponsor for MOSAICC (reference: UHDB/2021/027). As the sponsor is an NHS organisation, NHS indemnity will apply for legal liability arising from the design, management and conduct of the research.

11.2 Funding

National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Project number: NIHR129617)

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13 APPENDICES

13.1 Appendix 1 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

13.2 Appendix 2 – Expected adverse events/reactions.

- Alkalosis (defined as arterial blood gas value of pH ≥7.55)
- Hypokalaemia
- Hypernatraemia
- Hyperosmolarity
- Hypocalcaemia
- Hypoglycaemia
- Deterioration of hemodynamic status associated with volume overload
- Extravasation
- Tissue necrosis caused by incorrect administration (intra-arterial, paravenous)

If an SAE/SAR, as defined in Section 4.8, occurs this should be recorded and reported as described in Section 4.8.