THE GEORGE INSTITUTE
for Global Health

CLINICAL TRIAL PROTOCOL

AMENDMENT NO. 2

Prevention of Serious Adverse Events Following Angiography:

A Department of Veterans Affairs Cooperative Study CSP #578

PROTOCOL NUMBER: GI-RM-3783

PROTOCOL NAME: PRESERVE

VERSION NUMBER: 3.0

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A collaboration between the United States Department of Veterans Affairs Collaborative Studies Program and the George Institute for Global Health, Australia, funded by the National Health and Medical Research Council

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1 GENERAL INFORMATION

SPONSORS

The PRESERVE Study Collaboration (PSC) is a joint international research activity involving the United States Department of Veterans Affairs (VA) Cooperative Studies Program (CSP) and The George Institute for Global Health (TGI) in Australia. The PSC will oversee and manage the study entitled, "Prevention of Serious Adverse Events Following Angiography (PRESERVE)" (also referenced as CSP #578). The VA CSP is the originator of this research project. TGI, Australia will act as the Regional Coordinating Centre responsible for undertaking PRESERVE in Australia, New Zealand and Malaysia. .

The PSC will be led by representatives of the VA CSP and TGI. It is recognized that the collaborators have particular policies and regulations that each must respectively comply with over the course of the collaboration. However, every effort will be made to conduct study responsibilities jointly or as similarly as possible.

Project Originator & US Sponsor:

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Australian Sponsor:

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2 SYNOPSIS

AUS Sponsor & Coordinating Centre	The George Institute for Global Health, Australia (Renal and Cardiovascular Divisions)
Project Title:	Prevention of Serious Adverse Events following Angiography
Study Phase	IIIb
Primary Objective	To assess the effectiveness of bicarbonate compared to saline and N-Acetylcysteine (NAC) compared to placebo for the prevention of a composite primary end-point consisting of death, need for dialysis, and persistent decline in kidney function, in high risk patients within 90 days of undergoing angiography.
Type of patients	Patients scheduled to undergo angiography, who are at increased risk of developing contrast-induced acute kidney injury, including: 1) patients with diabetes and eGFR <60 ml/min/1.73m^2, or 2) any patient with eGFR <45 ml/min/1.73m^2
Number of patients	Total 8680, competitive recruitment. In Australia, New Zealand and Malaysia, a total of 1000 patients with approximate recruitment of 70 patients per site.
Trial design	Factorial design, prospective, multi-centre, double-blinded randomised controlled trial
Study treatment	Using a 2 x 2 factorial design, patients will be randomized in a 1:1:1:1 ratio to receive one of four treatment combinations: • IV isotonic saline (NaCl) + oral NAC • IV isotonic sodium bicarbonate (NaHCO3) + oral NAC • IV isotonic saline (NaCl) + matching placebo for NAC • IV isotonic sodium bicarbonate (NaHCO3) + matching placebo for NAC
Treatment duration	The study interventions of IV sodium bicarbonate and IV sodium chloride are administered before, during and after angiography and oral NAC is administered before and after angiography for a total of five days. Additional IV fluid may be administered as clinically indicated.
Recruitment period	February 2013 - February 2016 (estimated dates)
Study period	Q1 2013 to Q1 2017 (estimated dates)

Study duration	The total duration for one subject will be approximately 12 months, including the 5-day treatment period (administration of the oral NAC for 5 days does not necessitate extension of hospital admission beyond that required for routine patient care) and 12-months follow up. The total study duration is expected to be approximately 36-42 months.
Inclusion criteria	Patients able to provide informed consent who: • are having planned elective or urgent coronary or non-coronary angiography with iodinated contrast media in which it is anticipated that there will be an interval of ≥3 hours between the identification of the indication for angiography and the time of the planned procedure. • have pre-angiography eGFR < 60 ml/min/1.73m^2 with diabetes or pre-angiography eGFR < 45 ml/min/1.73m^2 with or without diabetes. This screening SCr will be measured as part of routine clinical care within 30 days prior to angiography.

Exclusion criteria	Patients that meet (or are expected to meet) any of the following exclusion criteria at the time of the planned angiography will be ineligible for enrolment in the Study:
	• Currently receiving hemodialysis, peritoneal dialysis, continuous renal replacement therapy, or slow low efficiency dialysis (SLED).
	• Stage 5 CKD (eGFR < 15 ml/min/1.73m^2).
	• Known unstable baseline SCr at the time of angiography, defined as a change in SCr of ≥ 25% over the 3 days prior to angiography.
	• Decompensated heart failure requiring any of:
	  ○ Intravenous inotropic or vasodilator medications (inamrinone, milrinone/primacor, dobutamine, nesiritide/natrecor)
	  ○ Intra-aortic balloon pump
	  ○ Isolated ultrafiltration therapy
	• Any emergent angiography (occurring less than 3 hours between the determination of need for angiography and the time of the planned procedure).
	• Receipt of intravascular iodinated contrast within the 7 days preceding angiography.
	• Receipt of oral or intravenous NAC within 48 hrs of the planned time of study angiography.
	• Aged less than 18 years.
	• Women who are pregnant or breastfeeding.
	• Women of child bearing age who will not or cannot use adequate contraception (Appendix).
	• Known allergy or contraindication to any of the study treatments.
	• Prior allergic reaction to iodinated contrast defined as hives and/or trouble breathing.
	• Unwilling or unable to provide consent to the study and study procedures.

3 SCHEDULE OF ASSESSMENTS

Study Period	Pre-Screening to Screening	Baseline	Early Post-Angiography Assessment	Late Post-Angiography Assessment			D35 Assessment	D90 Assessment	1-Year Assessment
Days (d) or Year (yr)	- 30 to 0	Day 0 (Pre-angiography)	During and up to 12hrs post-angiography	Hospitalisation>12 hs and up to 96hrs	96hr Renal Function	5-8d post-angiography	35-42d post-angiography	90d post-angiography	1 yr post-angiography
Clinical care SCr [a]	X[a]								
Hemoglobin & basic met. Profile [a]	X[a]								
Hemoglobin A1C (if diabetic) [a]	X[a]								
Eligibility assessment	X[b]	X[b]							
Informed Consent		X							
Demographics, medical history, medications, BP and weight		X							
Urine Protein		X							
Study SCr		X[c]			X[c]			X[c]	
Randomisation		X							
Study Treatment (IV fluids)		X	X						
Study Treatment (NAC/placebo)		X	X	X					
NAC/placebo pill count						X			
Urine pH			X						
Procedural data/complications			X						
Post-angiography events			X	X			X[e]	X[e]	
Treatment related adverse events		X	X	X		X[F2F/phone]	X[phone]		
Assessment of 1^0 outcome								X[e]	
Assessment of 2^0 outcomes					X[d]			X[e]	
Assessment of 3^0 outcomes [f]									X[f]

[a] denotes labs measured as part of routine clinical care by providers within 30 days prior to angiography

[b] denotes eligibility based on eGFR calculated from SCr performed as part of routine clinical care within 30 days prior to angiography

[c] denotes SCr sent to central study laboratory for endpoint ascertainment

[d] denotes assessment of CIAKI based on 96-hour study SCr

[e] denotes assessment to be done by pt telephone interview for post-angiography endpoint events and medical record review

[f] denotes assessment to be performed using data linkage to ANZDATA (development of ESRD) and Death Registry (long term-mortality) coordinated by the George Institute

4 KEY ABBREVIATIONS

AE	Adverse event
ANZDATA	Australian and New Zealand Dialysis and Transplant Registry
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
CTRA	Clinical Trials Research Agreement
DMC	Data Monitoring Committee
ESRD	End Stage Renal Disease
GI	The George Institute for Global Health
GCP	Good Clinical Practice
GP	General Practitioner
HREC	Human Research Ethics Committee
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
SAE	Serious Adverse Event
SCr	Serum Creatinine
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File

5 BACKGROUND AND RATIONALE

Burden of CIAKI

Contrast induced acute kidney injury (CIAKI) is defined as a sudden decline in kidney function following the intravascular administration of iodinated contrast media for diagnostic imaging[1-3]. While the threshold level of kidney injury used to define CIAKI varies across studies, the definition employed most commonly in research and clinical practice is an increase in the serum creatinine concentration (SCr) of at least 0.5 mg/dL and/or 25% within 3-4 days of contrast exposure[4-6].

Precise estimates of the incidence of CIAKI vary considerably based upon the risk profile of the patients studied, procedural factors and the definition threshold for changes in serum creatinine (sCr). Data from the Veterans Administration in the US[7] found that clinically stable patients with at least stage 3 chronic kidney disease undergoing non-urgent coronary angiography developed CIAKI in 8.5% of cases. Other studies have noted much higher rates in patient with higher baseline risk[8], increased by factors such as:

- Intravascular volume depletion
- Underlying renal insufficiency
- Diabetes mellitus
- Congestive cardiac failure
- Higher contrast dose
- Use of hyper-osmolar contrast
- Intra-arterial contrast administration

Consequences of CIAKI

CIAKI is not a benign, transient biochemical abnormality. Numerous observational studies have demonstrated an association with increased short-term mortality, with the odds ratios for mortality between 1.8 and 22[9 10]. In addition, prospective studies have confirmed this mortality association, with in-hospital mortality rates well over 10 fold higher in those patients developing CIAKI compared to those spared this post-procedure complication[11 12].

In addition to the increase in short-term mortality, numerous retrospective and prospective clinical trials have shown:

- Prolongation of hospital length of stay[10]
- Increased health care expenditures[13 14]
- Increased risk of vascular events (eg: stroke, myocardial infarction)[15]
- Increased risk of long term mortality [15]
- Increased risk of chronic kidney disease (CKD) and end stage kidney disease (ESKD)[15]

These associations and findings are entirely consistent with the now extensive evidence for the additional risk that renal dysfunction confers for heart disease and mortality[16], adding to the burden of disease from CIAKI.

Evidence for prophylaxis

Radiocontrast agents are believed to produce nephrotoxicity through acute sustained vasoconstriction and reduced renal perfusion resulting in regional hypoxia and tubular cytotoxicity[17]. Strategies to prevent CIAKI have targeted numerous elements of the causative pathway, including renal vasoconstriction, hypoxia-induced oxidative stress, and tubular acidification.

Clinical practice, however, is dominated by three treatments: pre-procedural volume expansion with normal saline or isotonic sodium bicarbonate (HCO3) or administration of N-acetylcysteine (NAC). Although evidence to support its use is not compelling[17], intravenous isotonic saline is routinely administered to high risk patients and is generally considered the standard of care. Recent meta-analyses of the effects of HCO3[18] and NAC[19] including 23 and 22 studies respectively, reached similar conclusions. This field is dominated by numerous small, low-quality studies leading to significant heterogeneity in study results and making summary estimates of effect problematic. Figure 1 illustrates numerous factors, including the number of events and patients in the studies, duration of follow up and study quality, which contribute to the heterogeneity of the HCO3 meta-analysis outcomes.

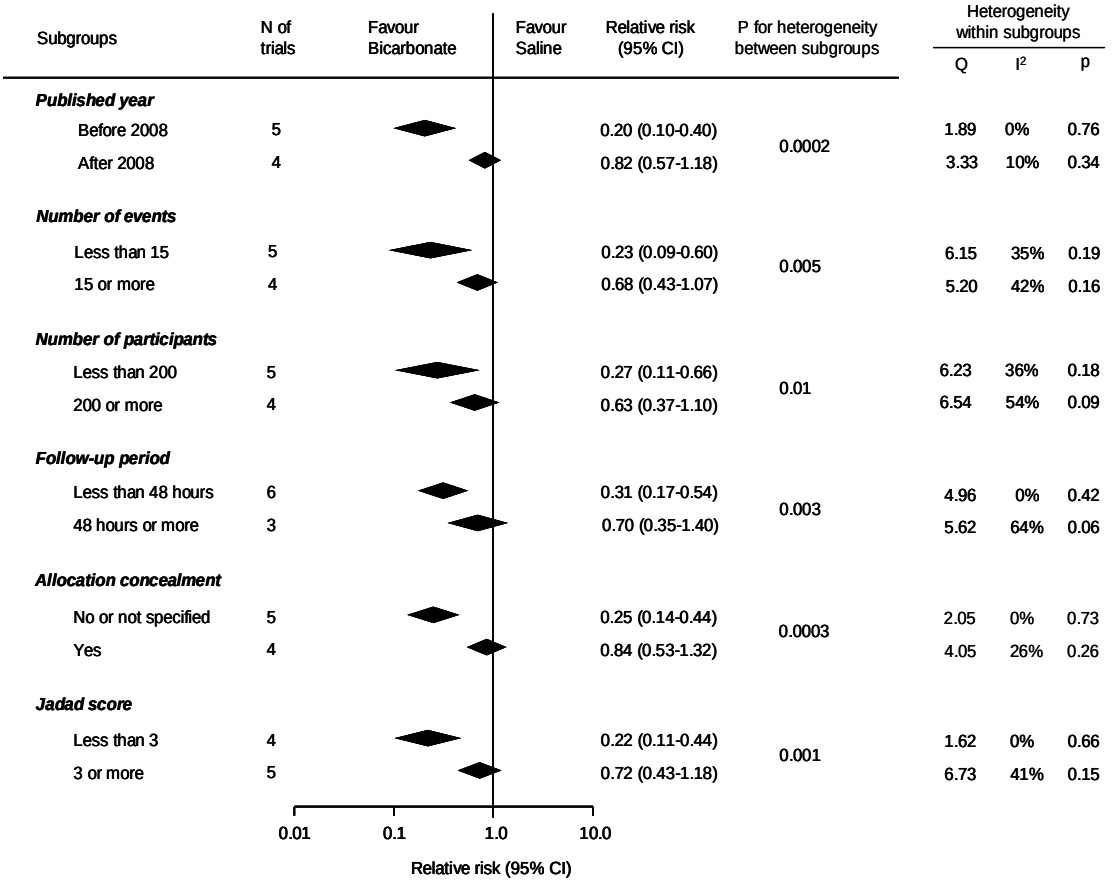

Figure 1: Subgroup analysis of possible sources of heterogeneity in the published studies of the effect of sodium bicarbonate upon CIAKI[18].

Three key characteristics of previous CIAKI prevention trials underlie the failure to provide clear evidence to guide therapy. First, all of the published clinical trials enrolled

relatively small numbers of patients and most assumed unrealistically large effect sizes for the tested interventions. As a consequence, these studies were underpowered to detect clinically plausible benefits of interventions and were particularly susceptible to type I error. As small studies with negative findings are less likely to be reported, this factor is likely to have substantially contributed to the publication bias identified in the meta-analyses. Second, many trials included patients at low-risk for CIAKI, which resulted in relatively few primary study events and diminished the ability to discern the effects of these interventions in higher-risk subjects, in whom the interventions would potentially have the greatest clinical utility. Third, nearly all previous trials used small increases in SCr as their primary endpoint and many did not assess serious adverse outcomes.

Results of a new study, the ACT trial, were presented at the American Heart Association meeting in late 2010 but are as yet unpublished. This trial randomised 2308 patients undergoing angiography to NAC or placebo and showed no difference in the primary end point of a >25% increase in serum creatinine at 4 days post procedure. This study recruited a relatively low risk population, seen in the low number of participants with baseline renal impairment and the small number of dialysis events in both arms of the study, which will have markedly reduced its ability to detect any difference from NAC use. Whilst undoubtedly an advance upon previous trials in the field, through its randomised allocation of treatment and recruitment of larger numbers of participants, the PRESERVE Study Management Committee is of the view that the ACT trial represents an important addition to our knowledge but does not provide definitive evidence to say that NAC is ineffective at preventing CIAKI.

Clinical implications and significance

Approximately 3.6 million coronary angiograms are performed annually in the USA[20] and a further 76,000 annually in Australian hospitals[21], making it one of the most common medical procedures performed in hospitals globally. CIAKI is predicted to develop in up to 25% of high-risk patients undergoing angiography, a group who are readily defined by pre-existing chronic kidney disease, diabetes and heart failure[22], and has serious downstream consequences including need for on going dialysis and death. Several treatments are widely used to mitigate this risk but the evidence to support such intervention is limited by the poor quality of the studies performed to this point. Such doubt means that ineffective treatments are being widely employed or that effective treatments are being under-utilised during one of the most common medical procedures in the world. As such, the PRESERVE Study has the potential to inform and shape clinical practice on a global scale.

6 OBJECTIVES

Primary objective

The PRESERVE Study will assess the effectiveness of bicarbonate compared to saline and NAC compared to placebo for the prevention of a composite primary end-point consisting of death, need for dialysis, or persistent decline in kidney function in high risk patients within 90 days of undergoing angiography.

Secondary objectives

To assess the effectiveness of bicarbonate compared to saline and NAC compared to placebo for the prevention of:

- The development of CIAKI, defined by an increase in SCr of at least 25% and/or 44µmol/L within 72 to 120 hours, but as close as possible to 96 hours following angiography
- The development of each component of the primary study outcome (death, need for dialysis, persistent decline in kidney function) within 90 days of undergoing angiography.
- The requirement for any hospitalisation and hospitalisation with acute coronary syndrome, heart failure or cerebrovascular accident.

Tertiary objectives

To assess the effectiveness of bicarbonate compared to saline and NAC compared to placebo for the prevention of the development of end stage kidney disease and mortality at 1 year following angiography.

7 STUDY DESIGN

7.1 OVERVIEW, NUMBER OF SUBJECTS AND CENTRES

The PRESERVE trial is a prospective, multi-centre, double-blinded randomised controlled trial which will recruit 8,680 participants (7680 participants in the United States and 1000 participants in Australia, New Zealand and Malaysia) scheduled to undergo angiography. Participants at increased risk of developing CIAKI will be enrolled, as defined by having diabetes and an eGFR <60 ml/min/1.73m2, or an eGFR <45 ml/min/1.73m2 irrespective of diabetic status. Using a 2 x 2 factorial design, patients will be randomized to receive: 1) either IV isotonic sodium bicarbonate (HCO3) or IV isotonic saline and 2) either oral N-Acetylcysteine (NAC) or matching oral placebo prior to and following the angiographic procedure.

The Study is a collaboration with investigators at the Veteran's Administration (VA) in the USA, coordinated by the VA Cooperative Studies Program Coordinating Center in Boston. The Asia-Pacific limb of the trial will recruit 1000 participants from approximately 15-20 high volume (>2500 angiography cases per year) hospitals.

7.2 OUTCOME MEASURES

7.2.1 PRIMARY OUTCOME MEASURES

The primary outcome is a composite of any of:

- Death within 90 days or
- Requirement for any form of dialysis within 90 days or
- Persistent decline in renal function as defined by an increase in SCr of at least 50% relative to baseline at 90 days following the index angiographic procedure.

7.2.2 SECONDARY OUTCOME MEASURES

The secondary outcomes consist of:

- CIAKI, defined as an increase in SCr of at least 44 µmol/L or at least 25% from the pre-procedure value at 96hrs (+/- 24hrs) following the angiographic procedure.
- The individual components of the composite primary outcome (as defined above):
    - Death within 90 days
    - Requirement for dialysis
    - Persistent decline in renal function
- Hospitalisation within 90 days of the index angiographic procedure with any of:
    - Acute coronary syndrome
    - Heart failure
    - Cerebrovascular accident

  Documentation of these events on the discharge summary

- All cause hospitalisation within 90 days of the index angiographic procedure assessed as episodes of hospitalization, days of hospitalization, and hospital free days (alive and not in the hospital) through to Day 90.

7.2.3 TERTIARY OUTCOME MEASURES

Tertiary (or exploratory) outcomes of the study are:

- Development of end-stage renal disease within one year following index angiographic procedure defined by the entry to a dialysis program for ≥3 months, as documented by the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry and National Renal Registry in Malaysia.
- Death within one year following index angiographic procedure based upon notification of the fact and date of death to the Australian National Death Index and equivalent Death Registries in New Zealand and Malaysia.

These outcomes will be assessed using linkage of the study database to these existing Registries with participant consent for such linkage obtained at the time of study enrolment, prior to commencement of study specific procedures.

7.3 END OF STUDY

Enrolment in the Asia-Pacific region of the PRESERVE Study will end following the enrolment of approximately 1000 participants, depending upon the number of patient withdrawals, or earlier if deemed appropriate by the Study Data Safety and Monitoring Board and the Study Management Committee.

The study will enrol subjects over a period of 2.5-3 years. The total duration for one subject will be approximately 12 months, including the 5-day treatment period (administration of the oral NAC for 5 days does not necessitate extension of hospital admission beyond that required for routine patient care) and 12-months follow up. The total study duration is expected to be approximately 36-42 months.

7.4 TREATMENT ASSIGNMENT PROCEDURES & BLINDING

Patients will be assigned to one of the four study treatments (bicarbonate + NAC, bicarbonate + placebo, saline+ NAC, saline + placebo) randomly in a 1:1:1:1 ratio. Randomization will be accomplished using a permuted block scheme with variable block size and will be stratified by study site. The Study will use a web-based randomisation program/Interactive Web Response System (IWRS) with Study Coordinators entering a participant's unique study identification and study site into the program and receiving a patient randomisation number in return indicating blinded treatment assignment to one of the four study arms.

The randomization schedule will be generated by the US Sponsor randomization code administrator. The original copy of the Randomization Request Form and randomization characteristics will be retained in a secure place held in the Sponsor Biostatistics Department. Details of emergency unblinding procedures are given in Breaking the Code (Section 9.5).

8 PARTICIPANT ENROLMENT AND WITHDRAWAL

8.1 OVERVIEW

The study population will consist of patients undergoing coronary or non-coronary angiography at any of the study sites who are able to provide informed consent and are at high risk for the development of CIAKI by virtue of the presence of:

- Diabetes mellitus with eGFR less than 60 ml/min/1.73m^2
- Renal dysfunction as defined by an eGFR less than 45 ml/min/1.73m^2

Patients undergoing urgent angiographic procedures or with non-decompensated heart failure (i.e.: not being treated with intravenous inotropes or intra-aortic balloon pump) are eligible for the study. Patients requiring *emergent* angiography (where the interval between identification of the need for angiography and the planned time of the procedure is less than 3 hours) are to be excluded.

8.2 INCLUSION CRITERIA

Patients able to provide informed consent who:

- are having planned elective or urgent coronary or non-coronary angiography with iodinated contrast media in which it is anticipated that there will be an interval of ≥3 hours between the identification of the indication for angiography and the time of the planned procedure
- have pre-angiography eGFR < 60 ml/min/1.73m^2 with diabetes or pre-angiography eGFR < 45 ml/min/1.73m^2 with or without diabetes.

Diabetes mellitus will be defined as the use of oral hypoglycemic medications and/or insulin at the time of angiography. The screening serum Creatinine (SCr) will be measured as part of routine clinical care within 30 days prior to angiography.

IDMS traceable methodology
All laboratories should be using creatinine methods calibrated to be isotope dilution mass spectroscopy (IDMS) traceable. The eGFR equation to use will depend on whether the screening SCr value was measured using an isotope dilution mass spectroscopy (IDMS) -traceable or non-IDMS traceable laboratory methodology.

Laboratories using IDMS traceable methodology:
If the screening SCr is derived from a Study or Non-Study laboratory and it is known that the laboratory uses an IDMS traceable method, the eGFR value may be based on whichever creatinine-based GFR estimating equation is being used by the laboratory. This can be either the 4-variable Modification of Diet in Renal Disease (MDRD) or CKD-Epidemiology Collaboration (**CKD**-**EPI**) equation, applied to the screening SCr value.

Laboratories using Non-IDMS traceable methodology:
If the screening SCr is derived from a Study or Non-Study laboratory and it is not known whether the laboratory uses an IDMS traceable method, the eGFR calculation should use the MDRD formula for a non-IDMS traceable method. Refer to the Operations Manual for further instructions.

For patients with multiple pre-procedure SCr values in this 30 day time frame, eligibility will be based upon the latest SCr measurement prior to the index angiogram. For those patients who have not had a SCr measured within 30 days, the study personnel will inform the patient of the study and, if he/she is agreeable, informed consent will be sought and a screening SCr obtained prior to angiography to assess eligibility based on their underlying level of kidney function. If they meet the criteria, they will then be enrolled and randomized. If they do not meet criteria based on this SCr, they will be excluded.

8.3 EXCLUSION CRITERIA

Patients that meet (or are expected to meet) any of the following exclusion criteria at the time of the planned angiography will be ineligible for enrolment in the Study:

- Currently receiving hemodialysis, peritoneal dialysis, continuous renal replacement therapy, or slow low efficiency dialysis (SLED)
- Stage 5 CKD (eGFR < 15 ml/min/1.73m^2)
- Known unstable baseline SCr at the time of angiography, defined as a change in SCr of ≥ 25% over the 3 days prior to angiography (i.e. between the most recent measure and any other measurement taken within the 3 days prior to the angiography).
- Decompensated heart failure requiring any of:
    - Intravenous inotropic or vasodilator medications [inamrinone, milrinone/primacor, dobutamine, nesiritide/natrecor]
    - Intra-aortic balloon pump
    - Isolated ultrafiltration therapy
- The patient's planned angiography is emergent (i.e.: planned to occur less than 3 hours from the determination of the need for angiography)
- Receipt of intravascular iodinated contrast within the 7 days preceding angiography
- Receipt of oral or intravenous NAC within 48 hrs of the planned time of study angiography
- Aged less than 18 years
- Women who are pregnant or breastfeeding
- Women of child bearing age who will not or cannot use adequate contraception (Appendix)
- Known allergy or contraindication to any of the study treatments.
- Prior allergic reaction to iodinated contrast defined as hives and/or trouble breathing.
- Unwilling or unable to provide consent to the study and study procedures.

8.4 PARTICIPANT WITHDRAWAL

Patients have the right to refuse treatment (allowing follow-up for safety) or completely withdraw from the study at any time for any reason.

Should a patient decide to withdraw from study treatment, every effort should be made to contact the patient (or a knowledgeable informant) by phone according to the protocol schedule to determine whether any of the endpoint events have occurred unless the patient explicitly withdraws consent for follow-up and refuses to provide further information.

Should a patient decide to withdraw from the study, participating centres will be required to complete a Patient Withdrawal Form which will include details regarding the reasons for patient withdrawal. In addition, patients who withdraw from the study will be asked for permission to analyse their existing study data in addition to consent for extended follow up to linked datasets (ANZDATA and Malaysian National Renal Registries, AIHW National Death Index and Death Registries in the respective countries where feasible).

8.5 REPLACEMENT POLICY

If there are a sizeable number of patients who withdraw from the Study the Study Management Committee, with advice from the DMC, may extend enrolment beyond 1000 participants to make up for any loss in study power.

9 TREATMENT OF STUDY PARTICIPANTS

9.1 STUDY TREATMENT DESCRIPTION & DOSING SCHEDULE

The study treatments for PRESERVE include:

- Sodium Chloride (NaCl) 0.9% (150mEq/L) solution
- Sodium Bicarbonate ($NaHCO_3$) 1.26% (150mEq/L) solution
- Blinded N-acetylcysteine (NAC) 300 mg capsules

Intravenous NaCl 0.9% (normal saline), intravenous sodium bicarbonate ($NaHCO_3$) and N-acetylcysteine (NAC) are registered for use in Australia by the Therapeutic Goods Administration but they do not specifically have an approved indication for prevention of contrast-induced acute kidney injury.

All study treatments will be blinded and given drug code names to maintain the blind (Table 1 below). For the purposes of the study, the administration of study fluids around the time of angiography will be broken into three periods:

- Pre-angiography: the period from 12 hours prior to angiography up to the start of the angiography procedure.
- During angiography: the period from the start to the end of the angiography procedure.
- Post-angiography: the period from the end of the angiography procedure and extending to a minimum of 4 hours but no more than 12 hours following the end of the angiography procedure.

Table 1: Study Treatments and corresponding Drug Code Names

Study Drug	Strength (active)	Drug Code
Blinded Sodium Chloride (NaCl)	0.9% IV (150 mEq/L)	NaCl/NaHCO3-578(1000mL IV Bag)
Blinded Sodium Bicarbonate (NaHCO3)	1.26% IV (150 mEq/L)	NaCl/NaHCO3-578 (1000mL IV Bag)
Blinded N-acetylcysteine (NAC) or Matching Placebo	300 mg capsule (cap)	NAC-578 (48 count bottles)

Patients will be randomized to one of four treatment combinations:

- NaCl + NAC
- NaHCO3 + NAC
- NaCl + matching placebo for NAC
- NaHCO3 + matching placebo for NAC

The study interventions of IV sodium bicarbonate and IV sodium chloride are administered continuously throughout the pre-angiography, during-angiography and post-angiography periods (defined above) and oral NAC is administered for a total of five days starting immediately before angiography. The dosing schedule is outlined in the Table 2. The study IV fluid dosing strategy will mandate a minimum volume of study IV fluid, but will allow clinicians to administer additional study IV fluid as they deem appropriate for individual patients.

NAC or placebo will be administered a dose of: 1) 1200 mg orally, 1 hour (or as close to) prior to angiography; 2) 1200 mg orally, 1 hour (or as close to) post-angiography; then 3) 1200 mg orally, twice daily for the next 4 days. Refer to Section 9.2 for additional per-procedural management issues.

Table 2: Dosing Schedule

The table below outlines the mandatory study IV fluid administration protocol. A recommended Study IV fluid regimen for outpatients and inpatients is provided below however other study IV fluid regimens that are compliant with the protocol may be chosen by the provider.

Refer to the Study Operations Manual for further guidance.

MANDATORY STUDY TREATMENT ADMINISTRATION PROTOCOL			
Study Treatment	**Pre-angiography**	**During angiography**	**Post-angiography**
NaCl/NaHCO3-578	**Total dose of 3-12ml/kg** over 1-12 hours at infusion rate between 1-3 ml/kg/hr	**Only specification is infusion rate 1-1.5 ml/kg/hr** No min or max dose specification	**Total dose of 6-12ml/kg** over 4-12 hours at infusion rate between 1-1.5 ml/kg/hr Caution with bolus doses
Oral NAC or placebo **(NAC-578)**	Plus **blinded NAC-578** 300 mg, 4 caps (1200mg), 1 hr prior (or as close to) prior to procedure.	**N/A**	Plus **blinded NAC-578** 300 mg, 4 caps 1 hr (or as close to) after procedure, and then 4 caps (1200mg) twice daily (morning and night) for the next 4 days.
Recommended Study IV fluid Regimen for Outpatients and Inpatients (not mandatory)			
NaCl/NaHCO3-578	**Pre-angiography**	**During angiography**	**Post-angiography**
Outpatient/Day-stay procedure	3mL/kg/hr for minimum 1 hr OR 1mL/kg/hr for minimum 3 hrs, prior to angiography	**Only specification is infusion rate 1-1.5 ml/kg/hr** No min or max dose specification	1.5mL/kg/hr for minimum 4hrs following the end of the angiography
Inpatient procedure	1mL/kg/hr for minimum 6 hrs prior to angiography	**Only specification is infusion rate 1-1.5 ml/kg/hr** No min or max dose specification	1mL/kg/hr for minimum 6hrs following the end of the angiography

All clinicians and research staff involved in the prescription and management of blinded study treatments must read the Product Information/Investigator's Brochure. This document provides detailed information about the indications, dosage, side effects and contraindications of the study treatments. Study treatments will be dispensed by the investigator or an appropriately qualified designee.

9.2 ADDITIONAL PERI-PROCEDURAL MANAGEMENT ISSUES

Contrast Agents: While all contrast agents may be a source of potential clinical complications, the osmolality of the contrast agent is believed to potentially impact the risk for CIAKI. To provide care that is consistent with the most recent guidelines issued by the American College of Cardiology/American Heart Association[23] for the use of iodinated contrast in patients with CKD, patients in this trial can receive any of the following contrast agents:

- Iopamidol (Isovue)
- Ioversol (Optiray)
- Iopromide (Ultravist)
- Iodixanol (Visipaque)

Selection of any of the above contrast agents and the volume required for the study is at the discretion of the treating clinician(s). High osmolarity contrast media and the low-osmolality agent iohexol (Omnipaque), that have been associated with an increased risk of CIAKI, are strongly discouraged from being used.

Non-steroidal anti-inflammatory medications: Use of selective and non-selective non-steroidal anti-inflammatory medications other than once daily aspirin are recommended to be stopped at the time of the procedure and held for 96 hours following angiography, as the use of these medications is believed to increase the risk for CIAKI.

Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and diuretics: We will defer decisions on the discontinuation of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and diuretics to the treating clinicians because there are no conclusive data on the optimal approach to the management of these medications in patients with CKD undergoing angiography.

Additional bolus administration of IV fluids: Should the patient require bolus administration of IV fluid in excess of 250 ml during the angiogram, IV saline should be administered rather than study IV fluid since the bolus administration of large volumes of bicarbonate poses potential safety concerns due to abrupt systemic alkalemia.

Repeated angiographic procedure: Repeated angiographic procedures following the index angiography may be required in a proportion of patients. The Executive Committee have considered the likely frequency of study patients requiring repeat angiography within the first 90 days post-randomisation, and feel that the effect upon study power will not be large, so mandating the same study treatment (as prophylaxis for CIAKI) in subsequent angiographic procedures is not justified at this stage.

In Australia, this issue will be further monitored and the need to change this element of the study further considered by the local Study Management Committee.

9.2.1 COMPLICATIONS OF FLUID ADMINISTRATION

We anticipate that some patients will develop volume overload/pulmonary edema and/or elevated left ventricular end-diastolic pressure during coronary angiography. In such instances, providers performing angiography may discontinue post-procedure IV fluids resulting in patients failing to receive study IV fluid following the angiogram. It is likely that this event will occur in a small proportion of patients and be equally distributed across treatment arms. The Study will record the volume of study IV fluid administered in

both the pre-angiography and post-angiography periods in all patients and, given the importance of patient safety the investigators believe it would be inappropriate to require the administration of post-procedure study IV fluid in such instances. Since all analyses will be based on the intent-to-treat principle, these patients will not be excluded from the study analyses.

Refer to the Study Operations Manual for handling instructions and forms completion.

9.3 PACKAGING, LABELLING, SUPPLY AND STORAGE

Intravenous bags of NaCl/NaHCO3-578 will be manufactured and supplied by Baxter Healthcare Pty Ltd. Bottles of NAC-578 (containing NAC or matching placebo) will be manufactured and supplied by the VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Centre (PCC). NAC-578 will be provided to the study site in bulk boxes (not patient specific kits) containing 12 bottles per box, one bottle per patient. Each bottle of NAC-578 (300 mg NAC or placebo) provides 48 capsules of NAC or placebo (i.e. 5 days' supply and 8 extra capsules, if required), thus covering the full treatment period.

All the study treatments will be labeled in a double-blind format, with each IV bag of NaCl/NaHCO3-578 and each bottle of NAC-578 study drug labeled in compliance with applicable regulatory requirements.

An Integrated Web Response System (IWRS) will be used for the assignment of study treatments at randomisation, managing resupply and for the assignment of replacement vials/bottles in the event a patient loses a bottle of study medication or is admitted to a hospital without his/her study medication. Sites will be provided with an initial stock of study treatment following site activation and resupplied automatically using a pre-determined trigger level system.

Once the study treatments have been assigned to an individual patient, the study treatments must be ordered using the standard inpatient medication order or prescription procedure for that institution. A prescription form must be generated each time study treatment is dispensed for outpatient use and the Coordinating Centre may provide a study specific prescription form upon request.

The study site is responsible for the secure storage of study treatments at the site. The study treatments must be kept in a locked area with restricted access. The study treatments must be stored and handled in accordance with the manufacturer's instructions. The table below outlines stability monitoring responsibility and storage conditions for the study treatments.

Details on study treatment and handling procedures will be provided separately.

Table 3: Study Drug Stability and Storage

Study Treatment	Who is responsible for monitoring study drug stability and expiration dating	Storage
NaCl 0.9% for injection NaHCO3 1.26% for injection	Study Site is responsible for monitoring the stability and expiration dating of these medications to assure they will be stable from time of receipt to actual patient utilization.	NaCl and NaHCO3 stored at controlled room temperature, below 30°C and protected from freezing. Discard any unused portion.
NAC/placebo 300mg capsules	Sponsor will centrally monitor stability and expiration dating.	Stored at controlled room temperature, below 30°C

9.4 ASSESSMENT OF COMPLIANCE

Subjects will be instructed to return their unused study treatment (refer to Sections 10.2.2 & 10.2.4.3 for more information). Compliance will be assessed by capsule counts of the total number of capsules taken over the treatment period. Details will be recorded in the electronic case report form (eCRF).

Doses of study treatment above those prescribed must be reported to the Principal Investigator at the relevant study centre for action as medically appropriate. The total dose of NAC to be administered during the course of the study represents less than one-tenth of the dose of NAC used in the management of acetaminophen toxicity; thus the risk of toxicity from NAC over-dosage are negligible. Omitted or missed NAC capsules are not to be replaced.

Protocol deviations may occur, such as when the patients do not receive the correct or the full intervention, in error. Refer to Section 14.4 for "Management of Protocol Deviations".

Patients who deviate from the dosing schedule or treatment allocation for any reason will continue to be analysed according to the Intention-To-Treat-principle (ITT). The ITT principle is that participants in the trials should be analysed in the groups to which they were randomized, regardless of whether they received or adhered to the allocated intervention.

9.5 ACCOUNTABILITY AND DESTRUCTION

The investigator or designee will also keep accurate records of the quantities of the study treatments (NaCl/NaHCO3-578 and NAC-578) received, dispensed, used, and returned by each subject. The study monitor will periodically check the supplies of study treatments held by the investigator or pharmacist to verify accountability of all study treatments used.

For the reasons of safety, institutional regulation and storage capacity at sites, all used study treatments during the course of the study, may be destroyed by the investigational site staff according to local guidelines. This can only occur following monitoring inspection unless authorized in writing by the Coordinating Centre. A complete accountability of study treatments used by the patients must be available for verification

by the study monitor. Similarly, at the conclusion of the study, any unused study treatments may be destroyed locally following final monitoring inspection.

Documentation of study treatment destruction listing a complete inventory of study treatments destroyed must be filed and be available for verification in the investigator site file.

9.6 BREAKING THE CODE

The blind (or treatment assignment) will only be broken if knowledge of the specific drug is essential to the medical management of the patient. The investigator (or authorized designee) will contact TGI if they consider there is a need for unblinding and this will be adjudicated by the Study Management Committee.

Randomization data are kept in secure systems and will not be accessible by anyone else involved in the study at TGI with the exception of an authorised independent biostatistician who will carry out unblinding as required by the local Study Management Committee. An emergency contact list will be made available to all sites to handle emergency unblinding.

If the blind is broken, the Investigator will document the date, time of day and reason for code breaking. TGI will notify the US Sponsor as soon as possible. In any case of unblinding, the follow-up schedule of data collection should be maintained to enable full analysis of all patient data on an intention-to-treat basis.

10 STUDY PROCEDURES & DATA COLLECTION

10.1 PATIENT FINDING & ELIGIBILITY ASSESSMENT

The study personnel will review angiography logs/schedules in advance to identify patients scheduled for coronary or non-coronary angiography and assess patient's medical records for potential eligibility against the inclusion/exclusion criteria. Potentially eligible patients should be contacted at least one day prior to the angiography procedure by the study personnel to discuss the study and initiate the consent process. For patients that are willing and able, written informed consent will be obtained prior to the conduct of any study specific procedures (Section 14.1).

We believe that even for urgent angiograms for indications such as non-ST elevation MI or peripheral vascular occlusion, there will be sufficient time (>3 hours) prior to the procedure to determine eligibility, obtain consent, perform randomization, and implement the study interventions. Including these subjects will help ensure the recruitment of a high-risk patient population.

It is expected that more than 90% of patients will have had a SCr measured as part of routine care within 30 days prior to angiography. For those patients who have not had a SCr measured within 30 days, the study personnel will inform the patient of the study and, if he/she is agreeable, informed consent will be sought and a screening SCr obtained prior to angiography to assess eligibility based on their underlying level of kidney function. If they meet the criteria, then they will be enrolled and randomized. If they do not meet criteria based on this SCr, then they will be excluded.

At the time of study enrolment, if the patient meets the full eligibility criteria, randomization will be performed via IWRS to obtain random treatment assignment. If the patient screening renders the patient ineligible for the study this information should also be recorded in the IWRS. Instructions for the study IWRS website will be provided separately.

The screening log is designed to monitor patient recruitment at the study centre and to rule out selection bias. A screening log of all patients evaluated for enrolment in the study will be compiled monthly by research coordinators at each study site. The log will record all patients screened either randomised into the study or considered ineligible for the study. Additionally, the reason patients were excluded or the reasons eligible patients were not enrolled, and basic demographic information (age, ethnicity, gender) will be recorded in the log. A copy of the log will be retained in the investigator's study files. The coordinating centre will compile a cumulative screening log monthly, using information from each study site.

10.2 DATA COLLECTION AND STUDY PROCEDURES FOLLOWING PATIENT ENROLMENT

This section outlines the data collection requirements for the Study. All study staff are expected to refer to the Study Operations Manual for the day-to-day activities of the Study.

10.2.1 BASELINE DATA

The purpose of baseline data collection is to collect patient and study variables prior to study interventions. Following patient enrolment, the study personnel will review the medical record to obtain the following data elements:

- Hospitalisation data, including angiographic procedure date
- Basic demography (date of birth, gender and ethnicity)
- Targeted classes of pre-procedure medications administered within 24 hours prior to angiography including name and route, along with any instructions to omit medications before the procedure. The classes of medications include:
    - Non-steroidal anti-inflammatory drugs
    - ACE Inhibitors
    - ARBs
    - Diuretics
    - Statins
    - Anti-diabetic medications
- Administration and type of IV fluids within the 12 hours prior to the initiation of Study IV fluids
- Pre-procedure laboratory assessments obtained as part of routine clinical care prior to the index angiogram and within the timeframe specified below:
    - All SCr values during the 3 days prior to angiography. If no SCr values within 3 days prior to angiography, then the most recent value within the 30 days before angiography.
    - Hemoglobin level (most recent within the prior 30 days)

- Most recent basic metabolic profile (potassium, sodium, BUN/serum urea, serum glucose and serum bicarbonate) within the 30 days prior to angiography.
- If diabetic, HbA1C (most recent within the past year prior to angiography)

- Comorbid medical conditions:
  - Myocardial infarction (heart attack) - *Documented history of ST elevation MI and/or non-ST elevation MI*
  - Congestive heart failure (CHF) - *Documented history of congestive heart failure, diastolic dysfunction, and/or systolic dysfunction*
  - Peripheral vascular disease - *Documented history of peripheral vascular disease, vascular insufficiency, thoracic and/or aortic aneurysms, claudication or rest pain*
  - Cerebrovascular disease (stroke) - *Documented history of cerebrovascular accident (CVA) or transient ischemic attack (TIA)*
  - Chronic pulmonary disease (lung disease) - *Documented history of chronic obstructive pulmonary disease, restrictive lung disease, chronic pulmonary disease, emphysema, chronic bronchitis*
  - Hypertension - *Documented history of physician diagnosis or prescription of medication for hypertension*

- Most recent body weight within 72 hours prior to angiography (measured or estimated). This will be used to calculate dose of study IV fluids. If weight has not been measured within 72 hours prior to angiography, the study coordinator will obtain the patient's weight for the purposes of calculating the dose of IV fluids.
- Blood pressure most proximate to and within 72 hours prior to the index angiogram including date of assessment

Prior to angiography, the following study procedures must be undertaken:

- Collect one blood sample for pre-procedure study SCr (reference SCr) measurement. ***This sample will be obtained following patient randomization and immediately prior to the initiation of study IV fluids and NAC-578.*** It is possible that due to expected variation in SCr levels and measurements, the baseline routine SCr used to determine eligibility will differ from the reference SCr such that patients who meet inclusion criteria based on the baseline routine SCr would not have been eligible based on the reference SCr. Such patients will not subsequently be excluded or withdrawn from the study.

  This specimen will be analysed at the Study Hospital's local laboratory and a Central Laboratory. Handling and storage requirements of samples for Central Laboratory analysis will be provided in the study operations manual.
- Collect one urine sample to measure urine creatinine and urine albumin for ascertainment of baseline Urine Protein.
- Dispense study treatments according to treatment assignment given by IWRS
- Administer study treatments (refer to Study treatment description & dosing schedule, Section 9.1)

10.2.2 EVALUATION OF STUDY IV FLUID AND NAC/PLACEBO ADMINISTRATION

Study personnel will track and record from the source documents, the total volume and total duration of study IV fluid administered pre-procedure, intra-procedure, and post-procedure, and the administration of NAC or placebo capsules while the patient is in the hospital. NAC or placebo capsule administration outside the hospital will be captured during a follow up assessment 5-8 days following the angiography procedure. Refer to Adherence to Study Capsule Medication (Day 5), Section 10.2.4.3.

Study fluid and NAC/placebo administration and accountability will be captured on relevant electronic case report forms for this Study.

During and following the angiographic procedure, study IV fluids will be continued at the recommended dosing schedule outlined in section 9.1. If bolus administration of IV fluid in excess of 250 ml needs to be administered (eg. for hypotension) during the angiography, normal IV saline will be used. Refer to Complications of fluid administration, Section 9.2.1

10.2.3 EARLY POST-ANGIOGRAPHY ASSESSMENT

This time period is defined as the time during the index angiography and up to 12 hours following the index angiography. It is categorised into three key assessments:

- Study Procedures
- Angiography Procedure Related-Data
- 12 hours Post-Procedure Data

10.2.3.1 STUDY PROCEDURES

The following study procedures will be undertaken:

- At 1 hour (or as close to) after procedure, continue administration of study treatment (IV fluids and NAC/Placebo) and provide instructions to continue taking NAC/placebo for four days starting the day after the angiography procedure. Refer to Section 9.1 for treatment dosage regimen for IV fluids and NAC/placebo.
- Collection of one urine sample within 4 hours of the end of their angiography to test the pH (acid level) of the patient's urine.

10.2.3.2 ANGIOGRAPHY PROCEDURE RELATED-DATA

This data collection pertains to the period of time during which the angiography took place. The study staff will review the medical records subsequent to the angiography procedure and talk to the patients to collect the following information:

- Nature of and indications for angiography (coronary or non-coronary), including:
    - Type and volume of contrast administered
    - Performance of percutaneous intervention (angioplasty +/- stent) performed during the angiographic procedure
- Site of the arterial puncture for the angiogram

- Left ventricular end-diastolic pressure if measured
- Complications during the procedure, including:
    - Hypotension (*systolic blood pressure < 90mmHg and/or MAP < 55 mmHg*) necessitating administration of IV fluid in addition to the study IV fluid, including type and total volume of non-study IV fluid
    - Hypotension (*systolic blood pressure < 90mmHg and/or MAP < 55 mmHg*) necessitating the insertion of an intra-aortic balloon pump and/or vasopressor therapy including the type of agents used
    - Acute pulmonary edema necessitating the administration of IV diuretics

Assessment of angiography procedure-related complications will ensure that we capture pertinent events that could impact on the development of the primary and secondary outcomes.

10.2.3.3 12 HOURS POST-PROCEDURE DATA

This data collection pertains to the period of time during the 12 hour period following the index angiography. The study staff will review the medical records and talk to the patients to collect the following information:

- All non-study fluid administration
- Names of inotropes, vasodilators (nesiritide/natrecor) and/or vasopressors
- Episodes of hypotension (defined as SBP <90 mmHg and/or MAP < 55 mmHg)
- Performance and details of additional radiological procedures including angiography or computed tomography with intravascular iodinated contrast

The source of information for procedure-related data will include medical notes, brief structured interview with the patient and angiography staff.

10.2.4 LATE POST-ANGIOGRAPHY ASSESSMENT

This assessment period is defined as the time beyond 12 hours and up to 120 hours (5 days) following the index angiography and is categorised into three key assessments:

- Hospitalisation Data Beyond 12 hours and within 96 hours Post Procedure
- 96 hour Renal Function Assessment (Day 4)
- Adherence to Study Capsule Medication (Day 5)

10.2.4.1 HOSPITALISATION DATA BEYOND 12 HOURS AND WITHIN 96 HOURS POST-PROCEDURE

The following data will be collected for all patients who remain hospitalised beyond 12 hours following index angiography or for patients who are discharged following angiography and are then re-admitted to a hospital within 96 hours:

- Names of inotropes, vasodilators (nesiritide/natrecor or nitrates/GTN) and/or vasopressors within the 96 hours following the procedure

- Episodes of hypotension (defined as SBP <90 mmHg and/or MAP < 55 mmHg) in the 96 hours following the index procedure
- Performance and details of additional radiological procedures including angiography or computed tomography with intravascular iodinated contrast in the 96 hours following the index procedure
- Performance of any surgical procedures requiring general or epidural anesthesia in the 96 hours following the procedure
- Details of occurrence of any study end-points in the 96 hours following index angiography

To capture the above data in patients discharged from the study facility within the first 96 hours following the index angiogram, patients will be provided with a patient wallet card at the time of their discharge with instructions to call the study coordinator if they visit an emergency department and/or are hospitalized within the 96-hour time frame following the index angiogram.

The source of information will be via medical notes and patient interview. For patients who visit an emergency department, received dialysis or are hospitalised at a non-study facility, the study personnel will request access to pertinent medical records held at the non-study facility where they were treated. Access to medical records about the patient from a non-study facility will comply with local institutional or practice procedures.

10.2.4.2 96-HOUR RENAL FUNCTION ASSESSMENT (DAY 4)

An important component of one secondary outcome of the PRESERVE Study is the change in renal function between baseline and 96 hours following index angiography. This is ideally assessed by the collection of a serum specimen for measurement of SCr at a Central Laboratory, but patients unable to return to for central laboratory collection may obtain local laboratory values instead.

In patients who remain hospitalised at 96 hours post index angiography a blood sample will be drawn at 96 hours post-procedure with one aliquot of this sample sent to the Central Laboratory for subsequent analysis for the development of CIAKI. A second aliquot will be delivered to the study site laboratory for the primary clinician to review whether the patient experienced a post-procedure rise in SCr.

For participants discharged from the hospital within four days (within 96 hours) following the index angiography, they will be asked to return to the study site. At the visit to the randomising centre, one blood sample will be collected between 72 -120 hours, but as close to 96 hours post-angiography as possible. If this window period falls on a weekend, the patient can get the blood taken at the closest work day. As above, one aliquot will be sent to the central study laboratory to assess for the development of CIAKI with a second aliquot assessed by the investigator as a clinical measure of SCr.

Participants unable to return to the Study Hospital at D4:
For participants discharged from the hospital within four days (within 96 hours) following the index angiography AND who are unable to return to the Study Hospital, they may visit the nearest community-based pathology centre or the closest hospital instead. This specimen should be provided between 72 -120 hours, but as close to 96 hours post-

angiography as possible. A single sample will be collected and the SCr result sent to the Study Hospital investigator. Use of such a non-study pathology provider (community-based or hospital-based) must first be approved by the Coordinating Centre. Refer to the Study Operations Manual for instructions.

10.2.4.3 ADHERENCE TO STUDY CAPSULE MEDICATION (DAY 5)

(Allowable window range 5-8 days post index angiography)
At five days following the index angiography, the study personnel will (by telephone or in person if still in hospital) assess adherence to the oral study medication (NAC or Placebo) via a series of structured questions. This contact will also allow assessment of the success of patient blinding to treatment allocation.

For patients discharged from the study facility within the first 96 hours following the index angiogram, patients will also be asked to return their medication bottles to the study centre via pre-paid self-addressed pack or at the next study visit which will allow a pill count of returned study medication.

10.2.5 DAY 35 ASSESSMENT

(Allowable window range 35-49 days post index angiography)

At 35 days following the index angiography, the study personnel will, by structured telephone call to the patient, inquire about the development of any study end points or adverse events that they may have experienced and the relationship of these events to study treatment.

10.2.6 DAY 90 ASSESSMENT

(Allowable window range 90-104 days post index angiography)

At 90 days (or as close to) following the index angiography, the development of any of the following primary and/or secondary end-points within 90 days of the index angiography procedure will be assessed:

- Death including date and documented cause based on medical record documentation
- Need for renal replacement therapy including date of initiation, type, and duration of therapy
- Hospitalization including date and primary and secondary hospital discharge diagnoses (to assess for ACS, HF, and/or CVA)

The source of information will be via discharge summary notes and a structured visit or telephone interview with the patient. For patients who visit an emergency department, received dialysis or are hospitalised at a non-study facility, the study personnel will request access to pertinent medical records held at the non-study facility where they were treated. Access to medical records about the patient from a non-study facility will comply with local institutional or practice procedures.

D90 Blood collection at Study Hospital:
In advance of the participant's 90 days, they will be contacted by the study personnel regarding their 90 day blood collection. Participants will be asked to return to the study site to provide one blood sample at 90 days (allowable range of 90-104 days) following their index angiography for assessment of renal function (i.e. SCr) with measurement at the Local and Central Laboratory.

The Local Laboratory will report the results of the participant's D90 local SCr test. If the participant had a ≥ 35% increase in SCr relative to their D0 local SCr, the participant will need to be brought back to the Study Hospital for another blood sample to confirm these results, between 7-14 days after the D90 visit. In this situation, the same procedures to obtain the blood sample for SCr for analysis at the Central Laboratory must be followed. Refer to the Study Operations Manual for central laboratory instructions.

Participants unable to return to the Study Hospital at D90:
For participants who are unable to return to the Study Hospital (i.e., regionally based participants), they may visit the nearest community-based pathology centre or the closest hospital for the assessment of D90 renal function. This blood sample will need to be performed within the required timeframe and, if necessary, the additional Confirmatory D90 blood sample as described above.

A single blood sample will be collected with the local SCr result sent to the Study Hospital investigator. Upon review, if it is determined that the participant has had a ≥35% increase in SCr relative to their D0 local SCr, the participant will need to return to the same pathology provider for a D90 confirmatory blood sample between 7-14 days after the D90 visit.

In this situation, the same procedures to obtain the blood sample for SCr analysis at the pathology provider must be followed. Collection for Central Lab analysis will be waived for this group of patients. Use of such a non-study pathology provider (community based or hospital based) must first be approved by the Coordinating Centre. Refer to the Study Operations Manual for instructions.

For patients that have died within 90 days outside the study facility, we will attempt to ascertain primary and secondary endpoint data by reviewing medical records held at the study and non-study facility and if necessary, perform data linkage.

To facilitate data linkage, encrypted patient identifiers (name, date of birth and state of residence) will be sent offsite to an authorized third party, via the coordinating centre, who will perform linkage of study participants to the various datasets including various Births, Deaths and Marriages Registries in Australia, New Zealand and Malaysia (where feasible); Australian Institute of Health and Welfare National Death Index (AIHW NDI); and the ANZDATA Registry and National Renal Registry in Malaysia. Where required by law, independent ethics approval to perform data linkage will be obtained prior to implementation.

10.2.7 1-YEAR ASSESSMENT

Data linkage to ANZDATA and National Renal Registry in Malaysia, AIHW NDI and/or to the Births, Marriages and Deaths Registries in the respective countries will be performed to ascertain the development of ESRD (defined in Tertiary Outcome Measures in Section 7.2.3), date of initiation of renal replacement therapy within 1 year of the index angiographic procedure and death within 1 year. In addition, study personnel may be requested to review the medical records at the study facility to help complement and verify the data obtained through data linkage. Timing of performance of these linkages will depend upon the availability of data from the registries, which may lag 12-18 months after the end of each calendar year.

10.3 DATA HANDLING & MANAGEMENT

The procedures for data review and query management are described in the Data Management Document and Monitoring Plan. Data will be reviewed throughout the study according to these documents.

Data for this study will be captured via a Web-based Electronic Data Capture system using the electronic Case Report Forms (eCRFs). The investigator should ensure the accuracy, completeness and timeliness of the data reported to the Coordinating Centre in the eCRF and in all required reports.

For each subject enrolled, an eCRF must be completed. It will be transcribed by the site from the paper source documents onto the eCRF. The participants will be identified only by initials and a participant ID number/identification code on the eCRF. The name and any other identifying detail will NOT be included in any study data electronic file.

Data will be validated for accuracy and reliability using two methods:

1. A comprehensive validation check program will centrally verify the data according to the Data Management Document and automatically generate discrepancies for resolution by the investigator. Manual discrepancies can also be raised if necessary.
2. Verification and cross–check of the eCRFs against the investigator's records by the study monitor (source document verification) according to the Monitoring Plan, and the maintenance of a medication–dispensing log by the investigator.

An electronic audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person who made the change.

11 ASSESSMENT OF SAFETY

The study will adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 and comply with local regulatory requirements.

11.1 DEFINITIONS

11.1.1 ADVERSE EVENT (AE)

An AE or adverse experience is any untoward medical occurrence in a patient or clinical investigation participants administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment (the study medication). An AE, therefore, can be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study interventions.

11.1.2 SERIOUS ADVERSE EVENT (SAE)

Serious adverse events are that subset of AEs that are characterised by:

- Resulting in death,
- Being life-threatening, 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.
- Requirement for inpatient hospitalisation or prolongation of existing hospitalisation,
- Resulting in persistent or significant disability/incapacity
- Resulting in a congenital anomaly/birth defect.
- Any other important medical events.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning as defined in the bullet points above. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.1.3 SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable Product Information for an approved product or Investigator Brochure for a non-approved product.

11.2 REPORTABLE ADVERSE EVENTS (SERIOUS AND NON-SERIOUS)

For this study, there will be one category of reportable adverse events:

- Adverse events (serious and non-serious) related to any of the study treatments (possibly, probably or definitely). In this trial, the study treatment interventions are IV sodium chloride, IV sodium bicarbonate and oral NAC (or matching placebo).
- All treatment-related serious adverse events will be subject to expedited reporting (refer to Section 11.4.2).
- All of the components that make up the study endpoints (primary, secondary and tertiary) will be treated as 'disease-related' and exempted from expedited reporting to Health Authorities and Independent Ethics Committees. This measure is taken to preserve the integrity of the clinical study by avoiding systematic unblinding for adverse events that are commonly associated with the underlying disease independently of exposure to the study treatment, and that do not represent informative data when assessed individually.

However all protocol specified study endpoints must still be submitted to the Coordinating Centre within 24 hours of the Investigator becoming aware of the event (refer to Section 11.4.2). Study specific endpoints and treatment-related serious adverse events will be reported on the same "SAE_Endpoint Form".

11.3 PERIOD OF OBSERVATION

This study has several unique features that affect how AEs and SAEs are collected and reported. While participants are being followed for a period of 90 days (primary and secondary endpoints) following angiography, the study interventions of IV sodium bicarbonate and IV sodium chloride are administered for a less than one day and oral NAC is administered for a total of five days.

The period of observation for collection of study treatment-related adverse events (serious and non-serious) will commence from the time of randomization until four weeks after the last dose of study treatment.

If the investigator detects a SAE in a patient after the end of the period of observation, and considers the event related to prior study treatment, he or she should contact the Coordinating Centre to determine how the adverse event should be documented and reported.

11.4 OBLIGATIONS OF THE INVESTIGATOR REGARDING SAFETY REPORTING

The Investigator will submit reportable adverse events to the relevant ethics committees in accordance with local ethics committee reporting timeframe requirements. The George Institute will provide an Emergency 24 Hour Medical Coverage for study related medical emergencies outside regular business hours to allow for the provision of advice to investigators or research staff. Contact numbers will be distributed to all participating investigators in a separate document.

11.4.1 ADVERSE EVENTS (NON-SERIOUS)

All reportable adverse events (non-serious) occurring during the observation period set in this protocol will be reported to the Coordinating Centre on the Adverse Event Form and documented in source records.

11.4.2 SERIOUS ADVERSE EVENTS & STUDY ENDPOINTS

Reportable serious adverse events and study specific endpoints will be reported in an expedited manner to the Coordinating Centre as follows:

- Report in the SAE_Endpoint Form of the eCRF within 24 hours of the site becoming aware of the event. As soon as the SAE/Endpoint form is submitted electronically, the EDC system will automatically generate notices to the Sponsor and a specified list of representatives at the Coordinating Centre. The investigator must also inform the study monitor in all cases, preferably by phone. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the study treatment.
- ATTACH AND FAX the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identify is protected.
- Follow up of any SAE that is fatal or life threatening should be provided within one additional calendar week.
- Documented in the source records

11.4.3 FOLLOW UP

The Investigator should follow up the outcome of reportable serious adverse events until clinical recovery is complete and laboratory results have returned to baseline, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the Clinical Trial and that additional investigations may be requested by the Monitoring Team.

11.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Australian Sponsor will report in an expedited manner all SAEs that are both unexpected and related to study treatment (possibly, probably, definitely), to the Authorities, Independent Ethics Committees, as applicable and to the Investigators, within the required regulatory timeframes.

The Australian Sponsor will report all safety observations made during the conduct of the trial in the Clinical Study Report.

11.6 SAFETY OVERSIGHT (DMC)

SAEs would be monitored throughout the study by one central Data Monitoring Committee (DMC). A nominated pharmacist and biostatistician will generate tabulations of AEs and SAEs and present a summary of all AEs and SAEs to the DMC on a schedule set by the DMC. The DMC will also determine when they should be unblinded to treatment assignment for the reviewing of adverse event data. The DMC will

recommend to the US and Australian Sponsors whether the study should continue or be stopped for safety reasons. The DMC will also monitor the primary endpoint at pre-determined intervals and recommend to the Sponsor whether the trial should be stopped on grounds of efficacy or futility. Summary reports from the DMC will be provided to the applicable Independent Ethics Committees. Refer to Section 14.8 for more details on the DMC.

12 STATISICAL CONSIDERATIONS

The study will enrol 8,680 subjects over 2.5-3 years, randomising to one of four treatment arms, and evaluate each subject for the primary outcome at 90 days after the angiographic intervention. The Asia-Pacific limb of the study will contribute 1000 patients to the overall enrolment.

12.1 STUDY HYPOTHESIS

The PRESERVE Study will test two primary hypotheses:

(1) Peri-procedure infusion of sodium bicarbonate is superior to infusion of sodium chloride for the prevention of serious, adverse clinical events within 90 day of angiography
(2) Peri-procedure administration of oral NAC is superior to placebo for the prevention of serious, adverse clinical events within 90 day of angiography.

12.2 SAMPLE SIZE CALCULATIONS

The study sample size calculations are based solely upon the primary outcome and the ability of the study interventions to effect this outcome, using conservative values for the event rates, effect sizes and power. The model equation for the primary hypotheses is a logistic regression equation with three binary predictors of the composite primary outcome (referred to as MAKE-D in the equation):

$$\textbf{MAKE-D} = (\beta_1 * \textbf{Bicarbonate}) + (\beta_2 * \textbf{NAC}) + (\beta_{12} * \textbf{Bicarbonate} * \textbf{NAC})$$

Using data from the VA Austin database, which has comprehensive follow up of a large cohort of patients undergoing angiography, the power calculations are predicated upon a baseline primary event rate of 8.7% at 90 days follow up. These calculations are postulated upon an assumption of a 25% effect (relative reduction in primary outcome events) of both the interventions (bicarbonate and NAC), a type I error of 2.5% for each hypothesis, power of 90% and a 3% rate of loss to follow up.

It is possible that one of the interventions interacts with the other. For example, that NAC administration attenuates the effect of bicarbonate, and this would reduce the statistical power of the study. Fortunately, such attenuation of effect has not been observed in the trials that have used both agents for the prevention of CIAKI (ref: 103, 108, and 118). Nonetheless, it remains possible that small degrees of interaction do exist. Even with up to 30% attenuation of effect arising from interaction between bicarbonate and NAC, a study with 7680 participants would still have over 80% power based upon the assumptions above.

12.3 PLANNED INTERIM ANALYSES

Using the O'Brien-Fleming procedure, we will carry out an interim analysis after half the expected number of events (292 events) has occurred, roughly after 18 months, to determine if either intervention shows a substantial beneficial effect. This will compare the proportion of subjects with a MAKE-D event with and without the use of bicarbonate and will compare the proportion of subjects with a MAKE-D event with and without the use of NAC. At the interim one-year analysis, a z-value of 3.18 will be needed to reject the null hypothesis with Type I error of 2.5%. At the final analysis a z-value of 2.25 will be needed to reject the null hypothesis with Type I error of 2.5%.

12.4 FINAL ANALYSIS PLAN

The primary analysis will be based upon the principle of intention to treat.

Analytic reports will provide the proportions, the differences among proportions, the odds ratios, and the 95% confidence intervals for each of the summary statistics. This will be followed by a report of the results of confirmatory analyses. The confirmatory exploratory analyses will add to the basic model, factors related to disease severity, demographic and anthropomorphic measures, and structural factors such as medical site. The regression modelling will include a model with treatment by covariate terms to explore the possibility of treatment by covariate effects (that is, exploration of potential subgroup effects) and test that results vary or do not vary significantly by medical site. Finally we will explore the effect of including site as a random effect by extending logistic regression to generalized linear models that treat site as a random effect.

13 PARTICIPANT CONFIDENTIALITY & RECORD KEEPING

13.1 PARTICIPANT CONFIDENTIALITY

The investigator and trial staff must ensure that subjects' anonymity will be maintained, that their identities are protected from unauthorized parties and take measures to prevent accidental or premature destruction of these documents. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

The investigator should keep a subject enrollment log showing codes, names and addresses. The investigator should maintain subjects' written consent forms documents in strict confidence.

When archiving or processing data pertaining to the investigator and/or to the patients, the co-ordinating centre shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.2 INVESTIGATOR'S FILES / SOURCE DOCUMENTS/ RETENTION OF DOCUMENTS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories (1) investigator's Study File, and (2) subject source documents.

The Investigator's Study File will contain the protocol/amendments, schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. In addition, a copy of the site dataset will be made available to each investigator at the end of the study upon request to the local Sponsor,

A source document is a document in which data collected for clinical research is first recorded. Examples of source documents include subject hospital/clinic records, physicians' and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, patient study medication diary, study medication dispensation log, signed informed consent forms, consultant letters, and subject screening and enrolment logs. In addition, for this Study, the study personnel will be provided with paper source document worksheets to facilitate collection of study specific information.

The Investigator must keep these two categories of documentation file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, the Coordinating Centre must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Coordinating Centre to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

13.3 DIRECT ACCESS TO SOURCE DOCUMENTS

The investigator shall supply the coordinating centre on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor of the Study, the Coordinating Centre, the study monitoring committee or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

14 QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996 (ICH GCP), Declaration of Helsinki, relevant regulations and standard operating procedures.

14.1 OBTAINING INFORMED CONSENT

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site.

If the subject is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to subjects must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (e.g. the subject's thumbprint or mark). The witness and the person conducting the informed consent discussions must also sign and personally date the consent document.

The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

14.2 DELEGATION OF INVESTIGATOR DUTIES

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

14.3 ETHICS AND REGULATORY APPROVALS

Before the start of the study, the protocol, informed consent document, any proposed advertising material and any other appropriate documents will be submitted to the appropriate Independent Ethics Committees for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all subsequent and substantial amendments to the original approved documents. If applicable, the documents will also be submitted to the Regulatory Authorities where the trial is taking place for Clinical Trial Authorization, in accordance with local legal requirements.

Study medication can only be supplied to the investigator after documentation on **all** ethical and regulatory requirements for starting the study has been received by the Coordinating Centre.

Safety reports, annual progress reports and a final report at conclusion of the trial will be submitted to the Regulatory Authorities, research ethics committees and if applicable, to the study treatment manufacturer within the timelines defined in the Regulations.

14.4 MANAGEMENT OF PROTOCOL DEVIATIONS

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document. A protocol deviation may be an omission, addition or change in any procedure described in the protocol.

The investigator should not implement any deviation from or changes of the protocol without agreement by the Study Management Committee and documented approval from the Independent Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard(s) to trial participants. In the event of an emergency intended to eliminate an apparent immediate hazard to participants the Investigator may implement any medical procedure deemed appropriate.

Despite the fact that the most clinical trials are carefully planned, many problems can occur during the conduct of the study leading to protocol deviations. The table below describes examples of protocol deviations and the action to take for the PRESERVE Study.

Issue	Is this a Protocol Deviation?	Action to be taken
A patient who does not satisfy the inclusion and/or exclusion criteria is included in the trial	Yes	Notify the Coordinating Centre within 24 hours of being aware of this issue. Patient to remain in the Study, unless deemed inappropriate by the Investigator due to safety concerns. Enable full analysis of all patient data on an intention-to-treat basis.
A patient is randomized to the Treatment A but has been treated with the Treatment B	Yes	Incorrect Treatment B to cease as soon as possible. Commence with the correct Treatment A.
Patients omit some or all of their study medication	Possibly	If the patient does not receive their study medication, in error, whilst he/she is in hospital, this is regarded as a Protocol Deviation. After discharge, if the patient omits some or all of their study medication, this is considered non-adherence to study medication.
Active study treatment has been withdrawn by the Investigator or treating clinician. The treating clinician considers it is the patient's best interest to change the study treatment.	No	Further treatment is prescribed at the discretion of the clinical staff managing the patient. Patient is followed up in the Study unless consent is withdrawn.

Deviations from the protocol must be documented in the Protocol Deviation Form and promptly reported to the Study Management Committee and the Independent Ethics Committee (if applicable). The report should summarise the event and action taken.

14.5 GCP TRAINING AND SITE MONITORING

Study monitors from the Coordinating Centre will conduct a site initiation visit prior to the start of the study to ensure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and ensure that acceptable facilities are available to conduct the study.

In addition, periodic site monitoring will be performed according to ICH GCP, the Coordinating Centre's SOP and Monitoring Plan. For each site, a minimum of one site monitoring visit per year must be performed. The monitors will verify that the clinical trial procedures are being conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and the applicable regulatory requirements. Data recorded in the eCRF will be evaluated for compliance with the protocol and accuracy in relation to source documents.

At the end of the study, the monitors will conduct a close out visit.

14.6 AUDITS AND INSPECTIONS

The Investigator should permit auditing by or on the behalf of the Sponsors and inspection by regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. The Investigator will make every effort to help with the performance of the audits and inspections.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Coordinating Centre and request the Coordinating Centre, and if required, the Sponsors to participate in this inspection. Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Coordinating Centre (and Sponsor). The Investigator shall take appropriate measures required by the Coordinating Centre (and Sponsor) to take corrective actions for all problems found during the audit or inspections.

14.7 TRIAL EXECUTIVE COMMITTEE

The Executive Committee will oversee study operations, the performance of participating medical centres, and the quality of data collected. This Committee will also monitor adherence to the protocol. The Executive Committee formulates plans for publications and oversees the publication and presentation of all data from the study. Permission must be granted by the Executive Committee before data from the study may be used for presentation or publication. The members of the Executive Committee will be selected by the Study Chairmen from members of the Planning Committee and Participating Investigators. The Executive Committee will meet at least quarterly by conference call and in-person at least annually.

14.8 DATA MONITORING COMMITTEE (DMC)

An independent DMC will be established to review the progress of the study and monitor adherence to the protocol, participant intake, outcomes, complications, and other issues related to participant safety. They will also monitor the assumptions underlying sample size calculations for the study and alert the investigators if they see substantial departures as the data accumulate.

The DMC will be composed of experts in nephrology, cardiology, interventional radiology and clinical trials. The Study Chairmen will make nominations to the Director, Cooperative Studies Program, who will make the final selection for the Committee. The DMC will make recommendations to the Director of the Cooperative Studies Program as to whether the study should continue or be terminated. The DMC can consider participant safety or other circumstances as grounds for early termination, including either compelling internal or external evidence of treatment differences or feasibility of addressing the study hypotheses (e.g. poor participant enrolment, poor adherence).

The DMC will conduct an in depth assessment of safety and efficacy data every six months at which time the study biostatistician will provide the DMC with an interim summary report on the study status and on safety data for monitoring purposes.

14.9 TERMINATION OF THE STUDY

The study must be closed at the site on completion of all patient treatments and evaluations. Furthermore, the study may be closed at any time at the request of the study steering committee, the Investigator, or a regulatory authority, with proper and timely notification of all parties concerned. As far as possible, premature closure should occur after mutual consultation.

The Independent Ethics Committee will be informed and the Coordinating Centre or the investigator will supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements.

15 FINANCE AND INSURANCE

The George Institute for Global Health has received funding to conduct this trial in Australia by NHMRC (NHMRC grant number 1011387).

The George Institute for Global Health certifies that it has taken out a liability insurance policy which covers the liability of the Investigator. This insurance policy is in accordance with local laws and requirements. The insurance of the Coordinating Centre does not relieve the Investigator, the Sponsor or manufacturers of the study interventions of any obligation to maintain their own liability insurance policy as required by applicable law.

16 PUBLICATION POLICY

The study will be conducted in the name of the PRESERVE study investigators. The principal publication from the study will be in the name of the PRESERVE study Investigators with full credit assigned to all collaborating investigators, research coordinators and institutions. Where an individuals' name is required for publication it will be that of the Writing Committee, with the Chair and Co-Chair of the Writing Committee representing US and Australia listed first and subsequent authors listed alphabetically.

17 PROPERTY RIGHTS

All the results, data and documents, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor. The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Investigator shall not mention any information in any application for any intellectual property rights.

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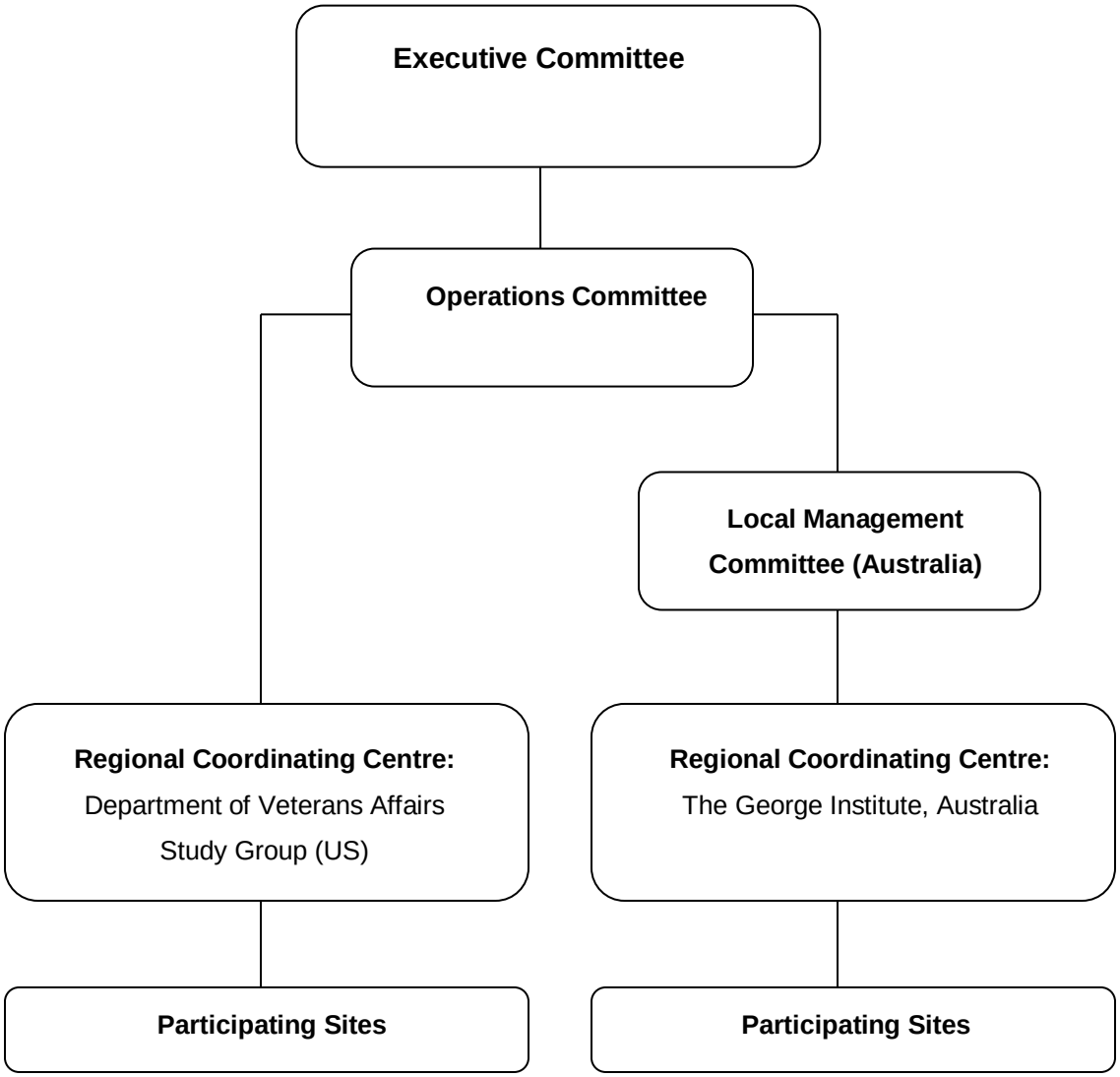
18 APPENDICES

18.1 APPENDIX 1: STUDY ORGANISATION AND STRUCTURE

The study will be conducted under the auspices of the US Department of Veterans Affairs Group and The George Institute for Global Health, Australia (GI), affiliated with the University of Sydney. It is anticipated that the individuals listed below may change throughout the course of the study and will not necessarily constitute a protocol amendment. All changes will be notified and approved by the George Institute for Global Health.



18.2 APPENDIX 2: LOCAL MANAGEMENT COMMITTEE

It is anticipated that the individuals listed below may change throughout the course of the study and will not necessarily constitute a protocol amendment. All changes will be notified and approved by the George Institute for Global Health.

Member Name	Position	Institution
Martin Gallagher	Coordinating Investigator	The George Institute, NSW
Alan Cass	Coordinating Investigator	The George Institute, NSW
Graham Hillis	Coordinating Investigator	The George Institute, NSW
Joanne Lee	Senior Project Manager	The George Institute, NSW
Rinaldo Bellomo	Coordinating Investigator	Austin Hospital, VIC
David Brieger	Principal Investigator	Concord Repatriation General Hospital, NSW
John French	Principal Investigator	Liverpool Hospital, NSW
Derek Chew	Principal Investigator	Flinders Medical Centre, SA
Phil Aylward	Principal Investigator	Flinders Medical Centre, SA
Ralph Stewart	Principal Investigator	Auckland City Hospital, NZ
Wan Azman Wan Ahmad	Principal Investigator	University Malaya Medical Centre, MYL

Responsibilities

Overseeing all aspects of the study development including:

- Liaison with Executive Committee
- Design, production and approval of final protocol and case report form
- Design, production and approval of generic patient information and consent form
- Database design and management
- Management of protocol deviations
- Management of study budget and liaison with funding bodies
- Preparation and arrangement of Investigator contracts
- Co-ordination and assistance with HREC applications
- Study set up, monitoring and close out site visits
- Protocol training of Research Coordinators and Principal Investigators
- Data collection and data entry/transfer
- Monitoring and assessment of adverse events
- Oversight of data analysis
- Approval of writing committee and approval of presentations and publications.
- Media liaison

18.3 APPENDIX 3: CONTRACEPTION PROTECTION

Women of childbearing potential must use an acceptable method of contraception to prevent pregnancy. Acceptable methods of contraception include the following:

- Barrier type devices (e.g. female condom, diaphragm and contraceptive sponge) used ONLY in combination with a spermicide.
- Intra-uterine devices.
- Oral contraceptive agents started at least 90 days before start of study.
- Depo-Provera (medroxyprogesterone acetate).
- Levonorgestrel implants.
- Naturally or surgically sterile (amenorrheic for at least 1 year and no record of child birth for naturally sterile persons).
- Male partner is sterile and is the only sexual partner

NB: True or periodic abstinence, the rhythm method or contraception by the partner only are NOT acceptable methods of contraception.