Academic and Clinical Central Office for Research and Development

Non-CTIMP Study Protocol

TAKO MEMRI

Manganese-enhanced Magnetic Resonance Imaging

in Takotsubo Cardiomyopathy

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CONTENTS

LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
AE	Adverse Event
AR	Adverse Reaction
CI	Clinical Investigator
ECG	Electrocardiogram
HASTE	Half Fourier Acquisition Single Shot Turbo Spin Echo
ISF	Investigator Site File
MEMRI	Manganese Enhanced Magnetic Resonance Imaging
ML	Millilitres
MRI	Magnetic Resonance Imaging
MG	Milligrams
NHS	National Health Service
PROBE	Prospective Randomised Open-label Blinded Endpoint
PI	Principal Investigator
SAR	Serious Adverse Reaction
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction

INTRODUCTION

1.1 BACKGROUND

1.1.1 Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy is an acute potentially fatal cardiac emergency that presents with sudden severe left ventricular dysfunction. It predominantly affects middle aged (50-74 years) women (90%) [Pattisapu et al, 2021] and is triggered by emotional or physical stress. Its symptoms are indistinguishable from acute myocardial infarction and 1 in 10 will die in hospital. However, patients with takotsubo cardiomyopathy have unobstructed coronary arteries, transient severe acute left ventricular dysfunction with “ballooning” of the ventricular cavity and absence of any myocardial infarction or scarring. Greater diagnostic recognition has led to a 4-5-fold rising incidence of takotsubo cardiomyopathy in both the United Kingdom and North America. With an incidence of 5,000 cases/year in the United Kingdom, it now represents 5% of all admissions for presumed myocardial infarction. [Singh et al, 2022]

Patients who recover from an acute takotsubo episode have substantially reduced long-term survival [Templin et al, 2015; Tornvall et al, 2016; Uribarri et al, 2019; Redfors et al, 2021]. Our own 5-year data of 620 patients in the Scottish Takotsubo Registry [Rudd et al, 2024] demonstrated a major excess of all-cause mortality compared with a 1:4 age and sex-matched general population (25% versus 15%; hazard ratio 1.78, $p<0.0001$). Importantly, this reduced survival was principally driven by cardiovascular mortality. In addition to mortality, there is also a substantial burden of morbidity with many patients experiencing hospitalisation for a recurrent takotsubo episode, stroke or myocardial infarction. In the international multicentre InterTak Registry, patients with takotsubo cardiomyopathy experienced a rate of major adverse cardiac and cerebrovascular events of 9.9% per patient-year, and a rate of death of 5.6% per patient-year [Templin et al, 2015]. This is consistent with our own data which showed that patients with takotsubo cardiomyopathy have 5-fold higher rates of major adverse cardiovascular events than the general population: hospitalisation for heart failure (9.8%), myocardial infarction (7.1%), stroke (3.9%) and recurrent takotsubo cardiomyopathy (10.2%).

Despite left ventricular ejection fraction recovering to normal during convalescence, persistent sub-clinical cardiac dysfunction has been consistently demonstrated [Scally et al, 2018]. Some patients continue to have debilitating symptoms like those with heart failure (fatigue, breathlessness, chest pain) which reduce their quality of life and cause at least one further hospital admission each year [NHS England]. Many have multiple recurrent episodes of takotsubo cardiomyopathy. A Swedish study reports an average cost of €10,360 to the health system in the first 6 months after a takotsubo diagnosis, with patients using repeated hospital, outpatient and primary care

resources [Wallstrom et al, 2019]. This would equate to over £50 million per annum across the United Kingdom, but the total burden to the NHS will be much higher considering the ongoing elevated risk of events beyond 6 months.

1.1.2 Detection of subclinical myocardial dysfunction

The observation that left ventricular dysfunction and reduced left ventricular ejection fraction rapidly recovers after an acute takotsubo episode (a characteristic feature of this condition) is often falsely reassuring for both the patient and the clinician. It also means that detection of residual left ventricular dysfunction despite apparent normal standard clinical assessments of contractile function can be challenging. We have previously demonstrated impaired myocardial cardiac energetic status using magnetic resonance spectroscopy [Scally et al, 2018]. We then went on to explore whether this perturbation in energetics influenced myocardial contractile performance through alterations in myocardial calcium handling.

1.1.3 Manganese-enhanced magnetic resonance imaging

Manganese is a naturally occurring essential trace element, required by the human body as a co-factor and enzyme activator [Frayn, 2010; Santamaria, 2008]. Its role has been demonstrated in the normal metabolic functioning of multiple organs in addition to the protection of mitochondrial membranes from oxidative stress via superoxide dismutase [Santamaria, 2008]. Manganese exhibits certain advantageous properties that make it a potentially powerful tool in magnetic resonance imaging. First, its paramagnetic properties reduce the T1 relaxation times of water, providing positive contrast in tissues where it accumulates, and excellent delineation of anatomical structures [Massaad & Pautler, 2010; Pan et al, 2010]. Second, it is a calcium analogue and is taken up by voltage-gated calcium channels and sodium-calcium exchangers on active viable myocytes [Du et al, 2001]. This is an active process which allows manganese to differentiate regions of altered myocyte function and, in combination with T1 mapping protocols, can be used to quantify myocardial calcium handling. Manganese therefore presents attractive opportunities both in terms of the practicalities of imaging and the tracking of active biological processes.

As part of a previous British Heart Foundation-funded Clinical Research Training Fellowship (Dr Nicholas Spath, FS/17/19/32641), we have shown that manganese-enhanced magnetic resonance is a better measure of myocardial infarction size than late gadolinium enhancement [Spath et al, 2018] and, using T1 mapping, we have described altered manganese uptake in patients with dilated cardiomyopathy [Spath et al, 2020] (Figure 1).

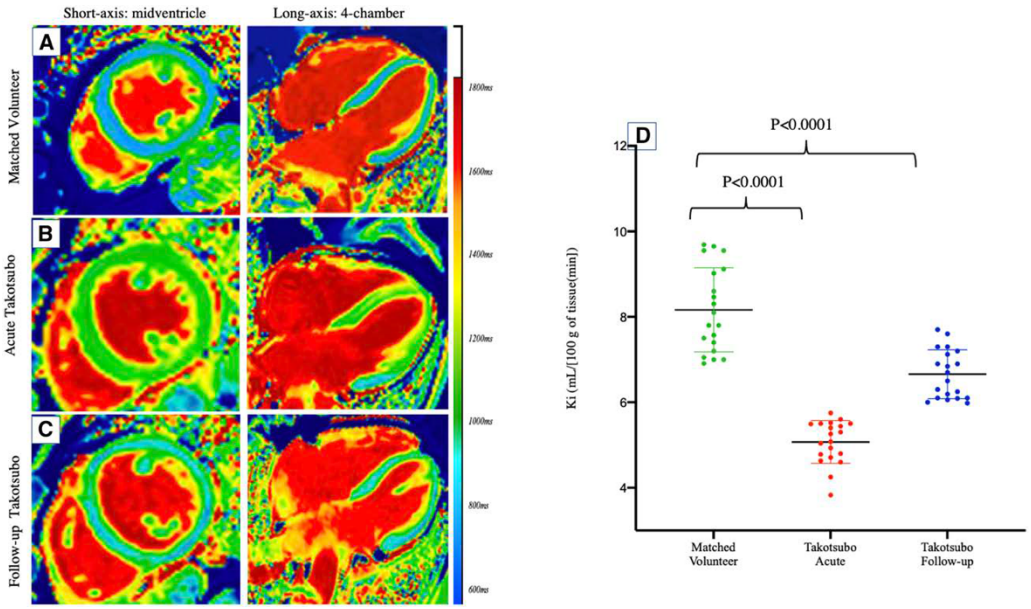
1.1.4 Magnetic resonance imaging in takotsubo cardiomyopathy

Using magnetic resonance imaging, we have previously reported the presence of severe global oedema of both the left and right ventricles

associated with profound cardiac energetic impairment in the acute stages of takotsubo cardiomyopathy [Dawson et al, 2015; Scally et al, 2016]. As part of a multicentre study, we have demonstrated persistent abnormalities of cardiac inflammation and energetics after an acute episode of takotsubo cardiomyopathy using magnetic resonance spectroscopy [Scally et al, 2018; Scally et al, 2019]. This occurred despite a normalisation of the resting left ventricular ejection fraction and was associated with some persistent symptoms and cardiac limitation during cardio-pulmonary exercise testing [Scally et al, 2018; Scally et al, 2019].

In a previous Medical Research Council Clinical Research Training Fellowship (Dr Trisha Singh, MR/T029153/1), we have demonstrated that there was a profound reduction in myocardial manganese uptake in patients with takotsubo cardiomyopathy, and this was most marked immediately after the acute episode [Singh et al, 2022b]. Whilst there was some recovery in the longer term, there remained a marked residual reduction in myocardial manganese uptake (Figure 1). This suggests that perturbations in myocardial calcium handling may underlie the pathophysiology of takotsubo cardiomyopathy. Moreover, given the absence of a simple measure of ongoing left ventricular dysfunction in patients with takotsubo cardiomyopathy, manganese-enhanced magnetic resonance imaging represents an excellent potential quantitative surrogate biomarker to determine candidate pathways that could then be taken forward for further assessment.

Figure 1
Manganese-enhanced magnetic resonance imaging and T1 maps in healthy volunteers (A) and patients with takotsubo cardiomyopathy during the acute phase (B) and at 6-12 months after recovery (C). Compared to healthy volunteers, myocardial manganese uptake (Ki) is markedly inhibited in patients with takotsubo cardiomyopathy, being nearly halved in the acute phase and remaining substantially reduced in the longer term (D).



4.3.3 Manganese-enhanced magnetic resonance imaging and role of sodium-glucose co-transporter

We recently assessed the effect of sodium-glucose co-transporter 2 inhibition on myocardial manganese uptake in patients with heart failure. In this preliminary pilot double-blind randomised study, dapagliflozin but not placebo appeared to improve myocardial manganese uptake in these patients. We are currently extending this work, but together with the time-course studies in patients with takotsubo cardiomyopathy, these promising early data suggest that the sodium-glucose co-transporter 2 may have a role in regulating myocardial calcium handling. We now need to confirm this in cohorts of patients with takotsubo cardiomyopathy.

1.2 RATIONALE FOR STUDY

We have recently demonstrated the proof-of-concept that manganese uptake is markedly impaired in patients with takotsubo cardiomyopathy, particularly in the acute phase but also in the longer term. This detection of covert left ventricular dysfunction is important because it provides a common pathophysiological indicator of the underlying dysfunction as well as providing a quantitative measure of disease activity.

We hypothesise that in patients with takotsubo cardiomyopathy:

1. Acute renin-angiotensin system activation but not beta-adrenoreceptor stimulation, causes impaired myocardial manganese uptake.
2. Chronic angiotensin receptor stimulation combined with vasoactive peptidases or sodium-glucose co-transporter 2 channels cause impaired myocardial manganese uptake.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

We propose to undertake experimental medicine studies in patients with acute or chronic takotsubo cardiomyopathy to explore whether neurohumoral activation or sodium-glucose transporters are implicated in the abnormal myocardial calcium handling of the left ventricle.

2.1.2 Secondary Objectives

As part of a planned subgroup analysis, we will undertake exploratory analyses to see if there are other factors that may determine myocardial

manganese uptake including cardiovascular risk factors. We will also explore the proportionate changes with acute versus chronic changes as well as compare the effectiveness of any reversal of altered myocardial calcium handling. We will also examine effects on cardiac and neurohumoral biomarkers to assess potential pathways of benefit. We will also explore correlations between myocardial manganese uptake and self-reported symptoms and objective assessments of exercise capacity.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

Left ventricular myocardial manganese uptake.

2.2.2 Secondary Endpoints

1. Assessing effects of renin-angiotensin system inhibition and beta-adrenoreceptor blockade on myocardial manganese uptake.
2. Assessing effects of angiotensin receptor/neprilysin inhibition and sodium-glucose co-transporter 2 inhibition on myocardial manganese uptake.
3. Assessing the effects of cardiovascular risk factors on myocardial manganese uptake.

2.2.3 Exploratory Endpoints

1. Correlation of neurohumoral markers and myocardial manganese uptake.
2. Correlations between myocardial manganese uptake and self-reported symptoms and objective assessments of exercise capacity in Takotsubo Cardiomyopathy.

3 STUDY DESIGN

This will be a prospective randomised open-label blinded endpoint (PROBE) study design with additional use of a cross-over design to improve statistical power. The following flow charts summarise what each study visit will involve for each different group of study participants.

Study 1:

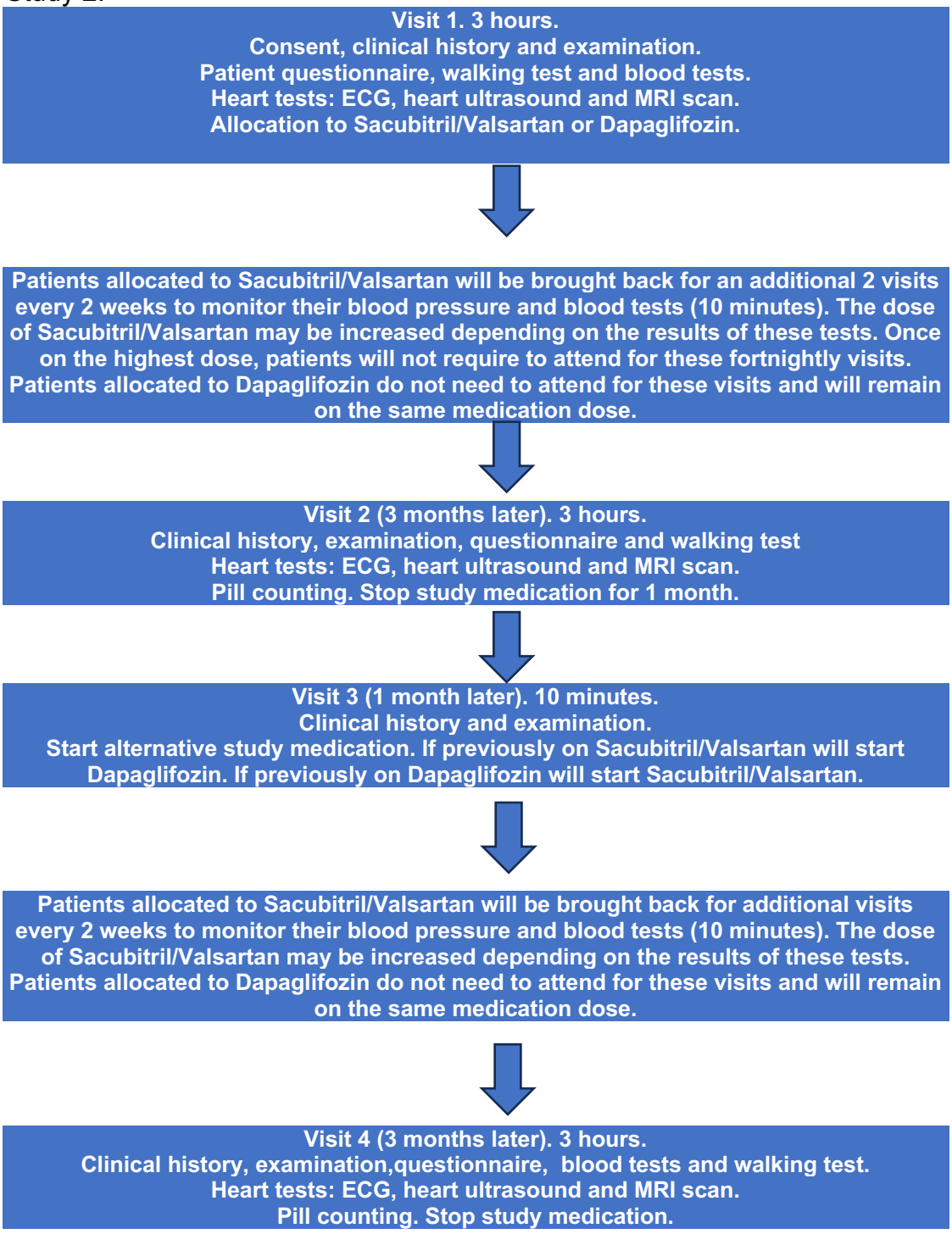
Visit 1
Consent, clinical history and examination.
Patient questionnaire, walking test and blood tests.
Heart tests: ECG, heart ultrasound and MRI scan.
Allocation to Bisoprolol, Valsartan or no medication.
3 hours.

Patients allocated to Bisoprolol and Valsartan will need to return for two additional visits 1 week and 2 weeks after starting medication. This is to check their heart rate, blood pressure and blood tests and to have their medication dose adjusted (10 minutes). Once on the highest dose, patients will not require to attend for these fortnightly visits. Patients randomised to no medication will not need to attend for these visits.

Visit 2 (4 weeks later)
Clinical history, examination, questionnaire and walking test.
Heart tests: ECG, heart ultrasound and MRI scan.
Adjustments to your medication and pill counting.
3 hours

Visit 3 (3 months later)
Clinical history, examination, questionnaire, blood tests, walking test.
Heart tests: ECG, heart ultrasound and MRI scan.
Stopping your medication and pill counting.
3 hours

Study 2:


Visit 1. 3 hours.
Consent, clinical history and examination.
Patient questionnaire, walking test and blood tests.
Heart tests: ECG, heart ultrasound and MRI scan.
Allocation to Sacubitril/Valsartan or Dapaglifozin.
Patients allocated to Sacubitril/Valsartan will be brought back for an additional 2 visits every 2 weeks to monitor their blood pressure and blood tests (10 minutes). The dose of Sacubitril/Valsartan may be increased depending on the results of these tests. Once on the highest dose, patients will not require to attend for these fortnightly visits. Patients allocated to Dapaglifozin do not need to attend for these visits and will remain on the same medication dose.
Visit 2 (3 months later). 3 hours.
Clinical history, examination, questionnaire and walking test
Heart tests: ECG, heart ultrasound and MRI scan.
Pill counting. Stop study medication for 1 month.
Visit 3 (1 month later). 10 minutes.
Clinical history and examination.
Start alternative study medication. If previously on Sacubitril/Valsartan will start Dapaglifozin. If previously on Dapaglifozin will start Sacubitril/Valsartan.
Patients allocated to Sacubitril/Valsartan will be brought back for additional visits every 2 weeks to monitor their blood pressure and blood tests (10 minutes). The dose of Sacubitril/Valsartan may be increased depending on the results of these tests. Patients allocated to Dapaglifozin do not need to attend for these visits and will remain on the same medication dose.
Visit 4 (3 months later). 3 hours.
Clinical history, examination,questionnaire, blood tests and walking test.
Heart tests: ECG, heart ultrasound and MRI scan.
Pill counting. Stop study medication.

Healthy volunteers:

Visit 1. 3 hours.
Consent, clinical history and examination.
Patient questionnaires, walking test and blood tests.
Heart tests: ECG, heart ultrasound and MRI scan.
3 hours.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to recruit 60 participants with an acute diagnosis (within 3 months) of takotsubo cardiomyopathy and 40 participants with a prior diagnosis (>6 months) of takotsubo cardiomyopathy as well as 20 age and sex-matched healthy volunteers. The study will end when the final participant attends for their final study visit. The expected length of recruitment period will be 24-30 months.

4.1.1 Study 1: Patients with Acute Takotsubo Cardiomyopathy

We will recruit 60 patients with acute takotsubo cardiomyopathy and 20 age and sex matched healthy volunteers.

4.1.2 Study 2: Patients with Prior Takotsubo Cardiomyopathy

We will recruit 40 patients with prior takotsubo cardiomyopathy (>6 months previously) for this second cohort of patients. We will recruit these patients contemporaneous with Study 1 so that we can use the same 20 age and sex matched healthy volunteers as a comparator.

4.2 INCLUSION CRITERIA

Takotsubo cardiomyopathy patients:

- Males and females >18 years of age
- Clinical presentation of takotsubo cardiomyopathy
- Have capacity to give formal consent

Healthy volunteers:

- Males and females >18 years of age
- Normal LV function
- No major co-morbidities such as ischaemic heart disease, heart failure, cancer or stroke
- Have capacity to give formal consent

4.3 EXCLUSION CRITERIA

- Unable to tolerate or contraindication to magnetic resonance imaging
- Renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m^2) – this would be assessed by performing a blood test
- Prior history of cardiomyopathy
- Current pregnancy
- Weight greater than 250kg
- Severe asthma for study 1 (given Bisoprolol is contraindicated in this condition)
- Type 1 diabetes mellitus for study 2 (given Dapaglifozin is contraindicated in this population)
- Significant hypotension (given the medications prescribed as part of the study can also cause hypotension as a side effect)
- Significant bradycardia for study 1 (given Bisoprolol can exacerbate any pre-existing significant bradycardia)
- Prescribed Digoxin (this medication interacts with the Manganese)
- Unable to give formal consent

4.4 CO-ENROLMENT

Co-enrolment with other studies may be considered in line with ACCORD co-enrolment policy. Co-enrolment between studies will be agreed by the respective PIs prior to beginning of the study. Individual patients who are eligible for co-enrolment will be discussed between research fellows and PIs as necessary. This will ensure co-enrolment:
1. Is appropriate (i.e. there are no contra-indications)
2. Would not jeopardise the integrity of either study
3. Would not compromise patient care and safety

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

For Study 1, potential participants will be identified by the co-investigator, who will be part of the patients' cardiology clinical care team. This will happen either whilst the participant is still in hospital or shortly after discharge. The co-investigator will provide an information sheet if the participant is interested in taking part in the study.

For Study 2, the co-investigator will identify participants via the Scottish National Takotsubo registry. PBPP and REC approvals are in place to obtain the contact details of patients identified as part of the Scottish Takotsubo Registry so that we can invite them to take part in research. Participants will also be identified by the patients' usual clinical care team when they attend for cardiology clinic follow-up. If they meet inclusion criteria they will be invited to take part in the study and their information and contact details passed on to the co-investigator who will contact them to arrange an initial study visit.

In addition to NHS Lothian, participants can be approached within the NHS Greater Glasgow and Clyde health board. Participants will be approached at the Golden Jubilee National Hospital which will act as a Participation Identification Centre (PIC). Participants will be approached in the usual way, by their usual clinical care team either whilst they are in hospital as an inpatient or at an outpatient clinic. All study activities including patient consent will still take place at the original research site at the University of Edinburgh. There is funding in place to ensure that patients travelling to Edinburgh from Glasgow are offered reimbursement for the cost of travel to the study site.

Healthy volunteers will be recruited via an advertisement process.

5.2 CONSENTING PARTICIPANTS

Participants will be enrolled following an opportunity to read the patient information sheet and ask questions. Informed consent can be taken by any of the study investigators and they will also decide if patients are eligible. Once written informed consent is obtained, screening for eligibility can begin. A screening log will be maintained which will contain anonymised data and will be kept in on Excel spreadsheet on a password-locked University of Edinburgh laptop. Consent will be confirmed at the beginning of any study activities.

5.3 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented if possible. The participant will have the option of withdrawal from all aspects of the study but continued use of data collected up to that point. To safeguard rights, the minimum personally identifiable information possible will be collected. If participants withdraw from the study, they will not need to be replaced.

6 INTERVENTIONS

6.1 STUDY MEDICATION

6.1.1 Identity of study medication

Study Medication	Medication form, dose and usual indication	Manufacturer
Bisoprolol	Oral tablet 2.5 mg once daily Dose increased to 5mg after 1 week then increased to 10mg after another 1 week Usual indication: Heart failure, hypertension, arrhythmias	Alliance Healthcare
Valsartan	Oral tablet 80 mg twice daily Dose increased to 160mg twice daily after 1 week Usual indication: Heart failure, hypertension	Alliance Healthcare
Sacubitril/Valsartan	Oral tablet 24/26 mg twice daily Dose increased to 49/51mg after 1 week then increased to 97/103mg after 1 week Usual indication: Heart failure	Novartis
Dapaglifozin	Oral tablet 10 mg once daily Usual indication: Heart failure, type 2 diabetes mellitus	AstraZenaca

6.1.2 Doses and treatment regimens

Patients in study 1 will be randomised 1:1:1 to no treatment, or open-label valsartan or bisoprolol.

Patients in study 2 will receive 3 months treatment with combination sacubitril and valsartan and dapagliflozin 10 mg in random order. This will be separated by a one-month medication “wash out period.”

Medications will be prescribed on a research specific prescription form by a co-investigator in the Clinical Research Facility. The medication will then be dispensed “off the shelf” from the Royal Infirmary of Edinburgh pharmacy department.

Randomisation will take place by block randomisation. An unbiased colleague will create the blocks for randomisation and the study investigators will be blinded to the blocks until the point of randomisation.

6.1.3 Storage

Study drugs will be stored in the pharmacy department, as per an agreement with the lead research pharmacist at the Royal Infirmary of Edinburgh. The pharmacy department will ensure that medications are stored as per manufacturer instructions.

6.2 CONCOMITANT AND POST-STUDY INTERVENTIONS

Following completion of the study, the study medications will be discontinued. For bisoprolol, the dose will be slowly down titrated before complete discontinuation. We aim to reduce the Bisoprolol dose by 2.5mg each week. All other study medications will be safe to stop immediately.

If participants are already prescribed medication which is the same, similar to or interacts with the study medication then one or more of their current medications may be changed. This would only be considered if it was safe to do so and after an informed discussion with the participant. In some cases, an alternative medication may be offered. At the end of the study, we will have a further discussion with participants regarding their medication. If we have discontinued a medication at the start of the study, this may be restarted again, but we will assess this on a case-by-case basis. We will inform the participants’ GPs which medication they should be prescribed at the end of the study.

6.3 COMPLIANCE WITH STUDY INTERVENTIONS

The investigators will assess treatment compliance at attendance of each of the study visits by pill counting at each visit after randomisation.

6.3.1 Accountability

Compliance will be assessed by interview and pill counting. If the patient is suspected to have taken a medication overdose they will undergo immediate clinical assessment by one of the co-investigators. This will include checking their heart rate, blood pressure and performing a clinical examination. They may also require blood tests. If there is any concern, the co-investigator will arrange for the patient to be admitted to hospital. If an overdose occurs this will be recorded as a Significant Adverse Event.

6.4 DISCONTINUATION OF STUDY MEDICATION

The study medication will be discontinued under the following circumstances:

1. At the request of the patient or if the patient withdraws from the study.
2. By the investigator or the responsible clinician if this was felt to be in the best interests of the patient.
3. On completion of the study.

The patient will be asked to return any unused study medication to the pharmacy department at the Royal Infirmary of Edinburgh.

6.4.1 Procedures for discontinuation of a subject from study medication

Brief interruptions of therapy will be permitted (<14 days) where there is a clinical need. If medication needs to be stopped for longer than 14 days then the patient will be withdrawn from the study. This will be documented in patients' medical records. Reasons for interruption or discontinuation of study medications include side effects of medications. The table below summarises some side effects associated with the study medication:

Study Medication	Potential side effects
Bisoprolol	Hypotension, bradycardia, erectile dysfunction, rash, cold peripheries
Valsartan	Hypotension, impaired renal function, nausea, diarrhoea, rash
Sacubitril/Valsartan	Hypotension, impaired renal function, nausea, diarrhoea, rash
Dapaglifozin	Diabetic ketoacidosis, genital infections (only applies to patients with type 2 diabetes mellitus)

6.5 IMAGING CONTRAST MEDIA

Mangafodipir
Mangafodipir trisodium (manganese dipyridoxyl diphosphate, MnDPDP; IC Targets, Norway) 0.05 mmol/mL solution for intravenous infusion. Each mL contains 37.85 mg of anhydrous mangafodipir trisodium, 0.05 mmol (50 µmol), equivalent to 35.55 mg of mangafodipir. 10 mL contains 378.5 mg of anhydrous mangafodipir trisodium, 0.50 mmol (500 µmol), equivalent to 345.5 mg of mangafodipir. The standard dose of Mangafodipir will be 5ml although this will

be subject to the results of an ongoing comparison study being undertaken at the Edinburgh Royal Infirmary.

The manganese will be administered by intravenous infusion over a period of approximately 10-15 minutes (0.4-1.2mL/min), during the cardiac MRI scan.

7 STUDY ASSESSMENTS

7.1 STUDY ASSESSMENTS

All patient's eligible for the study will have informed consent taken as well as a standardised clinical assessment. For patients in study 1 this will be carried out in the Clinical Research Facility or on the participants' inpatient ward. For patients in study 2 this will be carried out in the Clinical Research Facility. Participants will be reimbursed for travel costs to the Clinical Research Facility, up to a value of £50 per participant.

The different aspects of the study assessments are summarised in the table below:

Assessment	Description	Time required	Associated risks
Consent	The co-investigator will explain the study to potential participants with adequate opportunity for the participant to ask questions. If the participant agrees they will be asked to sign a consent form.	10 minutes	Nil significant
Medical history and physical examination	The co-investigator will check that patients don't have any study eligibility contraindications. They will also check the patients' past medical history, medications and allergies and will record their height, weight, heart rate and blood pressure and perform a physical cardiovascular examination.	15-20 minutes	Nil significant
Blood tests	A needle will be inserted to take blood tests to ensure the patient is eligible to take part in the study as well as to assess their current clinical cardiac status and for storage of samples.	10 minutes	Pain from needle used for taking blood tests

Patient questionnaire	Participants will be asked to complete a questionnaire about their symptoms and quality of life	10 minutes	Nil significant
ECG	We will perform an electrical tracing of the participants' hearts.	10 minutes	Irritation from sticky pads used for ECG
Cannula	A small needle will be inserted into the participant's arm, This will allow us to inject the manganese contrast.	10 minutes	Pain related to needle
Urine pregnancy test	This will be performed in female participants of child-bearing potential to ensure study eligibility.	5 minutes	Nil significant
Echocardiogram	We will perform an ultrasound scan of the participants' hearts.	20 minutes	Nil significant
6-minute walk test	We will ask the participant to walk on the flat for 6 minutes whilst monitoring their oxygen saturations via pulse oximetry.	6 minutes	Nil significant
MEMRI scan	An MRI scan of the heart will be performed and the patient will be injected with manganese contrast.	1 hour	Small risk of allergic reaction to manganese Claustrophobia
Randomisation to medication	Participants will be randomised to medication	10 minutes	Nil significant
Pill counting	We will count the participants' study medications.	5 minutes	Nil significant

7.2 STUDY VISITS

Study 1 participants will undergo 4 study visits if they are randomised to no medication and 6 study visits if they are randomised to medication. Study 2 participants will undergo 7 study visits in total. Healthy volunteers will attend for 2 study visits. The below tables summarise the different assessments participants will undergo at each study visit:

Study 1

Assessment	Screening and Randomisation visit	1 week (Patients on Bisoprolol/ Valsartan)	2 weeks (Patients on Bisoprolol/ Valsartan)	4±1 weeks	3±1 months
Assessment of Eligibility Criteria	☒				
Written informed consent	☒				
Demographic data, contact details	☒				
Clinical assessment as per study protocol	☒	☒	☒	☒	☒
Blood samples as per study protocol	☒	☒	☒		☒
Patient questionnaires as per study protocol	☒			☒	☒
12-lead ECG	☒			☒	☒
Transthoracic Echocardiogram	☒			☒	☒
6-minute walk test	☒			☒	☒
Urinary pregnancy test	☒			☒	☒
Manganese-enhanced Cardiac Magnetic Resonance Imaging	☒			☒	☒
Randomised allocation to Bisoprolol, Valsartan or no medication	☒				
Adjustment of medication dose		☒	☒	☒	
Stop medication					☒
Pill counting				☒	☒

Study 2

Assessment	Screening and Randomisation Visit	1 week (Patients on sacubitril/ valsartan)	2 weeks (Patients on sacubitril/ valsartan)	3±1 months	4±1 months	1 week (Patients on sacubitril/ valsartan)	2 weeks (Patients on sacubitril/ valsartan)	7±1 months
Assessment of Eligibility Criteria	☒							
Written informed consent	☒							
Demographic data, contact details	☒							
Clinical assessment as per study protocol	☒	☒	☒	☒	☒	☒	☒	☒
Blood samples as per study protocol	☒	☒	☒	☒	☒	☒	☒	☒
Patient questionnaires as per study protocol	☒			☒				☒
12-lead ECG	☒			☒				☒
Transthoracic Echocardiogram	☒			☒				☒
6-minute walk test	☒			☒				☒
Urinary pregnancy test	☒			☒				☒
Manganese-enhanced Cardiac Magnetic Resonance Imaging	☒			☒				☒
Randomised allocation to Sacubitril/Valsartan or Dapaglifozin	☒				☒			
Adjustment of medication dose		☒	☒			☒	☒	
Stop medication				☒				☒
Pill counting				☒				☒

Healthy Volunteers

Assessment	Visit 2 (2 weeks)
Assessment of Eligibilty Criteria	☒
Written informed consent	☒
Demographic data, contact details	☒
Clinical assessment as per study protocol	☒
Blood samples as per study protocol	☒
Patient questionnaires as per study protocol	☒
12-lead ECG	☒
Transthoracic echocardiogram	☒
6-minute walk test	☒
Urine pregnancy test	☒
Manganese-enhanced Cardiac Magnetic Resonance Imaging	☒

7.3 STUDY SCREENING

For Study 1, potential participants will be identified by the co-investigator either whilst the participant is still in hospital or shortly after discharge. A member of the study team will provide an information sheet if the participant is interested in taking part in the study.

For Study 2, the co-investigator will identify patients within the NHS Lothian Health Board via the Scottish National Takotsubo registry. Participants will also be identified within the NHS Greater Glasgow and Clyde Health Board by their usual clinical care team.

Healthy volunteers will be recruited via an advertisement process.

An anonymised screening log will be maintained by the co-investigator.

7.4 DEMOGRAPHIC DATA

This will include name, initials, age, sex, height, weight, CHI number, telephone number, address, postcode and email address if available.

7.5 CLINICAL ASSESSMENT

This will involve checking participants' height, weight, heart rate and blood pressure. The co-investigator will perform a physical clinical examination of the participants' cardiovascular system.

7.6 BLOOD SAMPLES

This will include blood sampling for standard biochemical and haematological analyses (Urea and Electrolytes, Full Blood Count and Liver Function Tests) to check participants are eligible and safe to take part in the study. Further samples will be taken for U and Es for safety monitoring purposes for participants randomised to Valsartan and Sacubitril/Valsartan. An N-terminal pro-brain natriuretic peptide will be taken for research purposes.

Furthermore, three blood samples will be taken from each participant and stored for potential future biomarkers.

7.7 URINE PREGNANCY TEST

This will be performed in female participants of child bearing potential.

7.8 PATIENT QUESTIONNAIRES

Quality of life, symptoms, physical and social function will be recorded using the Kansas City Cardiomyopathy Questionnaire (KCCQ-12), Health Status (EQ-5D-5L) and the Patient-Reported Outcomes Measurement Information System short modules on Anxiety, Depression, Fatigue and Physical Function.

7.9 12-LEAD ECG

An electrical recording of the participants' hearts will be undertaken.

7.10 6-MINUTE WALK TEST

Participants will be asked to walk on the flat for 6 minutes whilst having their oxygen saturations monitored via a pulse oximeter.

7.11 ECHOCARDIOGRAPHY

All study participants including healthy volunteers will be studied with a standard 3 MHz transducer and 2- dimensional, M-mode, Doppler and colour Doppler measurements taken. Ejection fraction will be quantified using the modified Simpson's technique and regional wall motion abnormalities assessed. If not performed as part of standard of care (whilst the participant is in hospital), we will organise a study specific transthoracic echocardiogram to be performed at visit 2 or as soon as possible as when is convenient for the participant.

7.12 MANGANESE-ENHANCED CARDIAC MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging will be performed at the Edinburgh Imaging Facility in the Queen's Medical Research Institute, University of Edinburgh.

7.13 STORAGE AND ANALYSIS OF SAMPLES

Blood samples for storage will be frozen (-70 degrees Celcius) and kept for a minimum of five years. They will be stored in a locked freezer in appropriately secured premises in the Laboratory at Edinburgh Royal Infirmary. The retained blood samples and participants data (including MRI images) will be used for secondary studies separate to this study as hypotheses arise. Anonymised blood samples may be sent to other academic institutions within the UK for analysis. Participants will be asked for their consent for storage of samples and use in other studies at the first study visit as part of the consent process.

8 DATA COLLECTION

Clinical Assessment
Any changes in medication, any hospital admission or any clinical symptoms will be assessed at the study visit by the investigator.

Blood Sampling
Blood samples will be collected as per standard clinical care. The results will be uploaded onto the patients electronic NHS Lothian medical record.

Electrocardiogram
Electrocardiograms will be recorded as per standard clinical care and uploaded onto the patient's electronic NHS Lothian medical record.

Echocardiography
Echocardiography will be performed according to standard clinical care. Echocardiograms will be uploaded to the EchoPAC data storage system as part of the patient's electronic NHS Lothian medical record.

Cardiac Magnetic Resonance Imaging with Gadolinium
Cardiac magnetic resonance imaging will be performed according to standard clinical care and uploaded onto the National PACS system.

Cardiac Magnetic Resonance Imaging with Manganese

All images will be acquired with a 3T Siemens scanner. A 60-channel cardiac coil will be used to perform standard cardiac imaging sequences (breath-held, electrocardiogram-gated) for 2-chamber, 4-chamber, long axis and short axis views of the heart. This will provide standard assessment of cardiac volumes, mass, and function including left ventricular ejection fraction and regional wall motion abnormalities. Myocardial T1 will be measured serially for 40-60 min after intravenous infusion of mangafodipir (5 mmol/kg, 1 mL/min; IC Targets, Norway). T1 imaging will be performed with Modified Look-Locker Inversion recovery (Siemens Healthineers) in both short axis (base, mid-cavity) images of the heart (4-chamber and 2-chamber views to capture the apex). Scanner-generated T1 maps will be analysed to quantify T1 within regions of interest.

8.1 SOURCE DATA DOCUMENTATION

The study database will be used to document all data collection which will include consent forms, patient questionnaires, case report forms and information about participant study visits. All patient-related data will be recorded in an pseudonymised way. Each patient will be unequivocally identified by a trial subject number, attributed at recruitment into the study. Key data from blood results, echocardiography and MRI reports will be documented in the study database. The original reports and images will be retained by the imaging core laboratory for future reference.

9 DATA MANAGEMENT

9.1 DATA STORAGE

Patient NHS electronic records will be accessed following formal and explicit patient consent. Pseudonymised data will be made available for other researchers to use where appropriate.

All identifiable participant information (name, age, sex, address and postcode, CHI number, telephone number, email address, height, weight, clinical condition, date of study enrolment and dates of MRI scan) will be stored in a secure manner accessible only to members of the research team on an NHS Lothian device. CHI number is required to review participants relevant medical history, medications, medical imaging and standard of care intervention results. This will be stored in a password protected Excel file on an NHS Lothian device.

All NHS Lothian computers used in the study will be encrypted, and password protected. Electronic data will be stored on (2-step) password-protected computers and only accessible to the study investigators. No personal identifiable information including CHI numbers will be accessed by members outside the research team or NHS Lothian.

Only study subject number will be transferred to the password protected University laptop.

The study will be guided by the principles of Good Clinical Practice and Data Protection Act in ensuring the confidentiality of personal data. Participant consent forms will contain personal data and a linked participant identification number. Hard copies of consent forms will be stored in a secure filing cabinet in a locked University Office (Room SU 305, Chancellor's Building). Study data will be kept on university password protected computers as linked anonymised data. This will enable the identification of each participant's data during the study, for any participant to withdraw and have personal data destroyed if they wish. All data will be anonymised after the study period.

9.2 PERSONAL DATA

The following personal data will be collected as part of the research:

- Name, age, sex, address and postcode, CHI number, height, weight, clinical condition, date of study enrolment and date of MRI scan
- Personal data will be stored or accessed for a period of 6 to 12 months after the study has ended on a password protected Excel file to

allow participants to be identified so we can follow up on their management and clinical course. Thereafter, pseudonymised data may be stored for a period of up to five years.

9.3 DATA INFORMATION FLOW

Patient's initials, name, signature, age and date of birth will be on the consent form which will be kept in locked cupboards in the clinical research facility. This will be pseudonymised with a unique patient code, and this will be stored on a password-protected Excel document.

9.4 EXTERNAL TRANSFER OF DATA

Data collected or generated by the study could potentially be transferred to any external individuals or organisations outside of the Sponsoring organisation(s) in a fully pseudonymised or linked pseudonymised format. With consent, anonymised data collected may be shared with other academic or commercial institutions.

9.5 DATA CONTROLLER

A data controller is an organisation that determines the purposes for which, and the manner in which, any personal data are processed.
The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

9.6 DATA BREACHES

Any data breaches will be reported to the University of Edinburgh (dpo@ed.ac.uk) and NHS Lothian (Lothian.DPO@nhslothian.scot.nhs.uk) Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

10 STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

In our prior study of manganese-enhanced magnetic resonance imaging in patients with takotsubo cardiomyopathy, we observed that manganese uptake was markedly suppressed during initial hospital admission (5.1±0.5 mL/100 g of tissue/min) and this partially recovered after 3 or more months (6.6±0.5 mL/100 g of tissue/min) but remained below that observed in matched healthy volunteers (8.2±1.1 mL/100 g of tissue/min; P<0.001) [Singh et al, 2022]. For study 1, this gives a 100% power to detect a similar difference between healthy

volunteers and patients not receiving any treatment (n=10) at both baseline and 3 months. In terms of treatment effects for studies 1 and 2, we anticipate an improvement of at least 0.6 mL/100 g of tissue/min which equates to just over a third of the difference between healthy volunteers and patients beyond 3 months (8.2 versus 6.6 mL/100 g of tissue/min). At 90% power and 2-sided $P<0.05$ this requires a sample size of 18 per group. To account for some, drop out, we have increased the number of healthy volunteers recruited to a sample size of 20. For study 2, we are exploring novel therapies with uncertain impact, but the detectable effect size will be much smaller (approximately half) given the paired comparisons, cross-over methodology and effective group sizes of 40.

10.2 PROPOSED ANALYSES

10.2.1 Imaging Analysis

Pseudonymised participant MRI data will be sent electronically to the University of Edinburgh for analysis. The first MRI scan will serve as a baseline for comparison, and the pre-contrast imaging will serve as control for each scan individually. Images will be analysed using commercially available cardiac MRI software (Circle Cardiovascular Imaging software, cvi42®, Circle Cardiovascular Imaging Inc. Calgary, Alberta, Canada) through which myocardial contouring and T1 map creation and analysis is performed.

Analysis will be performed in the Image Analysis Core of the Edinburgh Imaging facilities. A standardised approach to T1 image analysis will be employed for manganese uptake [Singh et al, 2022]. Briefly, the basal, mid-cavity, and long axis T1 maps will be divided into segments according to the standard 17-segment model recommended by the American College of Cardiology/American Heart Association [Cerqueira et al, 2002]. After contouring epi- and endocardial borders and defining right ventricular insertion points, regions of interest will be derived for each of the 16 segments with a 10-20% epi- and endocardial offset to reduce risk of blood pool contamination. Manganese uptake will be quantified using a two-compartment Patlak model as described previously [Singh et al, 2022b], and this has excellent repeatability and reproducibility [Singh et al, 2023]. All image analysis will be performed blinded to group, timing and treatment allocation.

10.2.2 Statistical Analysis

Summary data will be presented as number and percentage, mean ± standard deviation or median and interquartile range as appropriate. Based on our prior data, we anticipate that the data will be normally distributed. Within group and between group comparisons will be made with paired or unpaired Student's *t*-test or analysis of variance as appropriate. For study 2, we will explore whether there is any evidence of a time-order effect before proceeding to pool the data from all participants. This will greatly enhance our power to detect

meaningful differences. Repeated measures will be assessed by analysis of variance. Statistical significance will be taken as a two-sided P<0.05.

11 ADVERSE EVENTS

The Investigator, or a delegated researcher, is responsible for the detection and documentation of adverse events that may be related to participating in the study and that meet the criteria and definitions detailed below.

11.1 Definitions

An **adverse event** (AE) is an untoward medical occurrence in a study participant.

An **adverse reaction** (AR), in the context of this study, is any untoward and unintended response which is related to study medication or manganese contrast.

A **serious adverse reaction** (SAR) is any AR that:
- results in death of the clinical trial participant; is life threatening*;
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

A **suspected unexpected serious adverse reaction** (SUSAR) is any AR that is classified as serious and is suspected to be caused by the study medication or manganese contrast.

*Life-threatening in the definition of an SAE or SAR refers to an event where 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.

11.2 Identifying AEs and ARs

All AEs and ARs related to the imaging procedures will be identified from the time an MRI scan related procedure commences until 7 days after scan completion. All ARs to study medications will be identified from the time of medication commencement until 7 days after completion.

11.3 Recording AEs and ARs

AEs will be recorded in the electronic health record. There is no requirement to complete an additional AE form. When an AE occurs, it is the Investigator will review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. Any AEs that qualify as an adverse reaction (AR) to study procedures (imaging or medication) that meets seriousness criteria will be recorded and reported on an ACCORD SAE form, which will then be sent to the Sponsor via email (safety@accord.scot).

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as AEs/ARs if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of underlying disease should not be recorded as adverse events.

11.4 Assessment of AEs, SAEs, ARs, SARs and SUSARs

Seriousness, causality, severity and expectedness will be assessed by the PI. The Investigator is responsible for assessing each adverse event. The CI may not downgrade an event that has been assessed by an Investigator as a SAR or SUSAR, but can upgrade an AR, SAR or SUSAR if appropriate.

11.4.1 Assessment of causality

The Investigator will make an assessment of whether an AE is likely to be related to the study procedures (imaging or medication) and therefore be considered an AR according to the definitions below.

• Unrelated: Where an event is not considered to be related to the study procedures (imaging or medication)

• Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study procedures (imaging or medication).

11.4.2 Assessment of seriousness

Subsequent to the assessment causality, the Investigator will make an assessment of seriousness as defined in Section 10.1

11.4.3 Assessment of severity

The Investigator will make an assessment of severity for each SAR, and record this on the ACCORD SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

11.4.4 Assessment of expectedness of SARs

No SARs are considered expected by the sponsor for the purpose of expedited reporting of SUSARs based upon the reference safety information available in the most current version of the imaging contrast agents or study medications Investigator Brochure.

11.5 Reporting of SARs/SUSARs

As this trial is a non-CTIMP and involves procedures and interventions that are established in the medical community, with extensive information available regarding risks, only serious adverse reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the Sponsor.

Once the Investigator becomes aware that a study related SAR/SUSAR, has occurred in a study participant, the information will be reported to the ACCORD Research Governance & QA Office within 24 hours. If the Investigator does not have all information regarding an event, they should not wait for this additional information before notifying ACCORD. The ACCORD SAE report form will be used to submit the event report, and can be updated when the additional information is received.

The SAE form will be sent via email to safety@accord.scot within 24 hours
Only forms in a pdf format will be accepted by ACCORD via email.
Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the investigator and request the missing information.

All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File.

11.6 Reporting requirements

The ACCORD Research Governance & QA Office is responsible for pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

11.7 FOLLOW-UP PROCEDURES

After initially reporting a study related SAR/SUSAR, the Investigator will follow each participant until resolution or the completion of study follow-up. Follow-up information will be reported to the ACCORD office.

12 OVERSIGHT ARRANGEMENTS

12.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit study related monitoring and audits on behalf of the Sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the Sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if a study specific risk assessment is required.

If required, a study specific risk assessment will be performed by representatives of the Sponsor(s), ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans.

If considered necessary, ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary (delete where not required).

13 GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all necessary approvals will be obtained, and any conditions of approvals will be met.

13.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments.

Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

13.2.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the Sponsor(s). The Investigator or delegated member of the study team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The participant will receive a copy of the signed consent form, and a copy will be filed in the participant's medical notes.

13.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their study related duties.

13.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF (study database) at each Investigator Site.

13.2.4 Investigator Documentation
The Principal Investigator will ensure that the required documentation is available in local Investigator Site files.

13.2.5 GCP Training
For non-CTIMP (i.e. non-drug) studies all researchers are encouraged to undertake GCP training in order to understand the principles of GCP. This is not a mandatory requirement unless deemed so by the Sponsor. GCP training status for all investigators should be indicated in their respective CVs.

13.2.6 Data Protection Training
All University of Edinburgh employed researchers and study staff will complete the Data Protection Training through Learn.

NHS Lothian employed researchers and study staff will comply with the NHS Lothian mandatory Information Governance Data Protection training through LearnPro.

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies.

13.2.7 Information Security Training
All University of Edinburgh employed researchers, students and study staff will complete the Information Security Essentials modules through Learn and will have read the minimum and required reading setting out ground rules to be complied with.

NHS Lothian employed researchers and study staff will comply with NHS Lothian mandatory Information Governance IT Security training through LearnPro.

Non-NHS Lothian staff that have access to NHS Lothian systems will familiarise themselves and abide by all NHS Lothian IT policies, as well as employer policies.

13.2.8 Confidentiality
All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.2.9 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) regarding the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via usernames and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

14 STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Sponsor for classification, review and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC and local R&D for approval prior to implementation and prior to participants being enrolled into the amended protocol.

14.2 MANAGEMENT OF PROTOCOL NON COMPLIANCE

14.2.1 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the Sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC and local R&D for review and approval if appropriate.

14.2.2 Management of Deviations and Violations

Deviations and violations are non-compliance events discovered after the event has occurred. Each protocol violation will be reported to the Sponsor

within 3 days of becoming aware of the violation. If the study becomes multi-centre, deviation logs will be maintained for each centre.

Deviation logs/violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

14.3 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:
(a) the safety or physical or mental integrity of the participants of the study; or
(b) the scientific value of the study.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the Sponsor(s) (qa@accord.scot) must be notified within 24 hours. It is the responsibility of the Sponsor(s) to assess the impact of the breach on the scientific value of the study, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

14.4 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will be destroyed with permission from the Sponsor.

14.5 END OF STUDY

The end of study is defined as the last participant's last visit.

The Investigators and/or the Sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R&D Office(s) and Sponsor(s) within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the Sponsor(s) via email to researchgovernance@ed.ac.uk.

A summary report of the study will be provided to the REC within 1 year of the end of the study.

14.6 INSURANCE AND INDEMNITY

The Sponsor(s) are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the Sponsor(s)' responsibilities:

• The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

• Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The Sponsor(s) require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

• Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

15 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team.

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