Portsmouth Hospitals NHS Trust

Title:

The assessment of left ventricular function in septic shock; comparison of ejection fraction measurement (both by two dimensional and ~~three dimensional~~three-dimensional echocardiography), Global Longitudinal Strain, high sensitivity Troponin and NT-pro BNP.

Short Title: GLASS-heart

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Sponsor: Portsmouth Hospitals NHS Trust

Funder: AMBU

Cardiac Remote Management

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1.0 AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

2.0 SYNOPSIS

Study Title	The assessment of left ventricular (LV) function in septic shock; comparison of ejection fraction measurement (both by two-dimensional and three- dimensional echocardiography), Global Longitudinal Strain, high sensitivity Troponin and NT proBNP. The assessment of left ventricular function in septic shock; comparison of ejection fraction measurement (both by two-dimensional and three-dimensional echocardiography), Global Longitudinal Strain, high sensitivity Troponin and Pro NT BNP
Short Title	**GLASSheart**
Internal ref. no.	PHT/2017/431
Problem statement	2D Ejection Fraction (EF) is not universally accurate in identifying LV systolic dysfunction in septic shock. The early identification of systolic dysfunction can assist clinicians in guiding medical therapy to optimise cardiac output and organ perfusion. Other methods of LV assessment such as cardiac magnetic resonance imaging (MRI) or Positron emission tomography (PET) are not routinely performed on this population due to cost, time and practical limitations. The use of 3D EF is currently not routinely recommended by British Society of Echocardiography (BSE) guidelines. This study aims to determine which type of echocardiographic modality identifies the most patients with cardiac dysfunction. In addition, we would like to assess the feasibility of non-invasive cardiac output measurement in the critically unwell patient. Biomarkers commonly used to assess non-septic cardiomyopathies (i.e. NT-proBNP and high sensitivity troponins) will be measured to identity their potential relationship with septic cardiomyopathies. Additionally, individuals who have persistent impaired Global Longitudinal Strain (GLS) are at risk of long-term myocardial dysfunction despite apparent clinical recovery. The study aims to

	identify individuals who would benefit from further cardiology follow up.
Research question / hypothesis	• To identify a possible association between echo assessment with GLS, 2D EF and 3D EF and biomarkers which are conventionally used in myocardial dysfunction. • To identify if sequential echocardiographic scans assessing GLS, 2D EF and 3D EF are suitable to monitor progression of cardiac dysfunction following an episode of critical illness. • Is GLS a suitable early predictor of cardiac dysfunction (as currently defined by reduced EF) both in the short and longer term in comparison to traditional EF measurements.
Study Design	A single site, prospective, cohort study.
Study Participants	In-patients at Queen Alexandra Hospital, Portsmouth with Sepsis and septic shock, specifically: 1. Age 18 - 85yrs inclusive 2. Sepsis and septic shock as defined by Sepsis-3 criteria 3. Admitted to the Intensive Care Unit (ICU)
Planned Sample Size	108
Follow-up duration	1yr
Planned Study Period	3 years
Primary Objective	• Can 3D LVEF, or GLS, provide an earlier indicator of LV failure in sepsis and septic shock compared to 2D LVEF?
Secondary Objectives	• To explore any practical barriers to using GLS and three-dimensional echo methods by cardiac physiologists • Is three-dimensional EF feasible in the ICU population? • To investigate whether there is an association between major adverse cardiac events at 12 months post sepsis or septic shock and any abnormal echocardiography results at any time point

	• To investigate whether there is an association between major adverse cardiac events at 12 months post sepsis or septic shock and any abnormal biomarker results at any time point • To compare 2D and 3D echocardiographic measurements with GLS to determine whether currently used definition of abnormality in GLS is appropriate. • To compare 2D and 3D echocardiography measurements with GLS to identify if a range of abnormal GLS could be mapped to ranges of abnormal echocardiography results • To compare troponin and BNP results with GLS to identify if a range of abnormal GLS could be mapped to ranges of abnormal biomarker results
Endpoints	• GLS at 24h, 72h, 30 days and 90 days • 2D EF and 3D EF at 24h, 72h, 30 days and 90 days • NT-proBNP at 24h, 72h, 30 days and 90 days • High sensitivity troponin at 24h, 72h, 30 days and 90 days • ICU mortality • In hospital mortality • 30 or 90 day mortality • hospital re-admission of any cause • Major adverse cardiovascular events (MACE) at 12 months
Eligibility Criteria	Inclusion criteria: 1. Age 18-85yrs inclusive 2. Sepsis or septic shock as defined by Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3) 3. Admission to ICU 4. Informed consent taken after discussion with participant or with consultee if appropriate and a period of reflection of up to 18hours. All participants or consultees will be given Patient information sheet (PIS). Please refer to section 10.1 and 10.2

	discussing the issues concerning consent in an unconscious study participant. Exclusion ~~criteria :~~criteria: 1. Pregnancy or complications thereof 2. ESRF requiring dialysis or CKD with eGFR<30ml/min 3. Cardiac transplant recipient 4. Uncorrected valvular dysfunction (graded as moderate or severe) 5. Known structural heart disease 6. Pre-existing cardiomyopathy with bundle branch block on electrocardiogram (ECG) 7. Previous cardiac valve replacement 8. Post-operative within last 7 days 9. Atrial fibrillation/flutter or frequent ventricular ectopic beats during image acquisition 10. Death likely within 24 hours in the opinion of the assessing clinician

3.0 ABBREVIATIONS

BP	Blood Pressure
NT -proBNP	N terminal pro-B-Type Natriuretic Peptide
BSE	British Society of Echocardiography
CKD	Chronic Kidney Disease
CO	Cardiac Output
DCCQ	Department of Critical Care
ECG	Electrocardiogram
ECHO	Echocardiogram
EF	Ejection Fraction
e-GRF	Estimated Glomerular Filtration Rate
ESRF	End Stage Renal Function
GLS	Global Longitudinal Strain
GFR	Glomerular Filtration Rate
HR	Heart Rate
HF	Heart Failure
ICU	Intensive Care Unit
ICS	Intensive Care Society
LV	Left ventricle
LVEF	Left Ventricular Ejection Fraction
MACE	Major adverse cardiovascular events
NCEPOD	National Confidential Enquiry into Patient Outcome and Death
NHS	National Health Service
NRES	National Research Ethics Service
PiCCO	Pulse index Contour Continuous Cardiac Output
PEEP	Positive End-expiratory Pressure
PRA	patient research ambassadors

PPE	Personal protective equipment
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TTE	Transthoracic Echocardiogram/Echocardiography
UoP	University of Portsmouth
QAH	Queen Alexandra Hospital
2D	Two dimensional
3D	Three dimensional

3.0 *LAY SUMMARY*

Assessing Heart Function in Septic Shock (the GLASSheart study)

Background

Sepsis is a life-threatening condition that is triggered by infection. In sepsis, the body's defence mechanism is highly active which results in inflammation. Each year in the United Kingdom (UK), about 200,000 people develop sepsis. Previous research indicates that early recognition and treatment with antibiotics are the most important factors for patient survival. Septic shock is an advanced form of sepsis.

Ultrasound of the heart (Transthoracic Echocardiography (TTE) is used to identify the effect of sepsis on the heart. This is called septic cardiomyopathy, which means a poorly functioning heart muscle due to an infection in the blood. . In septic cardiomyopathy the main pumping chamber of the heart, the left ventricle (LV), begins to fail (dysfunction). This in turn will ultimately affect the blood supply of other organs. The current method for assessing the function of the heart with ultrasound is to measure the percentage of blood pump out of the heart with each beat ('ejection fraction' (EF). The way it is measured means it is not accurate for example in critically ill patients with sepsis or septic shock.

The aims

There are various novel ways to assess the pumping function of the heart. This can be done with 2D and 3D assessment. A further technique is GLS which measures the change of muscle size and movement at different parts of the heart muscle. The aim of this study is to assess which of these techniques is best to identify patients with LV dysfunction. The relationship of each of these tests with the patients blood test will also be assessed.

Methodology

Each patient will have four scans and three blood tests as part of the study alongside standard care, see table below.

1st scan (24hrs on meeting criteria	2nd scan (72hrs later)	3rd scan (30days +/-5 days after 1st)	4th scan (90days +/-5days after 1st)
2d echo	2d echo	2d echo	2d echo
3d echo	3d echo	3d echo	3d echo
GLS echo	GLS echo	GLS echo	GLS echo
BNP blood test		BNP blood test	BNP blood test
High sensitivity troponin blood test		High sensitivity troponin blood test	High sensitivity troponin blood test
Table 1) Schedule of data collection.			

4.0 BACKGROUND AND RATIONALE

Epidemiology

Sepsis-induced cardiomyopathy occurs in up to 14% of patients with sepsis, resulting in myocardial dysfunction [1]. Transthoracic echocardiographic (TTE) assessment of left ventricular ejection fraction (LVEF) is typically used to define sepsis-induced cardiomyopathy. Recent meta-analysis demonstrates that low LVEF was not associated with mortality in septic patients [2,3].

Critically ill patients with sepsis were statistically significantly more likely to have low Global Longitudinal Strain (GLS) compared with reduced LVEF [4,5]. However these studies have been conducted with a small sample size. In addition, there has been no previous exploration of the value of biomarkers and the correlation with LV function.

Benefits of Research

The aim of the study is to aid identification of septic cardiomyopathy with GLS earlier than with standard methods. This will enable to initiate treatment early and subsequently impact on patient outcome. TTE at 30 and 90 days in patient who have clinically recovered from septic shock will guide the need for cardiology follow up to detect signs of LV dysfunction early.

This study aims to identify these patients earlier and subsequently aims to improve quality of life, symptom relief and ultimately prevent the need for implantable devices to assist the heart in functioning appropriately.

Prompt and early identification of cardiomyopathy of sepsis facilitates targeted management and may prevent the global organ dysfunction associated with septic shock. Current methods for assessing cardiac function within critical care are limited to either 2D echocardiogram or invasive monitoring such as pulmonary artery catheters and pulse index contour cardiac output monitoring (PiCCO) or other similar devices. They all have relative advantages and disadvantages. Invasive methods can be associated with vascular complications. The use of the pulmonary artery (PA) catheter is not recommended in current practice.[6]. The use of 2D echo for estimation of EF is variable from point of image acquisition to visual interpretation. It is thought that reduced EF seen in 2D and 3D echocardiography is preceded by reduced GLS[1,2,4].

Global Longitudinal Stain (GLS)

Advanced echocardiographic techniques such as GLS have evolved for direct assessment of the myocardial function. This technique may be beneficial for the assessment of sepsis-induced cardiomyopathy [1,2,3,4,5]. It is different from 2D or 3D LVEF in that it allows more regions of the LV cavity to be assessed simultaneously via myocyte deformation, as compared to volumetric measurement of LV cavity function. Although the modalities of scanning are all assessing cardiac function, the processes by which they measure function differ.

With the use of advanced techniques, septic-induced cardiomyopathy may be commonly diagnosed. It may help identify patients who are critically ill from sepsis and target treatment accordingly. The current management pathways for patients with reduced EF would include follow-up with specialist heart failure input alongside treatment optimization with pharmacotherapy. If patients are found to have cardiac dysfunction early (as evidenced by reduced GLS or EF) then they could be referred on for specialist assessment and treatment early. The current management pathways for patients with reduced EF would include follow-up with specialist heart failure input alongside treatment optimization with pharmacotherapy.

The long-term effects of septic cardiomyopathy have not been studied with regards to heart failure. A single study has observed that only one-third of patients survive post septic shock or sepsis, and advanced echocardiographic imaging was not performed on any of the participants [27].

Biomarkers

Highly sensitive biomarkers have established roles in the detection of myocardial damage in the context of ischemia and strain. The new high-sensitivity troponin assays may allow clinicians to better stratify risk in other potentially high-risk populations [7]. However, the utility of troponin testing in septic cardiomyopathy is unclear and awaits further investigation [7]. Raised levels of high-sensitivity troponin were independently associated with an increased risk for thrombotic and vascular events as well as cardiovascular death[7,8]. This study looks to explore any association of high sensitivity troponin with reduced GLS.

Guidelines from the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) list as a class I recommendation the use of BNP or NT-proBNP values in the diagnosis and prognostication of heart failure [9]. Increased or persistent elevation in natriuretic peptide levels is a poor prognostic factor [10]. As a marker of LV dysfunction, natriuretic peptides are not helpful in diagnosing myocardial ischemia and acute coronary syndrome (ACS) [11]. However, B-type natriuretic peptide BNP and NT-proBNP levels may be useful for risk stratification in patients with acute coronary syndrome (ACS),

and they may predict clinical chronic heart failure. A multi-marker approach may improve risk stratification following myocardial injury [10,11]. There is an emerging role for natriuretic peptide biomarkers in population screening to detect incident HF [12,13,14]. Elevated plasma levels of natriuretic peptide biomarkers are associated with a wide variety of cardiac and non-cardiac causes [15,16]. Like natriuretic peptides, cardiac troponin levels may be of prognostic value in the setting of chronic or acute decompensated Heart Failure HF, but are more sensitive for myocyte injury or necrosis [17].

It is recognised that strategies that combine multiple biomarkers may be beneficial in guiding cardiac therapies in the future [18,19].

5.0 PRELIMINARY STUDIES AND EXPERIENCE OF INVESTIGATORS

Investigator Team

The investigators are clinically active members at Queen Alexandra Hospital, Portsmouth. The research team is ideally placed to deliver this study combining the expertise with Intensive Care Unit ICU and the Cardiology department. Whilst some members of the research team have limited research experience, they will be supported and mentored appropriately and all staff are GCP trained. There are no additional clinical training requirements for the study team.

The team is well supported by the Critical Care department which is frequently involved in large multicentre clinical trials.

Preliminary Studies

Previous audit and service evaluation have been performed in 2017 for submission as abstracts to Intensive Care Society (ICS) and British Society of Echocardiography (BSE) looking at feasibility of performing the novel echo techniques and to identify a subset of patients who may show normal EF but reduced GLS while in septic shock [1,2,3,4,5]. It showed a discrete group of septic patients in whom there was normal 2D LVEF, but a decrease in GLS. It also showed that although the number of scans able to permit retrospective GLS calculation was low, that this is due to an easily remedied factor at our control. The image optimisation to enable GLS calculation is subtly different than the requirements of standard 2D EF. Without knowing that GLS was to be performed, the staff had not acquired images compatible for GLS. Staff training has already been carried out to correct this and the majority of equipment on site now supports 3D and GLS.

The lead investigator is an experienced echocardiographer with accreditation by the BSE and has undertaken courses on 3D and GLS. Co-investigators are experienced clinical staff

with in depth knowledge of the intensive care patient and a focus in cardiology and/or echo. The cardiology and critical care departments are well resourced to support the study throughout its course.

6.0 AIMS AND OBJECTIVES

6.1 Primary Objective

Can 3D LVEF, or GLS, provide an earlier indicator of LV failure in sepsis and septic shock compared to 2D LVEF?

6.2 Secondary Objectives

- To explore any practical barriers to using GLS and three-dimensional echo methods by cardiac physiologists
- Is three dimensional EF feasible in the ICU population?
- To investigate whether there is an association between major adverse cardiac events at 12 months post sepsis or septic shock and any abnormal echocardiography results at any time point
- To investigate whether there is an association between major adverse cardiac events at 12 months post sepsis or septic shock and any abnormal biomarker results at any time point
- To compare 2D and 3D echocardiographic measurements with GLS to determine whether currently used definition of abnormality in GLS is appropriate.
- To compare 2D and 3D echocardiography measurements with GLS to identify if a range of abnormal GLS could be mapped to ranges of abnormal echocardiography results
- To compare troponin and BNP results with GLS to identify if a range of abnormal GLS could be mapped to ranges of abnormal biomarker results
- Can troponin or pro NT BNP measurements in combination with 3D LVEF, 2D LVEF or GLS provide an earlier indicator of LV failure in sepsis or septic shock

7.0 STUDY DESIGN

7.1 Summary of Study Design

A prospective, cohort study based at a single centre (Queen Alexandra Hospital, Portsmouth). There is no randomization involved in this study. There is no blinding in this study. There will be a single operator for performing the scans due to the level of

professional training and accreditation required to perform a GLS scan. Expected patient participation is 365 days (+/-7) or until mortality whichever occurs first.

7.2 Outcome Measures

Primary outcome measure:

To investigate if 3D left ventricle ejection fraction, or Global Longitudinal Strain, provides an earlier indicator of left ventricle failure in sepsis or septic shock compared to 2D LVEF.

Secondary outcomes measure:

1. To explore any practical barriers to using GLS and three-dimensional echo methods by cardiac physiologists
2. Is three dimensional EF feasible in the ICU population?
3. To investigate whether there is an association between major adverse cardiac events at 12 months post sepsis or septic shock and any abnormal echocardiography results at any time point
4. To investigate whether there is an association between major adverse cardiac events at 12 months post sepsis or septic shock and any abnormal biomarker results at any time point
5. To compare 2D and 3D echocardiographic measurements with GLS to determine whether currently used definition of abnormality in GLS is appropriate.
6. To compare 2D and 3D echocardiography measurements with GLS to identify if a range of abnormal GLS could be mapped to ranges of abnormal echocardiography results
7. To compare troponin and BNP results with GLS to identify if a range of abnormal GLS could be mapped to ranges of abnormal biomarker results
8. Can troponin or pro NT BNP measurements in combination with 3d LVEF, 2d LVEF or GLS provide an earlier indicator of LV failure in sepsis or septic shock

Safety outcomes:

- Any adverse events during performing the study procedures (AE's)
- Any adverse device events (ADE's)

8.0 STUDY PARTICIPANTS

8.1 Study Setting

Participants will have been admitted to Queen Alexandra Hospital, critical care unit with sepsis or septic shock as defined by The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [20].

8.2 Overall Description of Study Participants

Sepsis or septic shock patients within the first 24 hours of their admission to critical care. Eligibility will be met by the following inclusion and exclusion criteria:

8.3 Eligibility Criteria

Inclusion Criteria

1. Age 18-85yrs inclusive
2. Sepsis or septic shock as defined by Third International Consensus Definition for Sepsis and Septic Shock (Sepsis-3)
3. Admission to ICU
4. Informed consent taken after discussion with participant or with consultee if appropriate and a period of reflection of up to 18hours. All participants or consultees will have PIS given. Please refer to section 10.1 and 10.2 discussing the issues concerning consent in an unconscious participant

Exclusion Criteria

The exclusion criteria below specify conditions where the assessment of cardiac function is known to be altered or may not be reliable by the scanning method employed.

1. Pregnancy or complications thereof
2. ESRF requiring dialysis or CKD with eGFR<30ml/min
3. Cardiac transplant recipient
4. Uncorrected valvular dysfunction (graded as moderate or severe)
5. Known structural heart disease
6. Pre-existing cardiomyopathy with bundle block on ECG
7. Previous cardiac valve replacement

11. Post-operative within last 7 days
12. Atrial fibrillation/flutter or frequent ventricular ectopic beats during image acquisition
13. Death likely within 24 hours in the opinion of the assessing clinician

9.0 SAMPLING

The minimum sample size is 108. This was based on the use of repeated measures ANOVA comparing three arms at 4 time points, with the significance level of 5% and power of 90%. This is based on a medium assumed effect size 0.15.
Considering that echo image quality is unknown until after consent and enrolment onto study and 20% inflation to study size was added from the original calculated 89, meaning a total of 108 participants

10.0 STUDY PROCEDURES

Items in bold denote additions to standard care

	First 24 hours	At 72 hours	30 days	90 days
General procedures and safety				
Informed consent	X			
Demographics	X			
Medical and surgical history	X			
Vital signs (BP, HR)	X	X	X	X
Weight	X		X	X
PEEP	X	X	X	X
Adverse events potential	X	X	X	X
Concomitant therapy	X	X	X	X
ECG	X			X
2D ECHO	X	X	X	X
Local laboratory				
Chemistry	X	X	X	X
Haematology	X	X	X	X
Urinalysis	X			X
Hs Troponin	X		X	X
BNP/NT-proBNP	X		X	X

Investigational tool				
3D ECHO **GLS** **CO**	X X X	X X X	X X	X X
MACE follow up call/notes review at 12 months				

Table 2). Schedules of all procedures

10.1 Recruitment

The study will be conducted at Queen Alexandra Hospital, Portsmouth, under the lead of Emma Lane, with recruitment assistance from ICU research nurses and ICU team. Research staff alongside the clinical team will be involved in the identification of patients, which will take place on the critical care unit within 24 hours of admission and meeting sepsis 3 criteria for septic shock. If appropriate the participant will be given PIS regarding the study. If the participant is not able to receive the PIS due to lack of capacity then their representative will be given the information. Opportunity will be given to ask questions.

10.2 Screening and Enrolment

Patients already enrolled in other research trials will be invited and allowed to participate in the study if they so wish. This was discussed with public and patient involvement (PPI) representatives who felt that these patients should also have the opportunity to participate in the study, and should not be excluded.

If appropriate the participant will be given participant information sheet (PIS) regarding the study. If the participant is not able to receive the PIS due to lack of capacity then their personal consultee will be given the information.
Opportunity will be given to ask questions. Informed consent will be obtained prior to study procedures being undertaken. If informed consent cannot be obtained immediately we refer to the guidance provided by the MRC, on medical research involving adults who cannot consent (2007).

In the majority of cases it will not be possible to obtain consent from the participant at the time of enrolment. If informed consent cannot be obtained immediately we refer to the guidance provided by the MRC, on medical research involving adults who cannot consent (2007)

Participants having reduced level of consciousness due to illness or sedative medication used as part of their treatment. This makes attempts to obtain prior informed consent from the patient challenging and the following measures have been put in place:

Patient consent

Participants will need full capacity to consent. If they are unable to gain capacity to consent within 18hrs of meeting study eligibility, we will use personal consultee consent as outlined below. For participants able to consent, a written Participant Information Sheet (PIS) will be provided to the patient. A Consent Form will be provided indicating that:

- The information given, orally and in writing, has been read and understood
- Participation is voluntary and can be withdrawn at any time without consequence;
- That consent is given for access to medical records for data collection.

The Consent Form will also cover ongoing data collection and follow-up.

Participants will be given time to read the PIS and have an opportunity to ask any questions they may have about participation. After verifying that the PIS and Consent Form are understood, the person seeking consent will invite the patient to sign the Consent Form and will then add their own name and countersign it. A copy will be given to the patient, a copy placed in the patient's medical notes and the original kept in the Investigator Site File. If the participant is unable to physically sign the Consent Form (e.g. due to weakness, reduced dexterity), an independent witness can sign on their behalf.

The patient's General Practitioner will then be sent a letter by the recruiting site to inform them of their patient's participation in the study (provided consent has been given for this).

Personal Consultee

Due to the severity of illness and its impact on the mental state of the target population, it may not be possible to involve participants in the consenting process early on. Instead, consent will be obtained from patients once they have stabilised and are deemed to have capacity.

In the interim, once notified of the potential enrolment of a patient, a delegated member of the site research team will approach relative, friend or legal representative (Personal Consultee) as soon as appropriate and practically possible to discuss the study and to seek their opinion as to the patients' likely wishes and feelings regarding participation.

A separate consent form will be provided indicating that: the information given, orally and in writing, has been read and understood; the patients' participation is voluntary and can be withdrawn at any time without consequence; and that, in the Personal Consultees opinion, the patient would not object to taking part in research. Personal Consultees will also be

asked to indicate whether, in their opinion, the patient would agree to access to medical records for data collection.

10.3 Study Assessments

The overview of the study and schedule of assessments are outlined in Figure 1 and Table1 respectively. Once potential participants are identified and enrolled, the following assessments will take place:

- At baseline and within the first 24 hours, consent where able followed by collection of demographic and basic physiological data (standard to the monitoring of the critically unwell patient).
    - Ventilator settings (Positive End Expiratory Pressure, Pressure Support, inspired oxygen)
    - Estimated or actual weight as documented in patient notes
    - Urinalysis
    - ECG
    - Mean arterial pressure (MAP) and vital signs

Documentation will record medical drug history and currently given. In addition to baseline laboratory tests, biomarkers (high sensitivity troponin and NT-proBNP) will be requested. Within the first, 24 hours the echo scan will be performed.

- At 48-72 hours after the first scan, excluding baseline demographic information a repeat assessment will be performed. This will not include biomarker samples on this occasion.
- At 30 days, excluding baseline demographic information, a repeat assessment will be performed including biomarker samples.
- At 90 days, excluding baseline demographic information, a repeat assessment will be performed including biomarker samples.
- 12 months (+/- 5 days) post inclusion MACE evaluation by notes review and/or telephone call conversation

Demographics, medical and surgical history is available from the patient medical records.

The critical care unit in QAH operates an electronic patient information system, which facilitates with ease other secondary outcomes measure (vital signs, weight, PEEP, concomitant therapy, laboratory results) at the specified time points. Once the patient has

been discharged from critical care this information is no longer available in electronic format and will have to be retrieved manually.

A 12 lead-ECG will be recorded with the use of the hospital's standard machine by staff who are trained on its use.

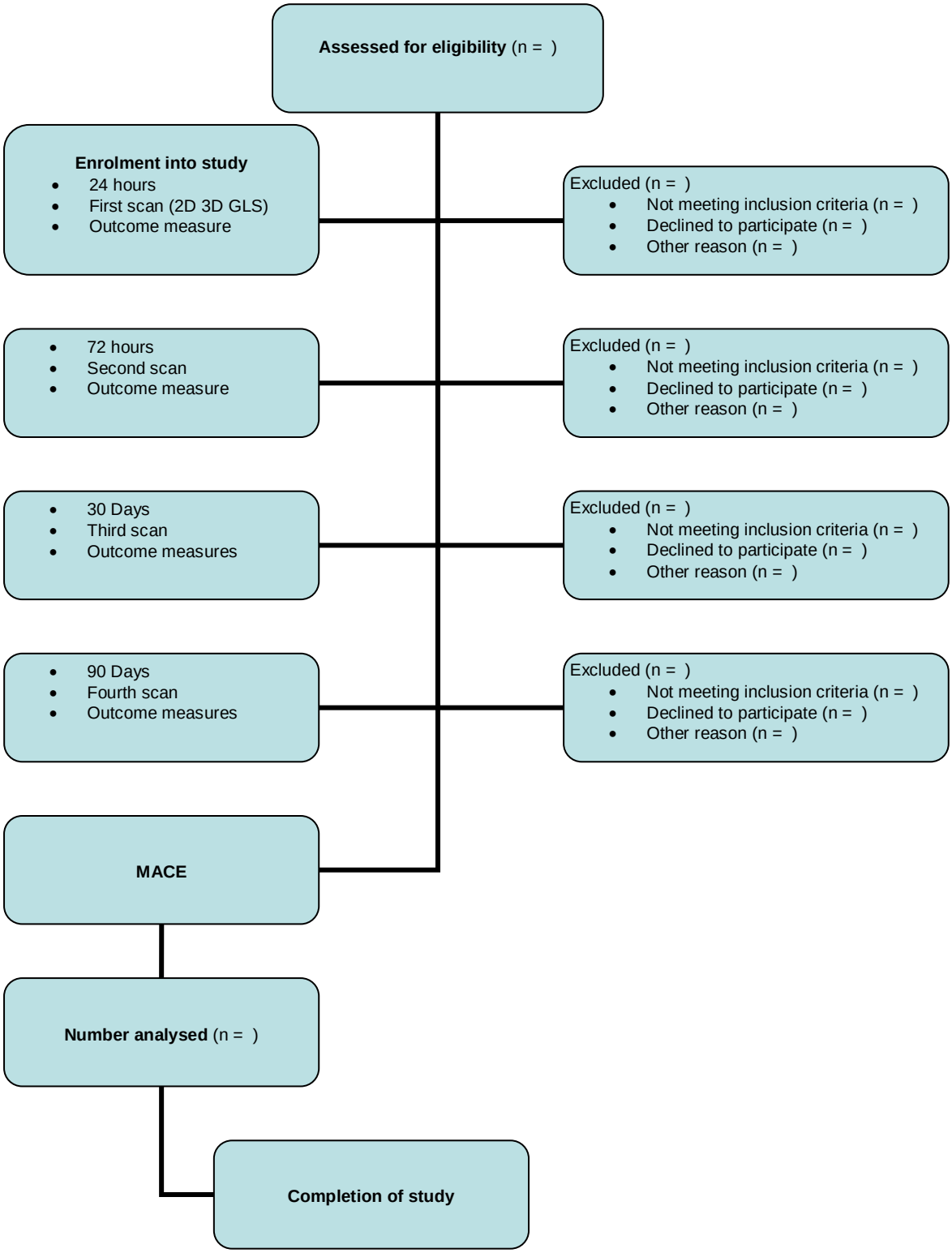
Laboratory assessments during admission for illness will include basic biochemistry and haematology. Biomarker assessments will have to be requested with prior agreement with the research laboratory based at QAH. The total volume of blood to be drawn for biomarker assessments will not exceed 10mls and will be divided into an EDTA (ethylenediaminetetraacetic acid) and SST (serum separating tube) bottle. The total volume to be drawn over the study for biomarkers and basic laboratory studies will not exceed 90mls.

Once participants have been discharged from critical care, they will be offered follow-up appointments at 30 days and 90 days from point of admission. If they remain within the hospital at 30 and 90 days, then assessment can be done whilst they are an inpatient.

MACE evaluation recorded at 12 months via notes review and/or telephone call to participant by heart failure nurses specialist to identify any out of area hospital admissions/interactions that are recorded as major adverse cardiovascular events such as: MI, stroke, hospitalization because of HF; and revascularization, including percutaneous coronary intervention, and coronary artery bypass graft

Some participants may be lost to follow-up or withdrawn from the study. This is detailed in section10.5.

Diagram 2). Overview of study pathway



10.4 Discontinuation/Withdrawal of Participants from Study Treatment

Participants have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care. Likewise the consultees have the same right to withdraw consent at any point while they are acting in that capacity. The investigator should document withdrawal for any reason in the source documents and in the case report form (CRF). Data taken up to point of withdrawal will be utilised, but this will be made clear during the consent process and on any PIS given to the participant. Reasons for removal or reduced follow-up from the study:

- Participant not able to attend follow-up visits, but may still be contacted by telephone or email for 12 months time point enquiry into adverse events/MACE
- By assessment of the investigator or clinician not to continue due to safety concern (e.g. adverse event, pregnancy)
- Palliation for end of life care

10.5 Definition of End of Study

The end of study is the date of the last study contact of the last recruited participant.

11.0 INTERVENTIONS

11.1 Description of tests:

Echocardiography

Echocardiography is a non-invasive bedside ultrasound test which, in this study, will take approximately 15minutes and has no radiation risk. This will be performed at 24hrs, 72hrs, 30 days (+/-5) and 90 days (+/-5). A standard operating procedure exists for performing echocardiogram. Additional information is provided in a PIS for participants. In accordance with local practice, PPE equipment is worn for this test. ECG electrodes and ultrasound gel can be a potential risk to the patient with regards to dermatological reaction/sensitivity, however both are hypoallergenic substances. If a patient is observed to have any reaction to these consumables alternatives will be sourced or patient will be excluded from study.

There are no drugs used in this study. There are no placebos or alternative treatments.

Blood collection for NT-proBNPand High Sensitivity Troponin I

These tests will be performed locally by the blood sciences department (Pathology) at the Queen Alexandra Hospital Portsmouth. In-line with local protocols for these tests they will be collected and handled as follows:

- **1x gold topped SST blood tube** will be collected and will be sufficient for analysis of both analytes.
- This blood tube will be correctly labelled and sent to Pathology for analysis (as per routine samples)
- The SST blood tube will be allowed to clot for 30 minutes after collection.
- This will be centrifuged at **2000 x g for 10 mins at room temperature** to obtain serum before analysis and reporting.

NT pro-BNP

The N-Terminal pro-B-type Natriuretic Peptide (NT pro-BNP) blood test will be performed on all participants on admission, day 30 and day 90. This is a validated and prognostic test for heart failure and it is of value in other forms of myocardial dysfunction. Results will be recorded in the CRF.

High-sensitivity troponin

The high-sensitivity troponin test will be performed on all participants on admission, day 30 and day 90. This is a validated and prognostic test for ischemic myocardial injury and it is of value in other forms of myocardial dysfunction. Results will be recorded in the CRF. Both test are additional tests to standard care.

Haematology and biochemistry

Routine, standard care tests such as; haematology (haemoglobin, platelets, white cell count) and biochemistry (sodium, potassium, urea, creatinine, eGFR, bilirubin, albumin) will be taken at all stages/visits. The results will be recorded in the CRF.

12.0 ASSESSMENT OF SAFETY

As this is a non-invasive study, no formal adverse event recordings or reporting will take place. The study is non-invasive and is low risk and low burden. However, if there are any incidents, for example allergy to ECG electrodes or ultrasonic gel, this will be recorded on the case report form (CRF). Attempts will be made at all time points to minimise pain, discomfort, distress, intrusion, inconvenience – asking for nursing assistance when required.

13.0 DATA HANDLING AND RECORD KEEPING

13.1Data Collection Forms.

The principal investigator (PI) will be responsible for ensuring the quality and security of all data recorded.

Data collection will be undertaken by the PI, investigators, specialist research nurses within the ICU and cardiology department and any other sub-investigators as per the delegation log. Data will come from a number of sources, and will require a variety of different collection and storage techniques*:*

Data source	***Data collection***
Echocardiographic imaging	***Imaging data is collected and stored initially on the individual echo machine, and is then transferred onto a secure server (McKesson). The participants images are identified by a unique identifier number linked to the participant ID.***
Medical notes, clinic letters and clinical databases	***Entered onto paper data case report form (CRF) as source data***
Consent form	***Completed by participant and kept in medical notes***
Laboratory reports – blood	***Printout from electronic results system (ICE) to be kept as source data in medical notes, and results entered onto paper CRF***

All CRFs will be kept in the Trial Master File (TMF), locked within the cardiology outpatient department. All data on the CRF and kept within the TMF will be anonymised. Source data which retains personal identifiable data will be stored within the participant medical notes which are also stored and archived according to standard procedures.

All electronic data will be stored anonymously on a secure network folder, accessible via a password-protected Trust computer

13.2 Data Management

Data management will be conducted by the investigators using clinical, access databases (Redcap) and excel documents, and will be accessed by named investigators only on Trust PCs that are password protected. Data will be monitored at the investigator site. If errors in clinical data are discovered during quarterly data entry checks, a query will be created. Queries are created when information is missing or is illegible and needs further clarification.

Query forms will be sent to the primary investigator for completion who will be acting as database manger for this study

The study database will be stored on a secure NHS server at Portsmouth Hospitals NHS Trust. All echocardiograms performed will be stored on 'McKesson' which is a server based cardiac image and information management system. This is the system in place for storing all echocardiograms performed at Queen Alexandra Hospital. Images from participants on this this study will be transferred to a separate private file which can only be accessed by principle investigator and is password protected .All images are stored under study number.

Trust standard operating policy is to archive study data for 15 years and then destroy.

14.0 DATA ANALYSIS

14.1 Description of Analysis Populations

Univariate one-way repeated measures analysis of variance (ANOVA) test will be used fro statistical analysis of data for primary research question/objective.
In addition to 20% inflation of minimum sample size at baseline data collection due to likelihood of poor echo imaging, the number of expected participants decreases over the subsequent 3 data collection points to account for expected mortality in this cohort. All withdrawal will be logged in a case report form. Furthermore the feasibility of 3D imaging is a secondary outcome of this study.

14.2 Analysis of Endpoints

Using the assistance of University of Portsmouth statistician, a recommendation of a sample size of 30 in each arm (90 in total), for the test of a single contrast at 0.05 significant level in a one way repeated measures analysis of variance with 3 levels will have 90% power to detect an effect size of 0.15.

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In addition to 20% inflation of minimum sample size at baseline data collection due to likelihood of poor echo imaging, the number of expected participants decreases over the subsequent 3 data collection points to account for expected mortality in this cohort. All withdrawal will be logged in a case report form. Furthermore the feasibility of 3D imaging is a secondary outcome of this study.

14.3 Procedure for Dealing with Missing, Unused and Spurious Data

Data will be checked for queries every 3 months by the principle investigator and the database updated where possible. These changes will be tracked using an excel document.

14.4 Procedures for Reporting any Deviation(s) from the Original Statistical Analysis Plan

Deviations from the original protocol will be documented, with justification and reason.

14.5 Interim analysis and criteria for early study termination

Not planned or required

15.0 ETHICS

15.1 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on any electronic and paper database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act 2018 which requires data to be anonymised as soon as it is practical to do so.

15.2 Other Ethical Considerations

The study will not be initiated before the protocol and all study relevant material such as the informed consent forms and participant information sheets have received favorable opinion from the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) departments. Any changes to protocol or relevant study documents will be approved by the Sponsor. Should an amendment be made that requires REC approval, as defined by REC as a substantial amendment, the changes will not be instituted until the amendment has been reviewed and received favorable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor amendments as defined by REC as a non-substantial amendment, may be implemented immediately; and the REC will be informed.

All participants will be able to consider continual participation in the study, as per Good Clinical Practice (GCP) guidelines.

Patients who are already enrolled in other research trials will be invited and allowed to participate in the study if they so wish. This was discussed with our PPI representatives who felt that these patients should also have the opportunity to participate in the study, and should

not be excluded.

Patient's privacy and dignity will be maintained as per NHS guidelines for the duration of the echo scan. Although the scan requires access to the chest, the patient will be covered with a sheet or gown and the curtains will be drawn at time of patient interaction.

15.3 Declaration of Helsinki

The study will be performed in accordance with the spirit and the letter of the declaration of Helsinki, the Good Clinical Practice Guidelines, the protocol and applicable local regulatory requirements and laws.

15.4 ICH Guidelines for Good Clinical Practice

All study staff must hold evidence of appropriate GCP training or undergo GCP training prior to undertaking any responsibilities on this trial. All research staff will monitored by the sponsor to ensure adherence to GCP.

16.0 PATIENT PUBLIC INVOLVEMENT (PPI)

16.1 Study design

This proposal originated from clinicians. Lay people will not be participating in data collection or analysis, but will be included as part of the ethical review panel, forming of lay summaries, all steering group meetings and reviewing information sheets

16.2 Study implementation

Public and patient involvement will be considered before data collection begins. Patient Research Ambassadors have been identified and invited to attend steering group meetings to give advice on all areas. A national group for Sepsis Survivors has been approached and is happy to be involved in a similar process.

16.3 Dissemination

The study will be included on the Portsmouth ICU and Wessex Intensive Care Society websites research pages which are in public domain. Patient Research Ambassadors will be

invited for advice on areas for public dissemination of results. Lay reports are to be written by PRA's and advice on public dissemination.

17 FINANCING AND INSURANCE

17.1 Research Costs

£28, 065.14

17.2 Service Support Costs

£1,500.27

17.3 Excess Treatment Costs

No excess treatment costs are expected as this is an observational study.

The NHS indemnity scheme shall apply for the management, design and conduct of the study.

17.4 Study Sponsorship

Portsmouth Hospitals NHS Trust shall act as Sponsor. A Trial Management Group (TMG) will convene quarterly to review the progress of the study. This will consist of the key members listed on the delegation log who are involved in the day to day running of the study. The TMG will oversee day to day management of the study and data quality and will advise the Sponsor of any concerns regardless. Within the Trust a Research Governance Group (RGG) convene regularly to review the progress of Sponsored studies. Any concerns raised with the study will be discussed and addressed at this meeting. In addition, an annual report will be submitted to the research ethics committee for review.

This study will be carried out subject to approval by the Portsmouth Hospitals NHS Trust Research and Development department, NHS Research Ethics Committee and the Health Research Authority. It will be carried out in accordance with the Data Protection act, International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines, Research Governance Framework for Health and Social Care and World Association Declaration of Helsinki (1964) and Scotland (2000) amendments.

18.0 TIMETABLE AND ORGANISATIONAL CHART

Month 1-3:	Ethics/R+I approvals, study set-up, CRF finalisation, database testing, writing SOPs etc	All investigators and PRA's
Month 4-5:	First inclusions, study management meeting and data review, protocol amendments (if required)	All investigators and PRA's
Month 6-18	Recruitment, data input and cleaning	Emma Lane Richard Clinton David Slessor Research nurses
Month 18/19	Last recruitment	Emma Lane Richard Clinton David Slessor Research nurses
Month 21/22 (90days +/- 5 after last recruitment)	Last follow-up visit	Emma Lane
Month 30/31 (1yr post last recruitment)	Last phone call/follow up	Emma Lane Mark Green
2023	Final data cleaning and analysis	Emma Lane UoP statistician
2024	Dissemination	Investigating team

19.0 RESOURCES, EQUIPMENT AND PHYSICAL FACILITIES

The following have been identified as resources and equipment required for the duration of the study and these are already part of routine stock:

- GE E9 or E95 TTE machine with 3D and GLS capacity.
- Echocardiography consumables such as electrodes and sonic gel.
- McKesson database/server.
- Consumables for blood tests.

The following requirements are additional tests or services for these patients, and while these facilities are available within this trust they will incur costs:

- Laboratory cost for blood test analysis and reporting.
- Outpatient clinic time for day 30 and 90 follow-up.

20.0 DISSEMINATION AND OUTCOME

Results of this trial will be submitted for external publication in a PubMed cited peer-reviewed journal, with a focus on Intensive Care and echocardiography. The manuscript will be prepared by the Chief Investigator in conjunction with the study team; authorship will be determined by mutual agreement. Any secondary publications and presentations prepared by Investigators must be reviewed by the Chief Investigator.

Available for public access public via PHT and Wessex intensive care Unit websites. The study will also be registered on a public database as part of ethical approval.

There is planned poster presentation at national and international conferences as well as public dissemination as advised by PRA's.

21.0 REFERENCES

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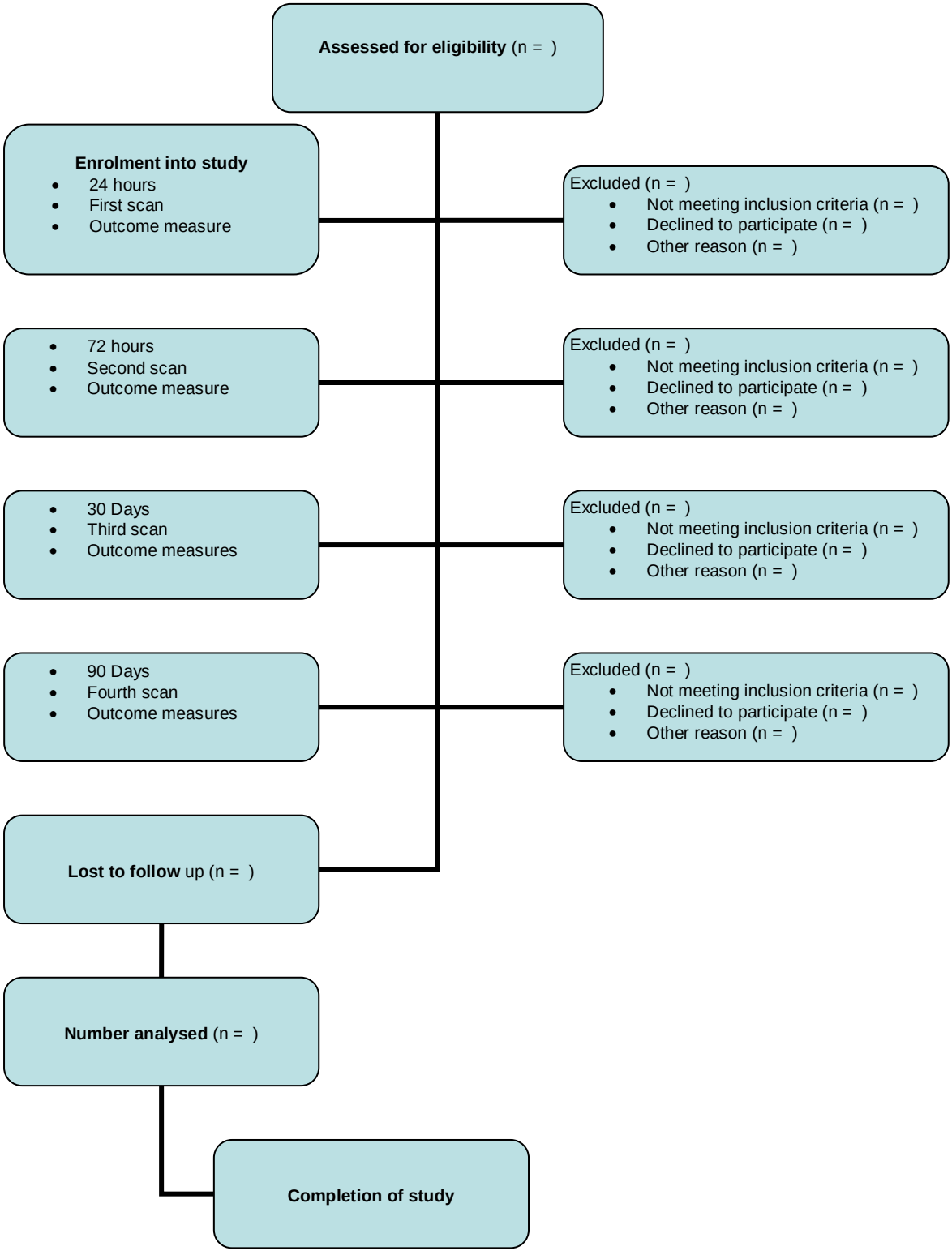
APPENDIX 1 SCHEDULE OF PROCEDURES

	First 24 hours	At 72 hours	30 days	90 days
General procedures and safety				
Informed consent	X			
Demographics	X			
Medical and surgical history	X			
Vital signs (BP, HR)	X	X	X	X
Weight	X		X	X
PEEP	X	X	X	X
Adverse events potential	X	X	X	X
Concomitant therapy	X	X	X	X
ECG	X	X		X
2D ECHO	X		X	X
Local laboratory				
Chemistry	X	X	X	X
Haematology	X	X	X	X
Urinalysis	X			X
Hs Troponin	X		X	X
BNP/NT-proBNP	X		X	X
Investigational tool				
3D ECHO	X	X	X	X
GLS	X	X	X	X
CO (3D ECHO)	X	X		

APPENDIX 2 STUDY FLOW CHART


Assessed for eligibility (n =)
Enrolment into study
24 hours
First scan
Outcome measure
Excluded (n =)
Not meeting inclusion criteria (n =)
Declined to participate (n =)
Other reason (n =)
72 hours
Second scan
Outcome measure
Excluded (n =)
Not meeting inclusion criteria (n =)
Declined to participate (n =)
Other reason (n =)
30 Days
Third scan
Outcome measures
Excluded (n =)
Not meeting inclusion criteria (n =)
Declined to participate (n =)
Other reason (n =)
90 Days
Fourth scan
Outcome measures
Excluded (n =)
Not meeting inclusion criteria (n =)
Declined to participate (n =)
Other reason (n =)
Lost to follow up (n =)
Number analysed (n =)
Completion of study