Academic and Clinical Central Office for Research and Development

Study Protocol

CARDIAC CARE

A multicentre prospective randomised open-label blinded end-point controlled trial of high-sensitivity cardiac troponin I-guided combination angiotensin receptor blockade and beta blocker therapy to prevent cardiac toxicity in breast cancer patients receiving anthracycline adjuvant therapy.



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PROTOCOL APPROVAL

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Cardiac CARE

EudraCT number 2017-000896-99

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

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For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood

Principal Investigator	Signature		Site	Date

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for University of Edinburgh and NHS Lothian
ACEi	Angiotensin Converting Enzyme inhibitor
AE	Adverse Event
AR	Adverse Reaction
ARB	Angiotensin 2 Type I receptor blocker (Candesartan)
B-Blocker	B adrenoceptor blocker (Carvedilol)
CI	Chief Investigator
CRF	Case Report Form
CRIC	Clinical Research Imaging Centre, The University of Edinburgh
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTCAE	Common terminology criteria for adverse events
CTIMP	Clinical Trial of Investigational Medicinal Product
cTnI	Cardiac troponin I
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EudraCT	European Clinical Trials Database
FEC	Fluorouracil, epirubicin, cyclophosphamide chemotherapy
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HER2	Human epidermal growth factor receptor-2
hs-cTnI	Cardiac troponin I concentration quantified using the ARCHITECT$_{STAT}$ high-sensitivity cardiac troponin I assay (Abbott Laboratories, Chicago, IL, USA)
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention To Treat
LVEF %	Left ventricular ejection fraction (expressed as a percentage)
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging
MUGA	Multigated Aquistion
PI	Principal Investigator
NIMP	Non-Investigational Medicinal Product

QA	Quality Assurance
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
URL	Upper Reference Limit

SUMMARY

Title	A multicentre prospective randomised open-label blinded end-point controlled trial of high-sensitivity cardiac troponin I-guided combination angiotensin receptor blockade and beta blocker therapy to prevent cardiac toxicity in breast cancer patients receiving anthracycline adjuvant therapy.
Short Title	Cardiac CARE
Clinical Phase	Phase II/III
Trial Design	Prospective randomised open-label blinded endpoint (PROBE) design.
Planned number of sites	4 sites planned in UK
Background	Adjuvant therapy reduces the risk of relapse and death in patients with breast cancer. Anthracyclines are the most widely used cytotoxic drugs. These medications can cause myocardial injury and heart failure. Concern about the impact of treatment related cardiac toxicity has increased with improved cancer free survival. Cohort studies indicate increasing heart failure prevalence 30 years after cancer treatment with 5% of patients receiving anthracycline developing symptomatic heart failure and up to 10% in those over the age of 64 years. The median time between the last dose of anthracycline and the detection of cardiotoxicity was 3.5 months with 98% of heart failure cases occurring within the first year of follow-up. There is recognised concern that late heart failure events are not captured in clinical trials which concentrate surveillance around the period that the study drug is administered. The progression from heart muscle injury at the time of chemotherapy to development of clinical heart failure is not understood and no preventive treatments are available. Previous studies have used the plasma myocardial injury marker cardiac troponin I (cTnI) to detect early muscle injury before systolic function is impaired. A single blood sample taken 3 months after commencing adjuvant therapy demonstrated 90% negative predictive value for heart muscle failure with a more sensitive cTnI assay. Previous and ongoing clinical trials have investigated whether administration of medications established in the treatment of heart failure can prevent systolic dysfunction in patients receiving chemotherapy. These studies are limited by (i) prescribing therapy to all patients resulting in substantial over-treatment and (ii) using either an angiotensin converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) or B-blocker rather than co-prescription which has the most robust evidence base for improving function and survival in patients with left ventricular systolic dysfunction.
Objectives	**Primary Objective** To determine whether known treatments for heart failure can prevent or reduce myocardial injury and the development of left ventricular systolic dysfunction. **Secondary Objective** To establish whether a novel highly sensitive plasma marker of myocardial injury can anticipate the development and monitor progression of left ventricular systolic dysfunction.

Population	The study will recruit at least 168 patients from several UK regional cancer centres. It is estimated a third of enrolled patients (n= ~56) will develop an elevated plasma cTnI concentration and they will be randomised 1:1 into treatment arm or standard care. **INCLUSION CRITERIA** • Female or male aged ≥18 years • Histological diagnosis of invasive breast cancer • ECOG performance status 0-1 • Planned to commence anthracycline for adjuvant or neo-adjuvant treatment of breast cancer. Patients scheduled for >300 mg/m^2 cumulative dose epirubicin or equivalent. • A life expectancy of at least 12 months • LVEF ≥ 50% on baseline MRI • Systolic blood pressure ≥ 105 mmHg and ≤170 mmHg • An eGFR >45 mL/min/1.73 m^2 • Provide written consent to take part in the study **EXCLUSION CRITERIA** • Pregnancy or breastfeeding • HER2 positive disease with planned trastuzumab therapy • Uncontrolled arterial hypertension defined as systolic blood pressure on treatment of >170 mmHg • Patients already taking B-blockers, ACEi or ARBs • Contra-indication to ARBs (eGFR ≤ 45 mL/min/1.73 m^2, previous hypersensitivity, renal artery stenosis) or B-blockers (asthma, pathological heart block and pathological sinus bradycardia) • Clinically proven intolerance to lactose monohydrate • A history of symptomatic heart failure • Contraindication to or inability to tolerate MRI scanning • Suspected poor drug compliance • Active alcohol or drug abuse • Patients previously treated with anthracyclines or trastuzumab • Uncontrolled concomitant serious illness, as determined by the investigator • Female or male aged <18 years • Not provided written consent to take part in the study • Previously randomised into this trial
Treatment	Candesartan will be started at 8 mg o.d. and increased at 3-day intervals to 16 mg and 32 mg o.d. Carvedilol will be initiated simultaneously at 6.25 mg b.d., and increased to 12.5 mg b.d. and 25 mg b.d. IMP will be dispensed on the day of randomisation and will continue until completion/withdrawal from the study.

Assessments	**Primary Endpoint** Change in LVEF on cardiac MRI scan conducted 6 months after final anthracycline dose compared to baseline cardiac MRI scan conducted before anthracycline therapy starts. **Secondary Endpoints** • Specificity of cTnI assay for left ventricular dysfunction: Post treatment LVEF will be recorded with cardiac MRI in all non-randomised participants and compared to baseline LVEF to define the specificity of the hs-cTnI assay for identifying low-risk participants who do not develop left ventricular systolic dysfunction. • The development of asymptomatic left ventricular dysfunction (a 10 percentage point fall or an LVEF less than 50%). • Resolution of myocardial injury. Whether plasma cTnI concentrations return to the normal reference range (<5 ng/L) at 2, 4 and 6 months after chemotherapy. • Clinical endpoints of death, cardiovascular death and heart failure. Heart failure will be defined by the diagnosis of clinical (symptomatic) heart failure (see below for definition). • Health economics: Confirm the feasibility of data capture and assess the quality of data obtainable in this patient population. Provide information that can inform the design of further research including sample size calculation and/or value of information analysis. • Heart rate and blood pressure at 2, 4 and 6 months following final dose of anthracycline.
Trial Duration	24 months recruitment
Follow up Duration	6 month follow up
Total Planned Duration	Clinical intervention duration : 30 months
IMPs	Candesartan and Carvedilol
IMP Route of Administration	Oral

Lay Summary	Breast cancer is common. The lifetime risk of women developing breast cancer in the UK is 1 in 8. Survival continues to improve. This improved survival is in part down to chemotherapy drugs called anthracyclines. This medication can cause the unwanted side effect of heart muscle injury. Breast cancer survivors have increased rates of heart problems including heart muscle failure. Research questions: We aim to test whether tablet medications called angiotensin receptor blockers (ARB) and B-blockers can prevent heart muscle injury related to chemotherapy. These medications are well established treatments for improving symptoms and survival in patients with heart failure. We will examine a blood test called cardiac troponin I which can detect very slight heart muscle injury. In the trial only patients with increased levels of this marker will be treated with ARB and B-blocker. What will happen to study participants? Breast cancer patients scheduled for anthracycline treatment will be approached to take part. If they give consent they will have a detailed magnetic resonance imaging (MRI) scan of their heart prior to starting chemotherapy. Patients not in the trial would routinely have radionuclide scans to monitor heart function. Patients receiving anthracycline have blood taken routinely 2 to 3 days before each cycle. Cardiac troponin I levels will be measured on these blood samples. Participants who have an elevation in cardiac troponin I will be allocated at random to treatment with a combination of ARB and B-blocker or standard care. What is measured in the study? The main measurement is whether ARB and B-blocker can prevent the decline in heart muscle function measured on MRI. We will follow-up patients to measure health events such as heart failure. The study will show whether a convenient blood test can detect those at risk of heart failure.

1 INTRODUCTION

1.1 BACKGROUND

Nearly 50,000 new cases of breast cancer are diagnosed in the UK each year. Advances in adjuvant systemic therapies have improved disease-free survival considerably. However, when given alone or in combination, these medications cause heart muscle injury.[1,2] Follow up studies of breast cancer survivors demonstrate excessive cardiac events including early and late development of heart failure. Prognosis from heart failure is poor.[3] The progression from heart muscle injury at the time of chemotherapy to development of clinical heart failure is not understood and no preventive treatments are available.

Currently, patients scheduled for only anthracycline therapy will have a radionuclide multigated acquisition (MUGA) scan to measure ejection fraction before chemotherapy starts. This involves an extra hospital visit and requires a radiation dose that can be up to 30 mSv over a treatment course in the subgroup of patients who go onto get additional treatment with trastuzumab. Previous studies have used the plasma myocardial injury marker cardiac troponin I (cTnI) to detect early muscle injury before systolic function is impaired.[4-6] Using a contemporary assay, one study found elevated cTnI concentrations in 94% of patients who developed systolic dysfunction.[4] A single blood sample taken 3 months after commencing adjuvant therapy demonstrated 90% negative predictive value for heart muscle failure with a more sensitive cTnI assay.[6] Previous and ongoing clinical trials have investigated whether administration of medications established in the treatment of heart failure can prevent systolic dysfunction in patients receiving chemotherapy. These studies are limited by (i) prescribing therapy to all patients resulting in substantial over-treatment and (ii) using either an angiotensin converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) or B-blocker rather than co-prescription which has the most robust evidence base for improving function and survival in patients with left ventricular systolic dysfunction.[7]

In this study, we will use surveillance with high-sensitivity cTnI (hs cTnI) blood testing in patients receiving cardiotoxic systemic therapy to identify early muscle injury enabling targeted protective treatment with ARB and B-blocker. Our group has

validated the clinical application of a hs cTnI assay, and demonstrated that this assay doubles the diagnosis of myocardial infarction in women with chest pain by defining a lower gender-specific reference range.[8] Moreover, we have demonstrated that concentrations below the 99th centile of the upper reference limit (URL) also contain important prognostic information and identifies individuals at heightened risk and increased mortality.[9, 10] We believe hs cTnI will improve detection of heart muscle injury compared to previous studies with the more insensitive contemporary assays.[9, 11] Increased concentrations of this plasma marker appear before the development of reduced left ventricular function and heart failure. Patients recruited into the study who exhibit a plasma cTnI concentration above a threshold defined by our cTnI monitoring study will be randomised to receive both carvedilol and candesartan (B-blocker and ARB) or continue with no treatment**.** These treatments have an established role in treatment of patients with left ventricular systolic dysfunction. Together ARB and B-blockade have an additive treatment effect and large effect size that has been demonstrated in patients with heart failure across a broad range of aetiologies including chemotherapy-related heart muscle disease.[3, 7]

1.1.1 Existing Research

Preliminary trials and observational studies indicate that ACEi/ARB and B-blockade prevent the development of heart failure in breast cancer patients receiving anthracycline and trastuzumab chemotherapy. Definitive evidence from a randomised controlled trial is required to determine whether combined ACEi and B-blocker can reduce chemotherapy-related cardiotoxicity in breast cancer patients. Preliminary data indicate that ACEi and angiotensin receptor blockade (ARB) reduce cardiac dysfunction in patients receiving trastuzumab and that efficacy is improved with early treatment.[5, 14] A retrospective evaluation of new symptomatic heart failure in anthracycline treated patients found that incidental B-blocker prescription was associated with reduced heart failure incidence (hazard ratio 0.2: 95% CI 0.1-0.7).[15] The results of the PRADA study were presented in abstract form in November 2015.[16] This study randomized patients receiving anthracycline or trastuzumab to treatment with the ARB, candesartan, and the B-blocker, metoprolol. Patients received ARB or B-blocker alone or in combination and were matched with a placebo group.[17] Candesartan treatment resulted in protection from myocardial dysfunction measured by LVEF on cardiac Magnetic Resonance Imaging (MRI). Overall decline in LVEF was 2.6 percentage points (95% CI 1.5-3.8) in the placebo group and 0.8 (95% CI 0.4-1.9) for candesartan (p = 0.021). A non-significant apparent trend for myocardial protection was seen for metoprolol. The study met its planned recruitment

target of 126 patients and it is notable that the authors chose not to present the full 2 × 2 table of results. The PRADA study shares 3 key weaknesses with other ongoing clinical trials in this area: (i) all patients receiving chemotherapy are randomised to a cardioprotective agent resulting in marked over treatment thereby exposing a large number of patients to unnecessary potential side-effects, (ii) unselected inclusion criteria will also serve to dilute any potential treatment effect by including patients who will derive no benefit; (iii) the study intervention is with either a B-blocker or ACEi/ARB e.g. lisinopril v carvedilol (NCT 01009918), perindopril v bisoprolol (NCT 01016886) or candesartan alone (NCT 00459771) (in PRADA there was a combined treatment group but the number recruited was too small to comment on efficacy compared to either agent alone).

Our research plan will be relevant to NHS breast cancer care pathways, recruiting patients receiving anthracycline and taking a precision medicine approach by targeting cardioprotective treatments only to at-risk patients.

1.1.2 Risks

We will assess candesartan (ARB) and carvedilol (B-blocker) which are widely used within the NHS with an established safety profile and cost-efficacy. No toxicity was reported in the PRADA study which examined ARB and B-blocker combination in an identical study population to ours. ARBs and B-blockers are in widespread use for hypertension, and other serious conditions including heart failure and following myocardial infarction. ARBs are associated with renal dysfunction. Patients in the study randomised to ARB and B-blocker will have renal function and blood pressure monitoring at dose titration clinics. We will follow the dose titration protocol used in the recently published PRADA study which examined the protective effects of candesartan and metoprolol in breast cancer patients. B-blockers may exacerbate psoriasis and asthma. Common side effects include lethargy and cold peripheries. For these reasons we believe that identifying an at-risk population of breast cancer patients to target cardioprotection and closer monitoring is key.

1.1.3 Benefits

Long term follow-up of breast cancer survivors demonstrates increased late cardiac events including symptomatic heart failure.[1, 15, 18, 19] Clinical studies that record cardiac events during the period of chemotherapy therefore underestimate the magnitude of the problem.[19] Improved survival has led to recognition of the late

impact of cardiac disease related to breast cancer therapies and a recent consensus statement from the European Society of Cardiology[19] highlighted the need for improved monitoring and preventive treatment.

Current clinical protocols for cardiotoxicity monitoring are suboptimal aiming to identify cardiac muscle dysfunction after it has become established. Cardiotoxicity is identified by assessment of cardiac function using imaging to measure ejection fraction with echocardiography or radionuclide scans. Patients with reduced ejection fraction have established cardiac injury. Management options at this point include cessation of chemotherapy and drug treatment for established left ventricular systolic dysfunction. A review of 48 cases receiving anthracycline followed by trastuzumab treatment at our institution found that patients received an average of 5 (range 2-14) radionuclide scans. Radionuclide scans are associated with a cumulative radiation dose of 6 mSV per scan. They have a negative impact on the patient journey necessitating extra visits to hospital and are expensive requiring radiotracer, technical staff and image interpretation. By demonstrating that early cardiac injury can be detected with the use of a high-sensitivity cardiac troponin I (cTnI) assay it will be possible in the future to screen out a low-risk population of patients who do not exhibit elevation of this marker during chemotherapy and do not require surveillance imaging.

1.2 RATIONALE FOR STUDY

Our prospective cohort studies including 6304 patients presenting to hospital with suspected acute coronary syndrome and 155 patients with moderate to severe aortic stenosis have confirmed that low cTnI concentrations (< 5 ng/L) are associated with low risk of future cardiac events.[9, 10] In two independent validation cohorts of patients presenting with suspected acute coronary syndrome we demonstrated that cTnI concentrations <5 ng/L had a negative predictive value of 99.4% for myocardial infarction or death at 30 days.[10] We further demonstrated that using the high sensitivity cTnI assay to define a gender specific upper reference limit (99th centile: ≥16 ng/L for women, ≥34 ng/L for men) in patients presenting with chest pain identifies a population of women at increased risk of cardiac events who would be missed with older contemporary cTnI assays.[8] Early data from our monitoring study in anthracycline-treated patients has shown an increase in cTnI concentrations with progressive cycles of treatment with many patients developing circulating concentrations >16 ng/L. Previous studies have reported a 10-15% incidence of **severe** left ventricular dysfunction and heart failure in anthracycline treated patients.

There is a continuum of heart muscle injury and the PRADA study illustrated the potential for cardiac MRI to detect smaller less severe changes in left ventricular function in these patients.[16] In order to capture patients with lesser degrees of cardiac dysfunction we plan to select a cTnI concentration threshold that will result in randomization of at least 33% of patients recruited into the study. Patients with cTnI concentrations above the threshold will be randomized to receive candesartan and carvedilol or to continue with routine clinical care.

Our research will examine the clinical efficacy of ARB and B-blockade in preventing the development of heart muscle failure in breast cancer patients receiving anthracycline-containing chemotherapy. These treatments have an established role in treatment of patients with left ventricular dysfunction. ARB and B-blockade have an additive treatment effect and strong treatment response has been demonstrated in patients with different heart failure aetiologies including chemotherapy related heart muscle disease.[7] Response to ARB and B-blockade includes improved survival, improved symptoms and recovery of left ventricular ejection fraction (LVEF). LVEF is a potent prognostic indicator in heart failure[20, 21] and changes resulting from therapy or disease progression are closely associated with outcomes.[22, 23] All patients will have LVEF monitored with serial cardiac MRI scans. Cardiac MRI is the most precise measure of cardiac function[12,13] and provides additional measures of systolic volume, extracellular volume and cardiac strain that will inform early mechanisms of chemotherapy-induced cardiac muscle injury. We have therefore chosen change in LVEF recorded 6 months following completion of anthracycline chemotherapy as the primary endpoint and surrogate marker of future heart failure events. The hypothesis is that carvedilol and candesartan will prevent development of cardiac dysfunction in at-risk patients identified by elevated plasma cTnI concentrations. Additional outcomes include treatment effect on ongoing cardiac injury (persistence of cTnI elevation), death and heart failure (definition provided in section 2.2), and a provisional health economic analysis of this selective intervention strategy to prevent chemotherapy-related heart failure.

The PRADA study has provided proof of principle that candesartan can protect against LVEF decline in breast cancer patients receiving chemotherapy. The event rate was low in this study with an average LVEF decline of only 2.6 (95% CI 1.5,3.8) percentage points in the placebo group. In this study 60% of patients received low dose anthracycline (FEC 240 mg/m^2). Around 20% of patients also received

trastuzumab and the final MRI scan was conducted variably according to the end of adjuvant therapy: either immediately following 4-5 months treatment of anthracycline or at 15 months following anthracycline and trastuzumab. We will ensure a higher event rate by 1. only approaching patients scheduled for higher anthracycline doses (>300 mg/m^2 cumulative dose epirubicin) and 2. restricting randomisation to high risk patients identified by cTnI elevation.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

The study hypotheses are:

1. All participants at risk of developing heart muscle failure will be detected by elevation of cTnI on serial testing validating the test as a simple screening tool for selecting participants for protective therapy and closer monitoring.
2. The development of heart muscle failure measured by cardiac ejection fraction in breast cancer participants receiving anthracycline will be prevented by carvedilol and candesartan.

2.1.1 Primary Objective

1. To determine whether known treatments for heart failure can prevent or reduce myocardial injury and the development of left ventricular systolic dysfunction.

2.1.2 Secondary Objectives

1. To establish whether a novel highly sensitive plasma marker of myocardial injury can anticipate the development and monitor progression of left ventricular systolic dysfunction.

2.2 ENDPOINTS

All outcome measures will be compared between (randomised) treatment groups except 2.2.2.1.

2.2.1 Primary Endpoint

Change in LVEF on cardiac MRI scan conducted 6 months after final anthracycline dose compared to baseline cardiac MRI scan conducted before anthracycline therapy starts.

2.2.2 Secondary Endpoints

2.2.2.1. Specificity of cTnI assay for left ventricular dysfunction: Post treatment LVEF

will be recorded with cardiac MRI in all non-randomised participants and compared to baseline LVEF to define the specificity of the hs-cTnI assay for identifying low-risk participants who do not develop left ventricular systolic dysfunction.

2.2.2.2. The development of asymptomatic left ventricular dysfunction (a 10 percentage point fall or an LVEF less than 50%).

2.2.2.3. Resolution of myocardial injury. Whether plasma cTnI concentrations return to the normal reference range (<5 ng/L) or baseline concentration if this was >5 ng/L at 2, 4 and 6 months after chemotherapy.

2.2.2.4. Clinical endpoints of death, cardiovascular death and heart failure. Heart failure will be defined by the diagnosis of clinical (symptomatic) heart failure (see below for definition).

2.2.2.5. Health economics for all enrolled patients: Confirm the feasibility of data capture and assess the quality of data obtainable in this participant population. Provide information that can inform the design of further research including sample size calculation and/or value of information analysis.

2.2.2.6. Heart rate and blood pressure at 2, 4 and 6 months following final dose of anthracycline.

2.2.2.7 Clinical endpoints of

- Hypotension: Systolic BP < 90 mmHg
- Bradycardia: HR < 50 bpm
- Hyperkalaemia (K+ ≥ 5.0 mmol/L)
- Worsening renal function: decrease in eGFR of > 25% from baseline or an increase in creatinine of > 30% from baseline
- Acute kidney injury: An eGFR drop to <45 ml/min/1.73m2
- Fatigue grade ≥2 by CTCAE classification
- New diagnosis of Atrial Fibrillation

Definitions for heart failure and hospitalisation due to heart failure

A heart failure hospitalisation is defined as an event that meets ALL of the following criteria:

1. The patient is admitted to the hospital with a primary diagnosis of HF.
2. The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable).
3. The patient exhibits documented new or worsening symptoms due to HF on presentation, including **at least ONE** of the following:
    a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)

b. Decreased exercise tolerance

c. Fatigue

d. Worsened end-organ perfusion (e.g. worsening abdominal or gastrointestinal function manifested by symptoms such as abdominal fullness, abdominal discomfort)

e. Other symptoms of volume overload (e.g. swelling of lower extremities, increase in abdominal girth, increase in body weight).

4. The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** one physical examination finding and **at least ONE** laboratory criterion), including:

a. Physical examination findings considered to be due to heart failure, including new or worsened:

i. Peripheral edema

ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)

iii. Pulmonary rales/crackles/crepitations

iv. Increased jugular venous pressure and/or hepatojugular reflux

v. S3 gallop

vi. Clinically significant or rapid weight gain thought to be related to fluid retention (usually > 3 – 4 pounds in 3-4 days).

b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including new or worsening:

i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT- proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.

ii. Radiological evidence of pulmonary congestion iii. Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT)

minute stroke distance (time velocity integral (TVI))

5. The patient receives initiation or intensification of treatment specifically for HF, including **at least ONE** of the following:

a. Augmentation of oral diuretic therapy

b. Intravenous diuretic, inotrope, vasopressor or vasodilator therapy

c. Mechanical or surgical intervention, including:

i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)

ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

3 STUDY DESIGN

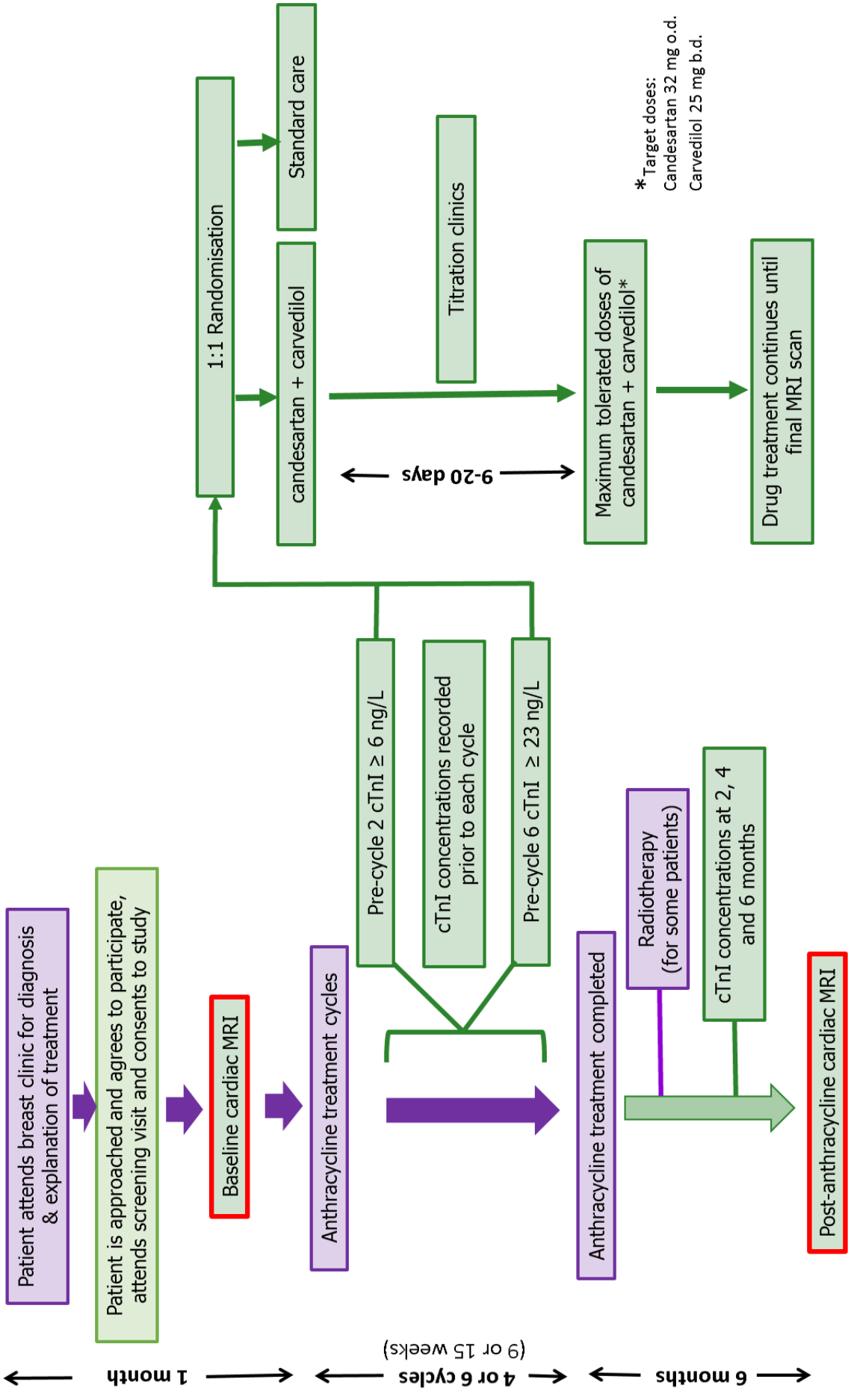
The study will recruit a minimum of 168 participants from several UK regional cancer centres. The study will have a 1:1 randomised group design comparing standard care to standard care plus candesartan and carvedilol treatment in participants who exhibit elevated cTnI concentrations during anthracycline treatment. It will have a prospective randomised open-label blinded endpoint (PROBE) design.

Figure 1 is a schematic of the study flow.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

The total enrolled will be at least 168. It is estimated a third of enrolled participants (n=~ 56) will develop a plasma cTnI concentration above the defined threshold for randomisation, set out in section 5.5.1, and they will be randomised 1:1 into treatment arm or standard care. The estimated 112 participants enrolled who do not develop a plasma cTnI concentration above the defined threshold for each cycle will not be randomised and will continue with standard care. Recruitment is expected to occur over a 2-year period.


Patient attends breast clinic for diagnosis & explanation of treatment
Patient is approached and agrees to participate, attends screening visit and consents to study
Baseline cardiac MRI
Anthracycline treatment cycles
Pre-cycle 2 cTnI ≥ 6 ng/L
cTnI concentrations recorded prior to each cycle
Pre-cycle 6 cTnI ≥ 23 ng/L
Anthracycline treatment completed
Radiotherapy (for some patients)
cTnI concentrations at 2, 4 and 6 months
Post-anthracycline cardiac MRI
1 month
4 or 6 cycles (9 or 15 weeks)
6 months
1:1 Randomisation
Standard care
candesartan + carvedilol
Titration clinics
9-20 days
Maximum tolerated doses of candesartan + carvedilol*
Drug treatment continues until final MRI scan
*Target doses:
Candesartan 32 mg o.d.
Carvedilol 25 mg b.d.

4.2 INCLUSION CRITERIA

- Female or male aged ≥18 years
- Histological diagnosis of invasive breast cancer
- ECOG performance status 0-1
- Planned to commence anthracycline for adjuvant or neo-adjuvant treatment of breast cancer. Patients scheduled for >300 mg/m^2 cumulative dose epirubicin, or equivalent, over 4 or 6 cycles
- A life expectancy of at least 12 months
- LVEF ≥ 50% on baseline MRI
- Systolic blood pressure ≥ 105 mmHg and ≤170 mmHg
- An eGFR >45 mL/min/1.73 m^2
- Provide written consent to take part in the study

4.3 EXCLUSION CRITERIA

- Pregnancy or breastfeeding
- HER2 positive disease with planned trastuzumab therapy
- Uncontrolled arterial hypertension defined as systolic blood pressure on treatment of >170 mmHg
- Patients already taking B-blockers, ACEi or ARBs
- Contra-indication to ARBs (eGFR ≤ 45 mL/min/1.73 m^2, previous hypersensitivity, renal artery stenosis) or B-blockers (asthma, pathological heart block, pathological sinus bradycardia)
- Clinically proven intolerance to lactose monohydrate
- A history of symptomatic heart failure
- Contraindication to or inability to tolerate MRI scanning
- Suspected poor drug compliance
- Active alcohol or drug abuse
- Patients previously treated with anthracyclines or trastuzumab
- Uncontrolled concomitant serious illness, as determined by the investigator
- Female or male aged <18 years
- Not provided written consent to take part in the study
- Previously randomised into this trial

Suspected poor drug compliance and active alcohol or drug abuse will be determined from previous history documented in the potential participant's medical notes.

4.4 CO- ENROLMENT

Participants should not take part in other clinical trials of Investigational Medicinal Products (or devices) until 2 weeks after finishing trial medication and/or final assessments unless agreed otherwise in advance. Proposals for co-enrolment

between CTIMP studies must be captured in a written, authorised agreement between the sponsors and investigators of each study. This will need to be considered even if participants have finished the trial medication of another study but are still technically enrolled in that study for follow-up visits etc. The sponsor guidelines (GL001 Guidelines for Co-enrolment) are available on the ACCORD website.

Participation in other research while taking part in this study is permissible. Co-enrolment will be documented in the CRF.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Patients aged ≥18 years commencing anthracycline for adjuvant or neo-adjuvant treatment of breast cancer will be invited to participate in the study. Anthracycline cardiotoxicity is dose dependent and only patients scheduled for >300 mg/m^2 cumulative dose epirubicin over 4 or 6 cycles will be approached. The sites will record the patients approached on the sponsor subject pre-screening log. All the cancer centres involved in the study have an established clinical trial infrastructure with oncology research nurses who are accustomed to coordinating identification and recruitment of patients attending both within the main and satellite centres.

5.2 CONSENTING PARTICIPANTS

The research study will be explained by the consultant oncologist or research nurse at the treatment planning clinic and the patient will be invited to participate. Patients will be given information on the research study to take away after the diagnosis visit. They will be contacted by telephone at least 24 hours after receiving the information and if they agree to take part they will be invited to a screening visit where the patient will provide consent. Full written consent will be obtained by physicians on the research team, the research nurse or a deputy. If appropriate, the research nurse will book the MRI scan prior to starting anthracycline chemotherapy.

5.3 SCREENING FOR ELIGIBILITY

Participant eligibility will be verified by a clinical trial physician after written informed consent has been obtained. Confirmation of eligibility will be recorded within the participants' medical records.

5.4 INELIGIBLE AND NON-RANDOMISED PARTICIPANTS

There are no particular arrangements for follow up or assessment of ineligible patients or patients that decline to participate.

The estimated 112 enrolled participants who do not exhibit an elevated plasma cTnI concentration above the randomisation threshold will continue with standard care. This means they will receive anthracycline treatment (and radiotherapy, if applicable) together with post treatment cTnI measurements and MRI scanning at 6 months post-treatment.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

After enrolment in the study and the baseline MRI scan, participants will have serial blood tests for cTnI concentration performed prior to each cycle of anthracycline. Participants will have 2 opportunities to be randomized; at cycle 2 and at cycle 6 for those participants receiving 6 cycles of anthracycline. The anthracycline cycle/cTnI concentration thresholds for randomisation are:

Anthracycline cycle 2. ≥ 6 ng/L
Anthracycline cycle 6. ≥ 23 ng/L

Participants who receive only 4 cycles of anthracycline can only be randomized at cycle 2.

The study will have a 1:1 randomised group design comparing standard care to standard care plus candesartan and carvedilol treatment in participants who exhibit elevated cTnI concentrations during anthracycline treatment. Eligible participants will be randomised using a web-based randomisation service hosted by the Edinburgh Clinical Trials Unit (ECTU) to avoid bias. Randomisation will be minimized according to the following binary criteria:

- Age; ≥65 or <65 years
- Baseline LVEF ≥60% or <60%
- cTnI concentration profile criteria for randomisation met by treatment cycle 2 or by cycle 6

Communication of randomisation to the clinical trial team will be web-based.

5.5.2 Treatment Allocation

Following randomisation, both the participant and the Investigator will be notified of the assigned treatment allocation. Participants randomised to the treatment arm will be dispensed the IMPs during the clinic visit and the research nurse will provide dosing instructions.

5.5.3 Emergency Unblinding Procedures

The study has a prospective randomised open-label blinded endpoint (PROBE) design and there will be no requirement for unblinding procedures.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the investigator or responsible clinician. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's case record form. The participant will have the options of (1) allowing us to use the data collected up until the time of withdrawal and allowing us to look at central NHS registers for future record linkage. (2) allowing us to use the data collected up until the time of withdrawal but not allowing for future record linkage. (3) not allowing us to use the data already collected and removing these data from our final analysis.

Withdrawal from study treatment will be distinguished from withdrawal from the study. Participants who are continuing with the study but have stopped taking IMP will be allowed to restart at the discretion of the supervising clinician. Participants can withdraw from some study procedures or study medication but still remain on the trial without a change of status. Participants who have withdrawn from the study (i.e. change of status) will not be permitted to restart the study.

An investigational product(s) can be discontinued under the following circumstances:

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

Participants exhibiting changes in renal function beyond the thresholds described in section 6.3 or an eGFR drop to <45 mL/min/1.73m^2 will have their ARB stopped. Participants unable to reach target dose because of symptomatic hypotension or severe asymptomatic hypotension (systolic BP <90 mmHg) bradycardia (heart rate <50 bpm) will continue in the study on maximal tolerated dose(s).

Study blood samples are not stored after lab testing. All samples will be disposed of by the NHS lab according to standard procedure.

Withdrawn patients will not be replaced.

6 INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification

Several generics exist for both IMPs. Any brand/generic of the IMPs stocked in NHS pharmacy is acceptable. Examples of trade names are given below; this list may not be exhaustive.

Candesartan: Candesartan Ranbaxy, Cilexetil, Blopress, Atacand, and Amias. These are supplied as 2, 4, 8, 16, or 32 mg tablets

Carvedilol: Coreg, Actavis Carvedilol, TEVA Carvedilol, Milpharm Carvedilol. These are supplied as 3.125, 6.25, 12.5, or 25 mg tablets or film-coated tablets.

6.1.2 Study Drug Manufacturer

Not applicable. Any preparation of Candesartan and Carvedilol which has marketing authorisation in the UK and is stocked by local hospital pharmacies at the participating sites, may be employed in this study.

6.1.3 Marketing Authorisation Holder

The NHS pharmacy can dispense any brand of Candesartan or Carvedilol currently in stock.

An example of a Candesartan MA Holder is Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, BN22 9AG and the MA number is PL 00289/1176.

An example of a Carvedilol MA Holder is Teva UK Limited, Brampton Road, Hampden Park, Eastbourne, BN22 9AG and the MA number is PL 00289/0548.

6.1.4 Labelling and Packaging

No specific arrangements are planned for labelling since we will use the licensed medicinal products that are currently available in the UK for both IMPs.

6.1.5 Storage

Storage and dispensing of the IMPs will be undertaken by the local hospital pharmacy department at each participating site. The IMPs will be kept in a secure place at each hospital pharmacy under conditions specified in the local internal procedures but must be stored below 25ºC in a dry place and protected from light.

6.1.6 Summary of Product Characteristics or Investigators Brochure

The NHS does not have a preferred brand or generic Candesartan or Carvedilol. Each hospital pharmacy may stock several brands and these may change over the course of the study. The pharmacy can dispense any brand of Candesartan or Carvedilol currently in stock. A representative Summary of Product Characteristics (SmPC) for each IMP will be given as a separate document.

6.2 PLACEBO

Participants will be randomised to candesartan and carvedilol or standard treatment. There will be no placebo treatment arm.

6.3 DOSING REGIME

Candesartan and carvedilol will be initiated and up-titrated at ≥3-day intervals with a similar protocol to the PRADA study. Participants receiving the study drugs will undergo a maximum of 4 dose up-titration clinic attendances. The up-titration protocol will be supervised by oncology research nurses with support from the oncologist and cardiologist. Participants will have a further blood test for renal function approx. 1 week after the forth dose titration clinic. The clinics will be run by research nurses in the oncology department with the support of a cardiologist and oncologist. Candesartan will be started at 8 mg o.d. and increased at ≥3-day intervals to 16 mg and 32 mg o.d. Carvedilol will be initiated simultaneously at 6.25 mg b.d., and increased to 12.5 mg b.d. and 25 mg b.d. Participants will be monitored for drug effect with blood pressure, pulse and blood testing for renal function. ARB will not be initiated if the serum potassium is >5.0 mmol/L.

Following the introduction of candesartan, eGFR and creatinine will be monitored at each dose titration clinic and compared to values recorded immediately prior to randomisation. A decrease in eGFR of up to 25% from baseline or an increase in creatinine of up to 30% will be accepted. Other causes of renal dysfunction such as dehydration and non-steroidal analgesia prescription will be considered. Participants exhibiting changes in renal function from baseline within these limits will have further dose increases at the clinical team's discretion or remain on established doses. Participants exhibiting changes in renal function beyond these thresholds or an eGFR drop to <45 mL/min/1.73m^2 will have their ARB stopped. Participants unable to reach target dose because of symptomatic hypotension or severe asymptomatic hypotension (systolic BP <90 mmHg) bradycardia (heart rate <50 bpm) will continue in the study on maximal tolerated dose(s).

6.3.1 Cessation of study drugs

Drug treatment will continue until the final MRI scan. If LVEF is normal, the medication will be stopped after the scan has been reported. ARB and B-blocker may be continued at the discretion of the supervising clinician if there is concern with respect to the presence of left ventricular dysfunction.

6.4 PARTICIPANT COMPLIANCE

Randomised participants attending for anthracycline therapy will be asked about study drug compliance. At the end of the study, participants will be encouraged to bring back the used and unused study drug and will be asked about compliance. Participants will be asked to detail drug compliance during the period after randomisation with a diary card to record the number of capsules taken and to indicate any reason for non-compliance. This information will be collected on the CRF and will be used to inform the DMC and TSC, and will be reported in the final study report.

Non-compliance to the protocol study procedures will be documented by the investigator and reported to the sponsor as required in section 14.2. Follow up as per the protocol will be attempted for all non-compliant participants.

6.5 OVERDOSE

6.5.1 Candesartan

No lethality was observed in acute toxicity studies in mice, rats, and dogs given single oral doses of up to 2000 mg/kg of Candesartan cilexetil. In mice given single oral doses of the primary metabolite, Candesartan, the minimum lethal dose was greater than 1000 mg/kg but less than 2000 mg/kg.

The likely manifestation of over dosage with Candesartan would be hypotension, dizziness, and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. If symptomatic hypotension occurs, supportive treatment including intravenous fluid replacement may be instituted as required together with cessation of the drug. Candesartan cannot be removed by hemodialysis.

6.5.2 Carvedilol

Over dosage may cause severe hypotension, bradycardia, cardiogenic shock, and cardiac arrest. Respiratory problems, bronchospasms, vomiting, lapses of consciousness, and generalized seizures may also occur. In the event of overdose

the participant should be placed in a supine position and kept under observation and treated under intensive-care conditions if necessary. The following agents may be administered:

For excessive bradycardia: Atropine, 2 mg IV.
To support cardiovascular function: Glucagon, 5 to 10 mg IV rapidly over 30 seconds, followed by a continuous infusion of 5 mg per hour; sympathomimetics (dobutamine, isoprenaline, adrenaline) at doses according to body weight and effect.
If peripheral vasodilation dominates, it may be necessary to administer adrenaline or noradrenaline with continuous invasive monitoring in a high-dependency environment. For therapy-resistant bradycardia, pacemaker therapy should be performed. For bronchospasm, β-sympathomimetics (as aerosol or IV). In the event of seizures, slow IV injection of diazepam or clonazepam is recommended. In the event of severe intoxication where there are symptoms of shock, treatment with antidotes must be continued for a sufficiently long period of time consistent with the 7 to 10 hour half-life of Carvedilol.

6.6 OTHER MEDICATIONS

6.6.1 Non-Investigational Medicinal Products

This trial will not be using any Non Investigational Medicinal Products (NIMPs). Participants prescribed medication as part of routine care can take or can continue to take during the trial.

6.6.2 Permitted Medications

All other medications apart from those outlined in section 6.6.3 are permitted. All concomitant medications will be documented in the eCRF at the screening visit. B-blockers in the form of eye drops are permitted.

6.6.3 Prohibited Medications

Participants already taking B-blockers, ACEi or ARBs are excluded from the trial. Other types of antihypertensive medication are permitted.

7 STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

Safety assessments will include the monitoring of Adverse Events and Serious Adverse Events by the Investigator. Participants randomised to cardioprotection therapy will have blood pressure and pulse recorded at each dose titration clinic and weekly kidney function testing until one week after the final drug titration.

7.2 STUDY ASSESSMENTS

Pre -Baseline

1. Clinic list reviewed by site staff to identify potential participants
2. Cancer diagnosis in clinic and treatment plan decided by clinical team
3. Potential participants approached and given PIL by oncologist/research nurse. MRI, MUGA and study explained.
4. RN calls patient and if patient wants to participate arranges screening visit in cancer centre

7.2.1 Visit Schedule for participants receiving 6 cycles of anthracycline.

	Screening visit (1)	Screening cardiac MRI (2)	Cycle 1	Cycle 2	IMP titration	Cycle 3	Cycle 4	Cycle 5	Cycle 6	IMP titration	Radiotherapy	2m post-C6 (4)	4m post-C6 (4)	6m post-C6 (4)
Week(*)	-8 to -4	-4	0	3		6	9	12	15			23	32	40
Consent	X													
Demographics	X													
Medical History	X													
Pregnancy test (women only)	X													
Incl/Excl criteria	X													
Conmeds	X													
EQ-5D questionnaire (5)			X				X		X			X	X	X
HE questionnaire (5)							X		X			X	X	X
cardiac MRI		X												X
Routine blood – request cTnI measurement (6)			X	X		X	X	X	X					
Study specific blood sample												X	X	X
Enter cTnI value in DB			X	X		X	X	X	X			X	X	X
Monitor AEs, SAEs (7)			X	X		X	X	X	X			X	X	X
Randomisation (8)				(X)					(X)					
Dispense IMP (9)				(X)		(X)	(X)	(X)	(X)			(X)	(X)	(X)
Titrate IMP (10)					(X)					(X)				
BP, pulse, eGFR, creatinine, potassium at IMP titration visits (11)					(X)					(X)				
BP, pulse, eGFR, creatinine, potassium (12)	X (13)		X	X		X	X	X	X			(X)	(X)	(X)
Drug compliance (14)						(X)	(X)	(X)	(X)			(X)	(X)	(X)

7.2.2 Visit Schedule for participants receiving 4 cycles of anthracycline.

	Screening visit (1)	Screening cardiac MRI (2)	Cycle 1	Cycle 2	IMP titration	Cycle 3	Cycle 4	Post anthracycline sample (3)	Radiotherapy	2m post-C4 (4)	4m post-C4 (4)	6m post-C4 (4)
Week(*)	-8 to -4	-4	0	3		6	9	12		17	26	34
Consent	X											
Demographics	X											
Medical History	X											
Pregnancy test (women only)	X											
Incl/Excl criteria	X											
Conmeds	X											
EQ-5D questionnaire (5)			X				X			X	X	X
HE questionnaire (5)							X			X	X	X
cardiac MRI		X										X
Routine blood – request cTnI measurement (6)			X	X		X	X					
Study specific blood sample								X		X	X	X
Enter cTnI value in DB			X	X		X	X	X		X	X	X
Monitor AEs, SAEs (7)			X	X		X	X	X		X	X	X
Randomisation (8)				(X)								
Dispense IMP (9)				(X)		(X)	(X)	(X)		(X)	(X)	(X)
Titrate IMP (10)					(X)							
BP, pulse, eGFR, creatinine, potassium at IMP titration visits (11)					(X)							
BP, pulse, eGFR, creatinine, potassium (12)	X (13)		X	X		X	X			(X)	(X)	(X)
Drug compliance (14)						(X)	(X)	(X)		(X)	(X)	(X)

(*) The weeks indicated are to be considered as a guide only, the exact time between chemotherapy cycles will be decided by the treating oncology team.

(1) Screening visit and consent - up to one month before MRI

(2) Pre-chemotherapy cardiac MRI - up to 4 weeks before the first dose of anthracycline.

(3) Blood sample scheduled for approximately 3 weeks after the final dose of anthracycline in participants receiving only 4 cycles anthracycline, scheduled to fit with a radiotherapy visit if applicable

(4) Post-anthracycline visits scheduled at 2, 4 and 6 months +/- 2 weeks

(5) EQ-5D5L, quality of life questions and health economics analysis completed during a clinic visit. If absolutely necessary, sites can post questionnaires to participants for completion at home.

(6) Routine bloods are taken up to a week before each cycle. Research team to request addition of hs-cTnI test. cTnI measurement is entered in the eCRF before/during participants chemotherapy visit

(7) Participants will be asked about AEs and SAEs at every visit with a research nurse

(8) A participant is randomised when the cTnI concentration reaches the threshold set for that cycle

(9) Participants randomised to the treatment arm will have IMP dispensed during the chemotherapy visit or as soon as possible afterwards.

(10) IMP titration follows the schedule set out in the protocol and will be administered by the research nurse. Up-titration of IMP will be ≥3-5 days after dispensing and again ≥6-8 days after dispensing.

(11) Any participant randomised to the treatment arm will have renal function tests performed from randomisation until 1 week after the last dose titration. During dose titration renal function will be checked at least once per week.

(12) Measured routinely before every dose of anthracycline chemotherapy. Randomised participants will additionally have renal function measured 2, 4 & 6 months post chemotherapy

(13) BP and pulse only measured, for all participants at screening visit

(14) Only participants randomised to the treatment arm will have drug compliance measured using participants diaries

Case report forms will be completed by the research nurse (or delegate) at each treatment cycle. Participant questionnaires recording NHS resource use and the EuroQoL EQ-5D-5L questionnaire will be administered at 0, 9, 18. 32 and 40 weeks. Participant participation in the study will be completed at the final MRI scan.

7.2.3 Cardiac MRI scan before anthracycline therapy

A baseline cardiac MRI scan (in place of the routine nuclear MUGA scan) will be performed up to 4 weeks prior to commencing adjuvant/neoadjuvant therapy.

7.2.4 Blood samples during anthracycline therapy

Plasma cTnI concentration will be measured on blood taken prior to each anthracycline cycle as part of routine clinical care. Plasma cTnI concentrations will be quantified using the ARCHITECT$_{STAT}$ hs cTn I assay (Abbott Laboratories, Chicago, IL, USA) during each 3 week chemotherapy cycle. Plasma cTnI concentrations will be quantified up to 4 days before each dose (cycle) of anthracycline from the routine

pre-chemotherapy bloods. These may be taken in the regional oncology centre or at the GP surgery. Blood samples will be sent to and analysed in local NHS laboratories according to standard local protocol.

7.2.5 Assessment and follow-up post anthracycline therapy

Additional blood samples for quantification of ongoing myocardial injury will be taken at 3 weeks following chemotherapy in participants receiving only 4 cycles of anthracycline. All participants will with have cTnI concentrations recorded at 2, 4 and 6 months following completion of anthracycline chemotherapy. Blood samples will be taken at the GP surgery or according to participant preference by the oncology research nurse at the regional cancer centre. Blood samples will be sent to and analysed in local NHS laboratories according to standard local protocol. Participants receiving anthracycline will have a cardiac MRI 6 months after the last treatment cycle. The most recent data examining anthracycline-associated cardiomyopathy indicates that this is the period when maximal depression in LVEF is observed.[24] Cardiac MRI and LVEF measurements will be conducted by dedicated research imaging facilities at each site. Results will be immediately available to inform ongoing participant management. LVEF measurements for the primary study endpoint will be conducted by the Image Analysis Core laboratory at the Clinical Research Imaging Centre at the University of Edinburgh. This Core facility has experience of previous cardiac magnetic resonance imaging clinical trials (EMPIRE study[25] and ongoing EME funded MAR3RS study: EudraCT 2012-00244825). Analysts will be independent to the research team and blinded to treatment allocation.

7.2.6 Health Economic Assessment

The health economic analysis aims primarily to identify important drivers of differences in costs and QALYs between standard care and hs cTnI guided cardioprotection. As such the main objectives are to confirm the feasibility of data capture, assess the quality of data obtainable in this patient population and to provide information that can inform the design of further research into the cost-effectiveness of hs cTnI guided cardioprotection. If the data quality allows, consideration will be given to undertaking a cost-effectiveness analysis using a net benefit framework to allow sample size calculation and/or value of information analysis as a tool for further research design.

Health utility (preference based quality of life) will be measured using the EuroQoL EQ-5D-5L questionnaire administered at chemotherapy cycle 1 by a research nurse then approximately every 9 weeks by post or in clinic until study completion (5 times).

The EQ-5D score will define a utility function which by weighting the Kaplan-Meier estimated survival function will generate a QALY estimate for each trial arm over the follow-up period.

The cost analysis will be conducted from an NHS and Personal Social Services perspective with an additional analysis from a societal perspective. Wherever possible the analytical specification will follow that of the NICE Reference Case. Resource utilisation and costs will be captured using a combination of case report forms completed by the research nurse (or delegate) and participants questionnaires posted to the participant or completed in clinic approximately every 9 weeks from baseline on 4 occasions. The questionnaire will be developed from the UK Cancer Costs Questionnaire.[26] Recorded activity will include NHS utilisation within primary and secondary care for the NHS perspective, and additionally patient/carer out-of-pocket expenses for an extended health care sector perspective. In the societal perspective costs arising within the informal health care sector like patient-time costs, unpaid caregiver time costs and transportation costs will be included as well as non-health sector related costs. Lost societal productivity will be measured by recording employment status, return to work, financial burden on carers, welfare support, use of social services and the third sector. Unit costs will be assigned to measured activity using national standard sources such as the NHS Reference costs.

Future long term analysis of secondary care costs at 5 and 10 years will be made possible based on linked Scottish Morbidity Record (SMR01) data for participants resident in Scotland and Hospital Episode Statistics in England. A descriptive breakdown of cost differences between the intervention and control group will be presented for all the different perspectives.

8 DATA COLLECTION

8.1 Data Entry

Research staff at each site will enter data onto an eCRF via a secure, web-based portal. Access will be password protected and limited to nominated staff recorded on the delegation log. Members of staff will be identifiable by a unique username and password. Site staff will be responsible for recording full and accurate data onto the database. Anonymised data only will be recorded on trial paperwork and the eCRF. Designated staff at ECTU will follow ECTU SOPs to obtain missing data and resolve queries with site staff and to ensure data quality and completeness of data across sites.

The trial database is a bespoke, ECTU-developed web-interface. Each component of the interface is built and maintained according to ECTU SOPs. The trial database includes in-built systems to ensure the validity and quality of the data, and to generate queries. Cross validation will be employed and data entry will be single entry. The trial data will be held on a secure server at Edinburgh Clinical Trials Unit (ECTU), protected by network firewall and antivirus software. The database servers and file servers are backed up on a daily basis. LTO (linear tape open) and DLT (digital linear tape) tape backup devices with autoloaders write the data to the backup tapes. Specialist software is used to manage the catalogues and automate the scheduled execution of the data backup processes. Full backups occur over the weekend and incremental backups occur during the week. Backup tapes are stored in data grade fire safes capable of withstanding intense temperatures of fire for over two hours. The integrity of backups is tested with sampled restores of data to alternative non-production locations. Data storage media used in the backup processes is controlled and decommissioned appropriately. Network attached storage devices are also used to store replicated copies of large file stores. These devices are protected by strict firewalls. Data that is stored within databases associated with CTIMP studies will have full audit logs enabled so that a history is maintained of who did what and when.

Physical security - Access to the server room is controlled and is limited to essential personnel only.

Logical security 1 - Access to the web-interface will be via the encrypted Secure Socket Layer protocol. Authorisation will be via a unique username/password combination.

Logical Security 2 - Read-only access to the data repository will be provided to analysts on a named basis for a fixed period of time to allow analyses to be undertaken.

8.2 Data transfer

At time intervals agreed with each site, the MRI imaging will be transferred from each participating centre to the CRIC. Each site will upload pseudo-anonymised scans to a web portal. This approach automatically stores the uploaded scans in a database in a secure and backed-up storage area which can be accessed for analysis in the Image Analysis lab in CRIC.

8.3 Source Data

Data recorded by designated trial staff on the trial specific eCRF will be obtained from the source documents, these include the medical notes, lab results, medical

images and paper questionnaires completed by the subjects. Trial specific paperwork completed during the trial will form Source Data and be kept at site.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

Primary endpoint: A review of LVEF changes (measured by radio-isotope scan) in 48 participants receiving adjuvant chemotherapy at Edinburgh Cancer Centre between 2010 and 2012 demonstrated that 15% sustained at least a 10-percentage point fall after anthracycline treatment and 31% exhibited the same magnitude of ejection fraction fall during trastuzumab treatment. Given the capacity of cardiac MRI to detect smaller changes in LVEF we have assumed that at least 20% of breast cancer participants receiving anthracycline chemotherapy will develop reduced LVEF. We plan to randomize at least 33% of participants using the cTnI concentration threshold defined in the monitoring study. We assume that this threshold will select all participants developing meaningful reductions in LVEF. From these figures we will randomize 23 participants per group to detect a difference of 5-percentage points between groups (standard deviation 5 [27]), at 90% power, p=0.05. A standard deviation of 5 was used in the PRADA study sample size calculation.[17] Allowing for 17% missing data (in line with PRADA[17]) brings this to 28, and a total randomised trial size of 56. 33% of participants in the group initially enrolled are expected to be randomised, so the total enrolled will be at least 168. First secondary endpoint: To assess the specificity of the cTnI assay for left ventricular dysfunction in non-randomised participants, we which to show that there is zero LVEF% change with equivalence limits of ±2%). Using a paired t-test to test for a zero change, using two-sided p=0.05, 90% power and a standard deviation of differences of 5%, we need complete pre and post-anthracycline MRI scans in 68 non-randomised participants.

9.2 PROPOSED ANALYSES

The MRI Imaging from all the sites will be transferred to CRIC for detailed MRI analysis by two cardiac MRI analysts. The image analysts at CRIC will be blinded to treatment allocation and are not involved with scanning or contact with patients. CRIC will provide these data for the study database. The Data Analysis will be conducted independently of data entry. ECTU statisticians will be responsible for the data analysis.

The primary analysis will be change in LVEF on cardiac MRI 6 months following completion of anthracycline between randomized treatment groups, using linear regression, adjusted for the age and baseline LVEF. This will be an intention-to-treat, and treatment effect will be expressed by a point estimate and its 95% confidence interval. We will keep missing values to a minimum, and the primary analysis will be a complete case analysis. If there are sufficient missing data to cause concern, multiple imputation will be used as a sensitivity analysis.

The specificity of the cTnI assay for left ventricular dysfunction in non-randomised participants will be assessed by calculating the mean of the within-person changes between participants' pre and post-anthracycline MRI scans, plus its 95% confidence interval. This confidence interval will be compared to the equivalence limits of ±2%. Specificity will be evaluated by the data monitoring committee who will advise whether conducting post-anthracycline cardiac MRI scans on remaining non-randomised participants in the study will be necessary.

Other secondary outcomes will be analysed appropriately – linear regression for continuous outcomes, logistic regression for binary outcomes, and Cox proportional hazards for survival analysis, adjusted as for the primary analysis. A full Statistical Analysis Plan will be finalized before database lock.

10 PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below. Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SmPC). The SmPCs will be filed as a separate document.

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after informed consent until the participant has completed the study at MRI scan 6 months post anthracycline treatment, or until the subject withdraws, must be recorded in the Case Report Form (CRF) or AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

10.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- 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.

*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.

^Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be caused by the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SmPC) or Investigators Brochure.

10.2 IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs/SAEs at every visit with a research nurse during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded. AEs and SAEs may also be identified via information from support departments e.g. laboratories.

10.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

10.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study

10.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

Trial participants will undergo several cycles of anthracycline and may also have radiotherapy. Therefore over the course of the trial we expect the participants to have many side effects related to their cancer treatment. These will be recorded routinely for all participants by RNs in their medical notes and classified using the CTCAE v4.1. The sites will not record/report any of these events as AEs. Examples of common side effects include nausea, vomiting, diarrhea and neutropenia.

The sites will only record symptoms of interest that could be considered an AR to the study intervention. We will only record the following symptoms of interest on an AE form.

- Angioedema
- Dizziness and syncope
- Dyspnoea- (not meeting criteria for new or worsening heart failure)
- Nasopharyngitis

Other potential AR will be recorded in the eCRF and are listed as endpoints in section 2.2.2.7.

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any cardiac symptoms develop. If there is any doubt as to whether a clinical observation is an AE of special interest, the site staff can discuss with the CI, or designee, if the event is to be recorded.

If results that would be abnormal for a chemotherapy patient are recorded or the participant reports any cardiac symptoms the site staff should report this to the PI. At sites where the PI is an oncologist, these results should also be reported to the study site cardiologist (sub-Investigator).

In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

10.4 ASSESSMENT OF AEs AND SAEs

Seriousness, causality, severity and expectedness will be assessed by the Principal Investigator. Cases that are considered serious, possibly, probably or definitely related to IMP and unexpected will be reported as SUSARs.

The Investigator is responsible for assessing each AE, although at some sites this may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting AEs.

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

10.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

10.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.
- 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 drug. The assessment of causality will be made against the reference safety information found in section 4 of the Summary of Product Characteristics

Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated.

10.4.3 Assessment of Expectedness

If an event is judged to be an AR, the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SmPC.

The event may be classed as either:

Expected: the AR is consistent with the toxicity of the IMP listed in the SmPC.

Unexpected: the AR is not consistent with the toxicity in the SmPC.

10.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE according to the CTCAE v4.1 classification and record this on the CRF or 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.

10.5 REPORTING OF AEs TO THE SPONSOR

All adverse events for each participant will be recorded on the AE log and will be assigned the appropriate MedDRA Systems Organ Class (SOC) code.

10.6 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE 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 SAE, they should not wait for this additional information before notifying ACCORD. The SAE report can be updated when the additional information is received.

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

Details of the SAE will be entered into the study database by site staff. The Investigator will sign the SAE form by logging into the study database using the Investigators login ID and password. This information will populate the ACCORD SAE report template which is submitted via email to Safety.Accord@ed.ac.uk. If the study database fails to automatically email the SAE form to the sponsor the site can transmit it by fax to ACCORD on **+44 (0)131 242 9447** or by hand to the office or submit via email to Safety.Accord@ed.ac.uk. Only forms in a pdf format will be accepted by ACCORD via email. All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF). 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.

10.6.1 Events That Do Not Require Reporting on a SAE Form

Participants receiving chemotherapy may require admission to hospital for appropriate medical intervention following development of some of the more severe known side effects of treatment. These events are not regarded as unexpected for the purpose of this trial, they will be recorded in the study database (and will therefore be available for the DMC), but will not be reported to the sponsor as SAEs.

- Hospitalisations for:
    - Protocol defined treatment (e.g. planned anthracycline treatment)
    - Pre-planned elective procedures unless the condition worsens
    - Treatment for progression of the participant's breast cancer

- Admissions for supportive treatment during an episode of febrile neutropenia, unless this proves fatal or requires admission to a high dependency or intensive care facility
- Admissions to control symptoms of vomiting unless the condition is life threatening or proves fatal

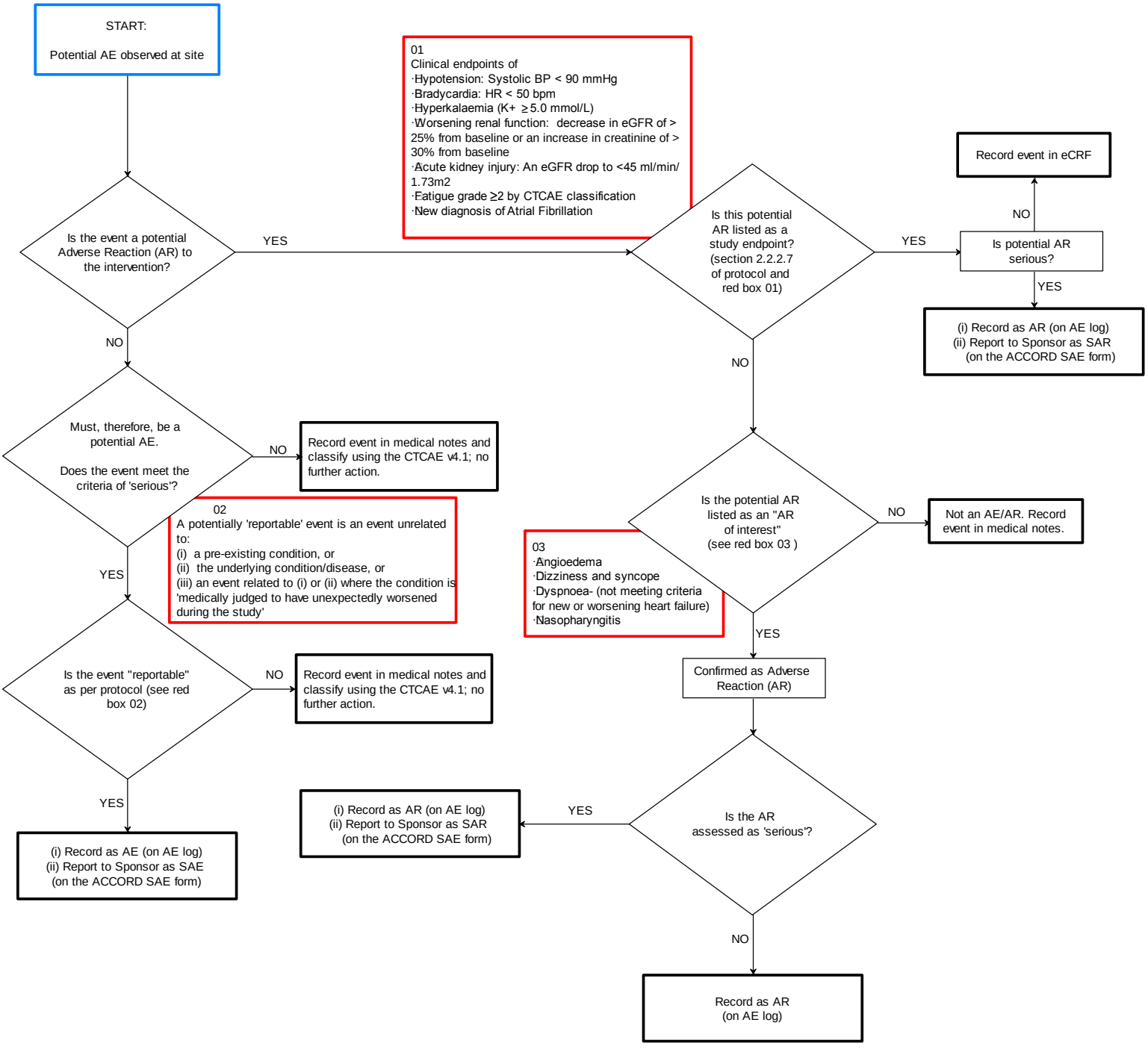


Figure 2 is a flow chart summarising AE, AR and SAE reporting.

10.7 REGULATORY REPORTING REQUIREMENTS

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

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

10.8 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator will follow each participant until resolution or death of the participant. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

10.9 PREGNANCY

Pregnant patients are excluded from this study. Pregnancy is not considered an AE or SAE; however, the Investigator will collect pregnancy information for any female participants while participating in the study. Study participants becoming pregnant during the study have be withdrawn and have their cardioprotection medication stopped. The Investigator will record the information on a Pregnancy Notification Form within the study database. On completion this form will be submitted from the database to the ACCORD office within 14 days of being made aware of the pregnancy.

All pregnant participants will be followed up until following the outcome of the pregnancy.

11 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a project management group consisting of the chief investigator, lead research staff from selected sites, a patient representative, trial research nurses, trial manager and data manager.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

11.2 TRIAL STEERING COMMITTEE

A trial steering committee (TSC) will be established to oversee the conduct and progress of the trial. The TSC will consist of an independent cardiologist, oncologist, statistician and public representative together with members of the project management group.

The terms of reference of the TSC, the draft template for reporting and the names and contact details are detailed in Appendix 2.

11.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of subjects in the trial. This will include an independent statistician, oncologist, and cardiologist.

The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in Appendix 3.

11.4 PATIENT ADVISORY GROUP

Patients and public representatives have been engaged from the start and several design features are a direct response to patient recommendations. The trial will be supported at a national level through the PPI committee of the NIHR Diagnostic Evaluation Cooperative and also through the national patient advocacy charity Independent Cancer Patient's Voice (ICPV) via our representative Elspeth Banks. Both organisations have provided review of the study.

We will convene a Patient Advisory Group to support the trial and ensure a broader range of patient views is incorporated. This will include 6-8 people affected by cancer, based in Edinburgh, and will be facilitated by the trial manager. Members will be identified from our existing contacts with patient groups and from breast cancer charities.

We envisage four meetings between the patient advisory group and the research team at key strategic points where patient advice can be particularly valuable:

- Set-up: advice on study materials, including patient information leaflets, consent forms, lay summaries. At this stage, we will also draw on local patient expertise in writing in Plain English from a member of the Patient Advisory Group at the Edinburgh Clinical Research Facility
- Recruitment: advice on optimizing recruitment and retention
- Initial findings: sharing initial analysis of study findings to ensure the patient perspective is included in our interpretation of results, particularly in relation to patient benefit
- Dissemination and public engagement: we will work with the Patient Advisory Group to determine the best methods to engage the public with our findings.

In addition, we may ask the group for advice if the need arises during the trial. The research team, including patient advisors and researchers, will undergo bespoke training on effective patient involvement in research in collaboration with Dr Allison Worth, Patient and Public Involvement Advisor for the Edinburgh Wellcome Trust Clinical Research Facility. This will establish understanding of the trial and the roles, responsibilities and mechanisms of working of all involved.

Our lead patient representative and co-applicant is Abigail Marks (AM).

11.5 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an 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.

11.6 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, 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. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

11.7 STUDY MONITORING AND AUDIT

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).

12 GOOD CLINICAL PRACTICE

12.1 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 required approvals will be obtained and any conditions of approvals will be met.

12.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

12.3 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. In accordance with the principles of ICH GCP, the following areas listed in this section are also the

responsibility of the Investigator. 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.

12.3.1 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 trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

12.3.2 Study Site Staff

The Investigator must be familiar with the IMP, 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 IMP, protocol and their trial related duties.

12.3.3 Data Recording

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

12.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.

ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs. Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

12.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

12.3.6 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. Identifiable 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 identifiable data, record, or other unpublished, confidential information 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 identifiable information to other parties. Any sharing of anonymised data at the end of the study will follow ECTU's procedures

12.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage,

processing and disclosure of personal information and will uphold the Act's core principles.

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

Published results will not contain any personal data and will be of a form where it does not identify individuals and re-identification is not likely to take place.

13 STUDY CONDUCT RESPONSIBILITIES

13.1 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 and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

13.2 PROTOCOL NON COMPLIANCE

13.2.1 Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

13.2.2 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, Regulatory Authority and local R&D for review and approval if appropriate.

13.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log within the eCRF and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.

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 sent by fax to ACCORD on +44 (0)131 242 9447 or may 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.

Drug discontinuation will be collected as a protocol deviation, and will include cause of discontinuation: whether related to adverse events of interest or participant preference.

13.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

13.4 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 trial; or

(b) the scientific value of the trial.

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

13.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. The CI and Local PIs are responsible for the secure archiving of trial site documents and database as per their trust policy.

When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

13.6 END OF STUDY

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

The Investigators and/or the trial steering committee and/or the co-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, Regulatory Authority, R&D Office(s) and co-sponsors 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 co-sponsors via email to researchgovernance@ed.ac.uk.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study.

Upon completion of the study, the Investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

The Investigator will submit a short confirmatory e-mail to the MHRA (CT.Submission@mhra.gsi.gov.uk) once the result-related information has been uploaded to EudraCT, with 'End of trial: result-related information: EudraCT XXXX-XXXXXX-XX' as the subject line. The Sponsor(s) will be copied in this e-mail (QA@accord.scot). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

13.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Drug treatment will continue until the final MRI scan. If LVEF is normal the medication will be stopped after the scan has been reported. ARB and B-blocker may be continued at the discretion of the supervising clinician if there is concern with respect to the presence of left ventricular dysfunction.

13.8 INSURANCE AND INDEMNITY

The co-sponsors 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 co-sponsors' 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 co-sponsors 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 Nation Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines. The trial

management group will decide the appropriate authorship for each publication or presentation.

14.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

All proposed publications and presentations must be discussed with the-CI and sent to ECTU prior to their release. Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion). At the end of the trial a general summary of the results will be made available for the public and will be accessible on the Edinburgh Clinical Trials Unit website (http://edin.ac/cardiac-care-trial).

14.3 REPRODUCIBLE RESEARCH AND DATA SHARING

Following publication of the primary paper, a de-identified individual participant data set will be submitted to data archiving for sharing purposes. Access to the de-identified dataset will be under a controlled access model in line with ECTU policies at that time.

14.4 PEER REVIEW

This study has been extensively peer reviewed by NIHR EME.

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APPENDIX 1: Summary of Product Characteristics

The NHS does not have a preferred brand or generic Candesartan or Carvedilol. Each hospital pharmacy may stock several brands and these may change over the course of the study. The pharmacy can dispense any brand of Candesartan or Carvedilol currently in stock.

A representative SPC for both Candesartan and Carvedilol will be contained in a SPC booklet which is maintained as a separate document.

The booklet containing a copy of the current version of a representative SPC for Candesartan and for Carvedilol have been uploaded with the REC application and hard copies will be placed in the Investigator site file. These will be updated as necessary during the trial to accommodate any changes that occur in the SPC.

APPENDIX 2: Trial Steering Committee

Responsibility for calling and organising the trial steering committee meeting will lie with the Chief Investigator Dr Peter Henriksen. At least one meeting will be conducted by milestone 4 (recruitment of at least one patient). The terms of reference of the TSC and the list of TSC members are detailed in the Cardiac CARE TSC charter which is filed in the TMF.

APPENDIX 3: Data Monitoring Committee

The terms of reference of the DMC are and the list of DMC members are detailed in the Cardiac CARE DMC charter which is filed in the TMF.

APPENDIX 4: Project timetable and milestones

The study will run for 43 months and the start date is 1st April 2017. Following a set up period of 5 months we will enter a 24 month recruitment period followed by 10 months to complete anthracycline treatment and follow-up MRI scans and a 4 month close down period.

Project milestones

Milestone 1: 1st December 2016– Completion of the analysis of ongoing observational cTnI monitoring study. This has been conducted in patients receiving breast cancer treatment in Edinburgh and Glasgow who would have been eligible for our proposed study. Data from this ongoing pilot study will be evaluated and used to confirm the cTnI threshold for randomisation.

Milestone 2: 1st April 2017 – **start date of project**. It is anticipated that completion of regulatory approvals for all sites may take up to 5 months

Milestone 3: 1st September 2017- patient recruitment begins

Milestone 4: 1st February 2018- recruitment of at least one patient.

Milestone 5: 1st April 2018- recruitment of at least one patient from all (3 sites).

Milestone 6: 1st September 2019 – Recruitment ends and at least 56 patient randomised

Milestone 7: 1st July 2020- final cardiac MRI scan

Milestone 8: 1st November 2020- Study close down and data presentation