

## PROTOCOL

- Full Title:** Preventing cardiac damage in patients treated for breast cancer: a phase 3 Randomised, Open label, blinded endpoint, superiority trial of enalapril to prevent Anthracycline-induced CardioToxicity (PROACT).
- Short Title:** Preventing Cardiotoxicity in Breast Cancer Patients: PROACT
- Lay Title:** PROACT: Can we prevent chemotherapy-related heart damage in patients with breast cancer?
- Trial Identifiers:** ClinTrials.gov: NCT03265574  
EudraCT: 2017-001094-16  
IRAS ID: 213348
- Protocol version:** 1.3, dated 27<sup>th</sup> September 2017
- Funder:** **National Institute of Health Research** – Research for Patient Benefit Programme (project reference PB-PG-0815-20061)
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**Dr Helen Hancock/Rebecca Maier, NCTU co-Investigators**

Signature \_\_\_\_\_ Date: \_\_\_\_\_

**Dr Adetayo Kasim, Trial statistician, Durham University**

### 1.2. Principal Investigator Signature

By signing this protocol page, I confirm I have read and agree to:

- Conduct the trial in accordance with the protocol, and the principles of GCP and the appropriate regulations
- Personally conduct and supervise the trial and ensure that all colleagues assisting with the trial are appropriately delegated and are informed about their obligations
- Ensure that the requirements with regard to obtaining informed consent are adhered to without exception
- Report all AEs and SAEs that occur during the course of the trial, in accordance with the protocol
- Maintain accurate and complete records to enable confirmation of adherence to the protocol

Principal Investigator's Name:

Principal Investigator's Signature:

Date:

Site name and identifier:

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**APPENDIX 1: FURTHER SAFETY INFORMATION**

**APPENDIX 2: AJCC Breast TNM Staging: The 8<sup>th</sup> Edition**

### 3. Protocol Synopsis

<b>Short Trial Title:</b>	Preventing Cardiotoxicity in Breast Cancer Patients: PROACT
<b>Protocol version and date:</b>	Version: 1.3 Date: 27 <sup>th</sup> September 2017
<b>Chief Investigator:</b>	Dr David Austin
<b>Sponsor:</b>	South Tees Hospitals NHS Foundation Trust
<b>Funder:</b>	National Institute of Health Research – Research for Patient Benefit Programme (project reference PB-PG-0815-20061)
<b>Trial Design:</b>	A multi-centre, prospective, randomised, open-label, blinded end-point, superiority trial.
<b>Trial intervention:</b>	Intervention: standard care plus enalapril maleate tablets given to a maximum of 10mg BD prior to and throughout epirubicin-based adjuvant chemotherapy.  Control: standard care
<b>Trial Participants:</b>	Adult patients, due to receive 6 cycles of epirubicin-based adjuvant chemotherapy (total planned dose of epirubicin must be >300mg/m <sup>2</sup> ) for their breast cancer.
<b>Sample Size:</b>	170 patients in total. 85 patients per arm; 85 will receive enalapril.
<b>Inclusion Criteria:</b>	<ul style="list-style-type: none"><li>• Adult patients with histopathologically* confirmed breast carcinoma who have received surgery for their breast cancer;</li><li>• planned to receive a 6 cycle adjuvant chemotherapy regimen containing &gt;300mg/m<sup>2</sup> of epirubicin;</li><li>• written informed consent.</li></ul> <p><i>*Patients with HER2+ breast cancer are eligible for inclusion.</i></p>
<b>Exclusion Criteria:</b>	<ul style="list-style-type: none"><li>• Positive baseline cardiac troponin T;</li><li>• known contraindication to ACE inhibitor e.g. renal artery stenosis, severe aortic stenosis;</li><li>• are taking, or have a previous intolerance to ACEI (e.g. angioedema);</li><li>• patient already taking agents acting on the renin-angiotensin-aldosterone system e.g. Aliskiren, angiotensin receptor blockers (ARBs), Entresto (sacubitril/valsartan), spironolactone, eplerenone;</li></ul>

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- LVEF <50%;
  - estimated GFR < 30 mL/min/1.73m<sup>2</sup> at baseline;
  - hyperkalaemia defined as serum potassium ≥5.5mmol/L;
  - symptomatic hypotension, or Systolic Blood Pressure <100mmHg;
  - poorly controlled hypertension (Blood Pressure >160/100mmHg, or ambulatory BP of 150/95mmHg);
  - previous myocardial infarction;
  - known metastatic breast cancer;
  - previous exposure to anthracycline chemotherapy;
  - are pregnant or breastfeeding;
  - for patients of childbearing potential only: refusal to use adequate contraception throughout the trial;
  - Previous Herceptin treatment or planned Herceptin treatment within four weeks following anthracycline chemotherapy;
  - any other cancer diagnosis;
  - participation in other interventional medicinal trials in the past 6 months;
  - judgment by the Investigator that the patient should not participate in the study.

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**Primary Objective:** To establish the effectiveness of the angiotensin-converting enzyme inhibitor (ACEI) enalapril maleate (enalapril) in preventing cardiotoxicity in patients with breast cancer undergoing adjuvant epirubicin-based chemotherapy.

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**Primary Outcome:** The primary outcome of PROACT is the presence or absence of cardiac troponin T release at any time during epirubicin treatment, and one month after the last dose of epirubicin.

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**Secondary Outcomes:** Secondary outcomes will focus on the effectiveness of enalapril in preventing cardiotoxicity. These include important measures of cardiac function which relate directly to patient outcomes:

- cardiac function assessed by echocardiogram, including global longitudinal strain (GLS), and measurements of left ventricular ejection fraction (LVEF), at baseline and following completion of anthracycline chemotherapy;
- cardiac troponin I release at any time during adjuvant chemotherapy and one month after the last dose of

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epirubicin;

- adherence to enalapril;
- side effects of enalapril;
- adverse events;
- any anxiety or distress related to trial participation.

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**Interventions**

**Intervention arm:**

All patients will receive standard care (adjuvant anthracycline-based chemotherapy).

Patients randomised to the intervention will begin enalapril at 2.5mg BD, which will then be titrated to a maximum of 10mg BD or their highest tolerated dose below 10mg BD. Patients will receive enalapril for at least 5 days prior to starting chemotherapy; chemotherapy will not be delayed by taking part in the trial. Enalapril will be continued during chemotherapy and stopped three weeks following the last epirubicin dose.

**Comparator arm:**

The comparator in this trial is standard care. All patients will receive standard care (adjuvant anthracycline-based chemotherapy).

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**Trial Period:**

The trial is anticipated to take 30 months, with recruitment expected to end during month 20.

Individual patients will be in the trial for up to 7 months following consent.

For the purposes of notification, the end of the trial is defined as the last visit for the last patient.

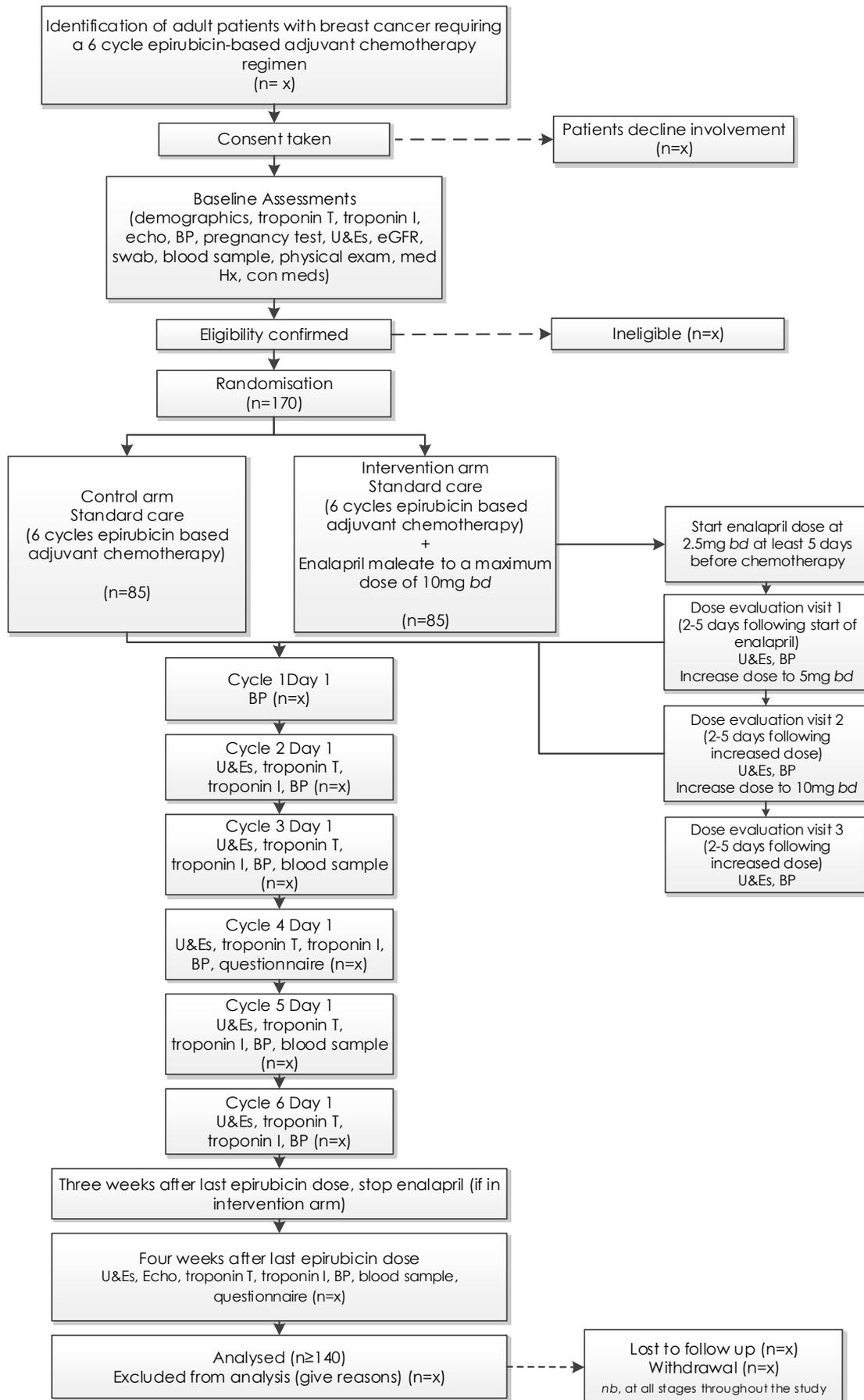
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**Trial Centres:**

NHS Trusts in the North of England:

- South Tees Hospitals NHS Foundation Trust
  - North Tees and Hartlepool NHS Foundation Trust
  - Newcastle-upon-Tyne Hospitals NHS Foundation Trust
  - Leeds Teaching Hospitals NHS Trust
  - County Durham and Darlington NHS Foundation Trust
-

#### 4. Trial Flow Diagram



## 5. Glossary of Abbreviations

<b>ACEI</b>	Angiotensin-converting enzyme inhibitors
<b>AE</b>	Adverse Event
<b>AR</b>	Adverse Reaction
<b>ARB</b>	Angiotensin Receptor Blocker
<b>CI</b>	Chief Investigator
<b>eCRF</b>	electronic Case Report Form
<b>eGFR</b>	estimated Glomerular Filtration Rate
<b>GCP</b>	Good Clinical Practice
<b>GLS</b>	Global Longitudinal Strain
<b>GP</b>	General Practitioner
<b>HRA</b>	Health Research Authority
<b>ICF</b>	Informed Consent Form
<b>IDMEC</b>	Independent Data Monitoring and Ethics Committee
<b>IG</b>	Information Governance
<b>IMP</b>	Investigational Medicinal Product
<b>IP</b>	Intellectual Property
<b>ISF</b>	Investigator Site File
<b>LVEF</b>	Left Ventricular Ejection Fraction
<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency
<b>MTD</b>	Maximum tolerated dose
<b>NCTU</b>	Newcastle Clinical Trials Unit
<b>NHS</b>	National Health Service
<b>NIHR</b>	National Institute for Health Research
<b>NUH</b>	Nottingham University Hospitals NHS Trust
<b>PI</b>	Principal Investigator
<b>PIS</b>	Patient Information Sheet
<b>R&amp;D</b>	NHS Trust Research and Development Department
<b>REC</b>	Research Ethics Committee
<b>RSI</b>	Reference Safety Information
<b>SAE</b>	Serious Adverse Event
<b>SmPC</b>	Summary of Product Characteristics
<b>SOP</b>	Standard Operating Procedure
<b>SUSAR</b>	Suspected Unexpected Serious Adverse Reaction
<b>TMG</b>	Trial Management Group
<b>TSC</b>	Trial Steering Committee
<b>TTE</b>	Transthoracic Echocardiogram

## 6. Trial Responsibilities:

**Sponsor:** South Tees Hospitals NHS Foundation Trust will act as the sponsor for this trial.

**Funder:** National Institute of Health Research – Research for Patient Benefit Programme (project reference PB-PG-0815-20061)

**Chief Investigator:** This is a multi-centre trial and Dr David Austin, Chief Investigator, will have overall responsibility for all aspects of the trial, including:

- Approvals and notifications as required for the trial
- Trial conduct in accordance with GCP
- Pharmacovigilance
- Management of the overall trial budget

**Trial Management:** A Trial Management Group (TMG) will be responsible for overseeing the progress of the trial. Operational aspects including day-to-day management of the trial will be co-ordinated by Newcastle Clinical Trials Unit (NCTU) in support of the Chief Investigator and his responsibilities.

### Principal Investigators:

This is a multi-centre trial involving Cardiologists and Oncologists. Each centre will have a lead Cardiologist and a lead Oncologist, one of whom will be Principal Investigator at their centre. Each Principal Investigator will have overall responsibility for the trial at their centre. All Principal Investigators shall be qualified by education, training and experience to assume responsibility for trial conduct, and will provide a current signed & dated curriculum vitae as evidence. Their responsibilities are:

- Trial conduct and the welfare of trial subjects at all times.
- Familiarity with the use of enalapril maleate (the investigational medicinal product), and its appropriate storage, administration and accountability in accordance with this protocol. Ensuring that the trial drug, enalapril, is not used for any purpose other than those specified in the protocol.
- Compliance with the protocol, and reporting requirements including adverse event reporting.
- Identification, consent, recruitment and treatment of subjects.
- Ensuring all trial-related medical decisions are made by the Principal Investigator or a delegated sub-investigator for the trial, who must be a qualified medical doctor.
- Ensuring that all approvals are in place locally, prior to the start of the trial at the centre.
- Compliance with the principles of GCP, the national legislation implementing the EU Clinical Trials Directive (2001/20/EC) and subsequent amendments, and the research governance requirements for conducting the trial within the NHS.

- Ensuring delegated trial site team members are appropriately qualified by education, training and experience to undertake their duties within the conduct of the trial.
- Availability for meetings, monitoring visits and any audit or inspection.
- Maintaining appropriate trial documentation.
- Maintaining a site file, including copies of trial approval, list of subjects and their signed informed consent forms.
- Documenting the appropriate delegation of tasks to all trial site team members.
- Ensuring data collected are accurate, timely & complete.
- Providing updates and data on the progress of the trial.
- Ensuring confidentiality is maintained during the project and archival period.
- Ensuring trial documentation is securely archived for a minimum of 15 years following the end of the trial.

## 7. Introduction

### 7.1. Background

Breast cancer is the most common malignancy among women worldwide, with over 50,000 new UK cases every year.<sup>1,2</sup> Treatment commonly includes surgery, anthracycline-based chemotherapy and radiotherapy, and is highly effective. However, anthracyclines can cause immediate, irreversible, damage to cardiac cells and, ultimately, impaired cardiac function and heart failure.<sup>3</sup>

Anthracyclines, including epirubicin, are administered in an outpatient setting and are usually well tolerated. However, they have a dose-dependent toxic effect on the heart<sup>4,5</sup> which can result in heart failure often only evident years after exposure. The long-term incidence is approximately 5%; this may be higher in older patients.<sup>4,6,7</sup> Asymptomatic left ventricular systolic dysfunction (LVSD) is more common, evident in 9.7% of patients with breast cancer within 12 months.<sup>8</sup> LVSD affects cardiac prognosis and limits subsequent cancer treatment options, particularly those that target the HER2 pathway such as trastuzumab (Herceptin).<sup>8,9</sup> Waiting until anthracycline-induced heart failure becomes clinically evident is ill-advised. Response to treatment is poor and survival at 2 years is 40%; considerably worse than other causes of heart failure and for breast cancer itself.<sup>10</sup>

The burden of cardiotoxicity is particularly important in a patient group in whom 78% will be alive 10-years following their cancer diagnosis.<sup>1,11</sup> Preventing cardiac damage would offer clear benefits to patients and substantial costs savings to the NHS.

### 7.2. Mechanism and identification of cardiotoxicity

Anthracyclines cause cardiotoxicity through the generation of reactive oxygen species resulting in cardiac cell death; these are highly toxic to proteins, lipids and DNA, to which the heart is particularly vulnerable.<sup>12,13</sup> The extent and consequence of cardiac cell death varies between individuals on the basis of anthracycline dose, age, gender, and pre-existing cardiovascular disease.<sup>3,12,13</sup>

Anthracycline-induced cardiotoxicity is irreversible; the initial insult triggers a pathway characterised by cardiac cell death and reduced cardiac contractility, before deterioration in LV systolic function and heart failure.<sup>12</sup> The early process of cardiac cell death is identified by the presence of the highly sensitive and specific blood marker cardiac troponin (T or I).<sup>14-17</sup> The absence of troponin effectively excludes cardiotoxicity.<sup>14</sup>

Detection of cardiotoxicity through serial monitoring of left ventricular ejection fraction (LVEF) can allow initiation of treatment with angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers.<sup>8</sup> However, this is resource intensive and limited by the conventional, but relatively insensitive and observer dependent, LVEF measurement.<sup>18</sup> There is no guidance for cardiac monitoring and treatment of patients receiving anthracyclines.<sup>3</sup> Once LVEF declines, treatment offers limited efficacy and functional recovery is uncommon.<sup>3,8,10,19</sup>

Earlier changes in cardiac function are detectable by the advanced echocardiographic techniques to measure global longitudinal strain (GLS).<sup>12</sup> GLS is more reliable, reproducible, and sensitive in

detecting functional changes than LVEF.<sup>12,20</sup> A recent systematic review identified early changes in GLS as superior to LVEF in quantifying cardiotoxicity at the patient level.<sup>21</sup>

### 7.3. Rationale for the evaluation of enalapril as preventative therapy

ACEI are of proven benefit in cardiovascular medicine, and are widely used. In primary care, they are a first line therapy for hypertension.<sup>22</sup> ACEI are well-tolerated and inexpensive; enalapril is the reference standard ACEI and has been extensively studied.<sup>23</sup> The cost is £2/patient per month.<sup>24</sup>

ACEI promote nitric oxide, and inhibit the production of angiotensin II which in turn reduces NAD(P)H oxidase responsible for superoxide formation.<sup>25</sup> Through these mechanisms, ACEI reduce the production of reactive oxygen species, thought to be responsible for anthracycline toxicity.<sup>25,26</sup> ACEI and angiotensin inhibition are protective of apoptosis in vascular endothelium and cardiac cells, prevent anthracycline cardiotoxicity in animal models and reduce oxidative stress.<sup>27-31</sup>

An Italian study assessed enalapril treatment in patients with a positive troponin during chemotherapy; not all were anthracycline-based regimens. By the second month, 41% of patients in the control group (n=58) had persistent troponin elevation, compared to 4% in the enalapril group (n=56). Based on echocardiography, no cardiotoxicity in the enalapril group was observed; cardiotoxicity was identified in 43% of controls (p<0.05).<sup>32</sup>

This early treatment trial, showing a marked effect, supports our hypothesis that ACEI will be effective as a preventative therapy.

### 7.4. Latest evidence

Treatment to prevent cardiotoxicity is attractive and feasible. However, knowledge is limited and the quality of existing studies is low. A Cochrane systematic review was unable to make definitive conclusions regarding the effectiveness of previously studied cardioprotective agents; no studies of ACEI were included.<sup>33</sup> A meta-review and further systematic review also found a lack of evidence to guide decision-making.<sup>19,34</sup> A recent European Society of Cardiology position paper also came to the same conclusion on preventative therapy.<sup>35</sup>

A recent single centre study tested candesartan (an angiotensin II receptor antagonist) and metoprolol started before and continued during anthracycline chemotherapy (n=120). LVEF measured by cardiac MRI declined less in candesartan treated patients; metoprolol was not effective. Epirubicin doses (commonly 240mg/m<sup>2</sup>) fell below those given in usual UK practice and consequently low levels of cardiotoxicity were found; this is consistent with our audit data for patients receiving 300mg/m<sup>2</sup> or less.<sup>36</sup> Findings from a pilot trial (n=90) in patients with haematological cancers receiving low dose anthracyclines (less than 140 mg/m<sup>2</sup> during the study), given enalapril and carvedilol started during chemotherapy, showed similar results.<sup>37</sup> These studies have limited relevance to patients treated in the UK.

One Italian four-arm trial proposes to compare ramipril and bisoprolol in the prevention of anthracycline and trastuzumab cardiotoxicity (NCT02236806).<sup>38</sup> Available details are limited; the

primary endpoint is unblinded assessment of LVEF, no detail of planned doses or type of anthracycline are available, and there is no independent data monitoring and ethics committee. Another Italian study ICOS-ONE (NCT01968200) compares enalapril prevention against enalapril treatment for troponin presence in patients with any cancer, including metastatic disease.<sup>38</sup> The statistical power (60%), heterogenous group and low dose anthracyclines, limit its applicability to UK practice.

### **7.5. PROACT: Focus and impact**

Increasing breast cancer survival, the frequency and impact of cardiotoxicity and the potential for a simple, safe and cheap preventative treatment make PROACT highly important for patients and the NHS.

There are currently no available relevant and robust randomised trials of ACEI in the prevention of anthracycline cardiotoxicity. PROACT will determine the effectiveness of enalapril in preventing cardiotoxicity in patients receiving epirubicin-based adjuvant chemotherapy for breast cancer. Results will also inform practice for other cancer types. Findings will directly inform clinical practice in confirming whether enalapril should be given routinely to patients receiving anthracycline-based chemotherapy for breast cancer.

## 8. Trial Objectives

PROACT will establish the effectiveness of the angiotensin-converting enzyme inhibitor (ACEI) enalapril maleate (enalapril) in preventing cardiotoxicity in patients with breast cancer undergoing adjuvant epirubicin-based chemotherapy.

Anthracyclines used in the treatment of breast cancer cause damage to heart muscle cells; this results in cell death (cardiotoxicity). In UK contemporary practice, epirubicin is the most frequently used anthracycline.

The null hypothesis is that there will be no difference in cardiotoxicity measured using cardiac troponin T between the intervention and control groups.

### 8.1. Primary Objective

To compare cardiac troponin T release in patients with breast cancer treated with anthracycline-based chemotherapy and enalapril, compared to those receiving anthracycline chemotherapy only.

### 8.2. Secondary Objectives

- To assess cardiac function echocardiographically, with measurements including global longitudinal strain (GLS), and left ventricular ejection fraction (LVEF), at baseline and following completion of adjuvant chemotherapy, using blinded echocardiography.
- To compare cardiac troponin I release during adjuvant chemotherapy and one month after the last dose of epirubicin;
- To quantify the level of adherence to enalapril;
- To quantify the side effects of enalapril in this patient population;
- To measure any anxiety or distress related to trial participation.

## 9. Trial Design

### 9.1. Summary

A prospective, randomised, open-label, blinded end-point, superiority trial in patients undergoing anthracycline-based adjuvant chemotherapy for breast cancer. Patients will be randomised in a 1:1 ratio to enalapril (intervention) or control (standard care). The trial will evaluate the effectiveness of enalapril in preventing cardiotoxicity detected by cardiac troponin T.

The trial is anticipated to take 30 months to complete and will randomise 170 patients due to receive anthracycline-based adjuvant chemotherapy for their breast cancer at participating NHS Trusts.

### 9.2. Primary Outcome

The presence ( $\geq 14\text{ng/L}$ ) or absence of cardiac troponin T ( $< 14\text{ng/L}$ ) release at any time during epirubicin treatment, and one month after the last dose of epirubicin.

### 9.3. Secondary Outcomes

In addition to a full description of the populations in each group throughout the trial, the following outcomes will be measured:

- cardiac function assessed by echocardiogram, including global longitudinal strain (GLS), and measurements of left ventricular ejection fraction (LVEF), at baseline and following completion of adjuvant chemotherapy;
- cardiac troponin I release during adjuvant chemotherapy and one month after the last dose of epirubicin;
- adherence to enalapril;
- adverse reactions to enalapril;
- adverse events;
- any anxiety or distress related to trial participation.
- cancer and chemotherapy outcomes in the population under study

### 9.4. Setting

Patients will be recruited and treated at four NHS Trusts: South Tees Hospitals NHS Foundation Trust, Newcastle upon Tyne Hospitals NHS Foundation Trust, North Tees and Hartlepool NHS Foundation Trust and Leeds Teaching Hospitals NHS Trust. All sites can accommodate the needs of this trial including research nurse support, facilities for trial interventions and assessments, and British Society of Echocardiography (BSE) accredited echocardiographers/or advanced trainee or consultant cardiologist to carry out scans in accordance with the trial protocol.

## 10. Trial Population

Participants will be recruited from adult patients, due to receive 6 cycles of epirubicin-based adjuvant chemotherapy (total planned dose of epirubicin must be  $>300\text{mg/m}^2$ ) for their breast cancer at recruiting centres, who agree to participate in the trial.

### 10.1. Inclusion Criteria

- Adult patients with histopathologically\* confirmed breast carcinoma who have received surgery for their breast cancer;
- planned to receive a 6 cycle adjuvant chemotherapy regimen containing  $>300\text{mg/m}^2$  of epirubicin;
- Written informed consent.

\*Patients with HER2+ breast cancer are eligible for inclusion.

### 10.2. Exclusion Criteria

- Positive baseline cardiac troponin T ( $\geq 14\text{ng/L}$ );
- known contraindication to ACE inhibitor e.g. renal artery stenosis, severe aortic stenosis;
- are taking, or have a previous intolerance to ACEI (e.g. angioedema);
- patient already taking other agents acting on the renin-angiotensin-aldosterone system e.g. Aliskiren, angiotensin receptor blockers (ARBs), Entresto (sacubitril/valsartan), spironolactone, eplerenone;
- LVEF  $<50\%$ \*;
- estimated GFR  $< 30\text{ mL/min/1.73m}^2$  at baseline;
- hyperkalaemia defined as serum potassium  $\geq 5.5\text{mmol/L}$ ;
- symptomatic hypotension, or Systolic Blood Pressure  $<100\text{mmHg}$ ;
- poorly-controlled hypertension (Blood Pressure  $>160/100\text{mmHg}$ \*\*, or ambulatory BP of  $150/95\text{mmHg}$ );
- previous myocardial infarction;
- known metastatic breast cancer;
- previous exposure to anthracycline chemotherapy;
- are pregnant or breastfeeding
- Previous Herceptin treatment or planned Herceptin treatment within four weeks following anthracycline chemotherapy
- for patients of childbearing potential: refusal to use adequate contraception throughout the trial;\*\*\*
- any other cancer diagnosis;
- participation in other interventional medicinal trials in the past 6 months;
- judgment by the Investigator that the patient should not participate in the study, for example, if the patient is unlikely to comply with study procedures, restrictions, and requirements.

\*<50% as defined by Simpson's biplane method; if absolute measurements are not possible, then a visually normal assessment of LVEF is acceptable for inclusion.

\*\*White coat hypertension is more common, and should be ruled out by an ambulatory blood pressure monitor

\*\*\*Female patients between the ages of 18 and 50 will receive a pregnancy test at baseline.

Adequate methods of contraception are those that can achieve a failure rate of less than 1% per year when used consistently and correctly, such methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomy/vasectomised partner
- true sexual abstinence (refraining from heterosexual intercourse during the entire period of study treatment)

## **11. Screening, Recruitment, Consent, Randomisation and Blinding**

### **11.1. Identification**

Patients scheduled to receive 6 cycles of adjuvant epirubicin-based chemotherapy for their breast cancer will be identified prior to the start of chemotherapy.

### **11.2. Recruitment and Informed Consent**

Patients will be sent or given a covering letter and patient information sheet describing the trial, and will be seen by one of the research team on the delegation log. The trial will be discussed with the patient, and after opportunity for questions, a delegated and trained member of the research team will seek consent. The time between giving the information and taking consent may be on the same day and all steps will be taken to ensure that patients are afforded a reasonable time frame to consider the trial and have had all their questions answered prior to consent.

Recruitment will continue until the target sample size is randomised. Patients who decline to participate in this trial will continue to receive care within the department as per standard care.

Written consent for the trial must be taken within 6 weeks prior to randomisation. The original, signed consent form will be retained in the Investigator Site File, with a copy filed in the clinical notes and a copy given to the patient.

A screening log will be kept to document details of all patients invited to participate in the trial, their reasons (if given) for not consenting, or not being randomised will be recorded (e.g. not meeting eligibility criteria for the trial).

### **11.3. Eligibility check**

Following consent, the Principal Investigator or a sub-Investigator on the delegation log will confirm the patient's eligibility prior to randomisation.

### **11.4. Screen Failures**

Following consent, patients who do not meet trial eligibility criteria prior to randomisation will be considered a 'screen failure' and withdrawn from the trial with no further data collected. Screen failure patients may be approached to participate in an observational registry at participating centres.

### **11.5. Randomisation**

Randomisation will be performed using a minimisation scheme to ensure patients randomised to each group are comparable at baseline. The minimisation scheme will account for a planned 6 cycle adjuvant chemotherapy regimen (Epirubicin and Cyclophosphamide (EC) or Fluorouracil, Epirubicin and Cyclophosphamide (FEC)), and HER2 (human epidermal growth factor receptor 2) status (positive or negative).

Eligible patients will be randomised by delegated and trained members of the research team at each centre using a 24-hour, central, secure, web-based randomisation system with concealed allocation.

Eligible patients will be randomised in a 1:1 ratio to receive standard care plus enalapril maleate (intervention under study) or standard care (control arm/standard care).

Randomisation system web address:

<https://www.sealedenvelope.com/access/>

This system is available 24 hours a day, 7 days a week.

In the event that the randomisation system is not accessible, the team should contact NCTU staff in normal working hours:

Email: [nctu.tees@newcastle.ac.uk](mailto:nctu.tees@newcastle.ac.uk)

Telephone: 01642 854 638

#### **11.6. Blinding**

The trial will employ a prospective randomised blinded endpoint design; analysis of troponin I and troponin T will be completed by laboratory staff who are blinded to the patients' trial allocation, as detailed in the trial PROACT laboratory manual.

All echocardiograms will be sent to an independent Core laboratory for assessment by a BSE accredited echocardiographer/or an advanced trainee or consultant cardiologist blind to the intervention.

#### **11.7. Un-blinding**

This is an open label trial and, as such, no un-blinding procedures are specified in this trial.

#### **11.8. Informing General Practitioners of Patient Participation**

Following explicit consent of the patient, General Practitioners will be informed of their patient's decision to participate and their randomisation status. A letter providing information about the study and inviting GPs to contact the investigators if they have questions will be sent following consent.

## 12. Adherence and Withdrawal

### 12.1. Assessment of adherence

Study visits have been planned to coincide with routine clinical practice where possible to enable adherence to the trial procedures.

Adherence with trial medication will be monitored and recorded throughout the trial for patients randomised to receive the trial intervention; enalapril maleate.

### 12.2. Withdrawal of participants

Patients may withdraw from the trial at any time if they wish to, without giving reason and without any adverse consequences for their ongoing clinical management. Patients in the intervention arm will need to stop taking enalapril maleate on the day they withdraw, and return all unused drug to the clinical research team.

All patients will be made aware of their right to withdraw from the study, and this information will be included in the patient information sheet.

Patients should be withdrawn from the trial by the clinical team if:

- the patient suffers unacceptable side effects caused by enalapril maleate;
- the patient becomes ineligible between randomisation and commencement of chemotherapy;
- the patient becomes pregnant or there is evidence that a patient fails to use adequate birth control;
- the patient has disease recurrence.

Data and blood samples for troponin assessment collected up to the point of withdrawal will be kept and used in the analysis of the trial.

Patients will be asked upon withdrawal:

- whether further data can continue to be collected from their medical records;
- whether samples collected for future research may still be analysed;
- whether they may be approached in future research connected to the trial.

This information will be captured on a withdrawal form, to be stored in the ISF and a copy of which sent to NCTU (by email), this will also be captured in the eCRF.

Data from patients who withdraw will remain in the overall analysis; however, dependent on the stage of withdrawal, then further patients may be recruited to ensure that the sample size is reached.

## 13. Trial Procedures

### 13.1. Summary of Trial Assessments

	Baseline (up to 6 weeks prior to randomisa- tion)	Day 1 (at least 5 days prior to Cycle 1 Day 1)	Dose evaluation visit 1	Dose evaluation visit 2	Dose evaluation visit 3	Cycle 1, Day 1	Cycle 2, Day 1	Cycle 3, Day 1	Cycle 4, Day 1	Cycle 5, Day 1	Cycle 6, Day 1	Trial Completi- on Visit <sup>b)</sup>
<b>Consent <sup>a)</sup></b>	X											
<b>Demographics</b>	X											
<b>Medical History</b>	X											
<b>Cancer history</b>	X											
<b>Performance Status</b>	X											
<b>NYHA Class</b>	X											
<b>Concomitant medications <sup>b)</sup></b>	X	X	X	X	X	X	X	X	X	X	X	X
<b>Physical Assessment (height and weight)</b>	X											
<b>Blood Pressure</b>	X		X	X	X	X	X <sup>c)</sup>	X				
<b>Troponin T</b>	X <sup>d)</sup>						X <sup>c)</sup>	X				
<b>Troponin I</b>	X						X <sup>c)</sup>	X				
<b>U+Es</b>	X		X	X	X		X <sup>c)</sup>	X				
<b>eGFR</b>	X											
<b>Pregnancy test <sup>e)</sup></b>	X											
<b>Echocardiogram <sup>f)</sup></b>	X											X
<b>Eligibility check</b>	X											
<b>Randomisation</b>	X											
<b>Enalapril (intervention group only)</b>		X	X	X	X	X	X	X	X	X	X	
<b>Adherence to enalapril (intervention group only)</b>		X	X	X	X	X	X	X	X	X	X	X
<b>Standard care adjuvant chemotherapy (all patients)</b>						X	X	X	X	X	X	
<b>Adverse Events</b>		X	X	X	X	X	X	X	X	X	X	X
<b>Buccal swab for future research</b>	X											
<b>Blood sample for future research</b>	X							X		X		X
<b>Acceptability of trial interventions assessment</b>									X			X

- a) Consent must be taken prior to baseline assessments and confirmation of eligibility, and within 6 weeks of randomisation.
- b) A list of all medication currently being taken by the patient, including total daily dose, should be recorded at baseline; changes and new medications must be recorded throughout the trial.
- c) All blood samples, including those for troponin T and I, MUST be taken before the next dose of chemotherapy is given; these and blood pressure monitoring can be performed up to 72 hours in advance of the day of chemotherapy.
- d) Troponin T at baseline will be used to assess eligibility
- e) Women between the ages of 18 and 50 must have a negative pregnancy test at baseline, and prior to randomisation and use adequate contraception from consent, throughout the trial.
- f) A Transthoracic Echocardiogram (TTE) must be performed at baseline. At the time of the TTE, blood pressure and heart rate should be measured, and recorded. A TTE will also be performed following the end of chemotherapy. Patients planned to receive Herceptin, must have their TTE performed prior to starting this. All TTEs must be transferred to the Core laboratory for analysis as part of the trial.
- g) Four weeks following the last dose of epirubicin.

## 13.2. Assessments

In addition to standard care procedures, a number of baseline assessments will take place prior to randomisation. Where routine assessments are the same as trial assessments for eligibility, and performed following consent to the trial, these will be used to assess eligibility for PROACT. These may include:

- Medical and cancer history
- Demographics
- U&Es
- Pregnancy test

If these aren't done routinely at that time-point, they will need assessment as part of the trial.

### 13.2.1. Demographic Information

The following demographic data will be recorded as part of the trial at baseline:

- month and year of birth
- gender
- ethnic group

### 13.2.2. Cardiovascular, Cancer and significant Medical History

A full medical history will be recorded for each patient at baseline and will include details of all clinically significant current and past cardiovascular medical conditions and a full cancer history. Cancer staging will be assessed according to the eighth edition of the American Joint Commission of Cancer (AJCC) Cancer Staging Manual, published 2016.

Review of other hospital notes (and GP notes) may assist in completing the medical history.

### 13.2.3. Performance Status

ECOG<sup>39</sup> Performance Status grade will be determined at baseline and assessed according to the following criteria:

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

#### 13.2.4. NYHA Class

NYHA Class<sup>40</sup> will be assessed at baseline, in accordance with the following criteria:

Class	Patient Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

#### 13.2.5. Physical Assessment

A physical assessment of height (measured in cm), and weight (measured in kg) will take place at baseline.

#### 13.2.6. Medications

A full list of current medications will be recorded at baseline. Changes and additions will be recorded for the duration of the trial until the trial completion visit, 4 weeks after the last dose of epirubicin.

Details of all chemotherapy, pre-medications and supportive treatments will also be recorded as part of the trial.

Details of concomitant treatments which may interact with enalapril can be found in the SmPC; e.g., non-steroidal anti-inflammatory drugs (NSAIDs), potassium supplements, diuretics, etc.

#### 13.2.7. Blood Pressure

Blood pressure (BP) will be assessed at baseline, prior to taking any blood samples. BP needs to be assessed whilst the patient is sitting. If the first reading provides a systolic value greater than 160mmHg, the test should be repeated on two further occasions, with the patient quiet and seated. If white coat hypertension is suspected, ambulatory BP monitor may be used to avoid inappropriate exclusion from the trial. Severe hypertension on ambulatory BP is defined as 150/95.

All patients will have their BP measured in the same way within 72 hours prior to day 1 of each cycle of chemotherapy and also at the trial completion visit.

For those patients randomised to receive enalapril, BP will also be measured on each of the days that they attend for a dose evaluation visit.

### **13.2.8. Troponin T and Troponin I**

Blood samples will be taken to assess troponin T and troponin I. Full details can be found in the PROACT laboratory manual.

#### **Eligibility blood sample**

At baseline, up to 5mL of blood will be taken in a serum-separation tube (SST) for the troponin T eligibility check. This blood sample will be collected and sent for immediate local processing. If the local processing laboratory finds that the sample collected is haemolysed, a repeat sample will be requested immediately. Serum from this sample will be sent for central analysis at Newcastle Laboratories (Newcastle-upon-Tyne Hospitals NHS Foundation Trust). If the serum sample is not sent on the same day, it will be frozen and transported the following day at -20°C. This baseline serum sample will be received and analysed in real time for Troponin T. The laboratory will confirm the Troponin T result with the site team and this will be recorded in the eCRF. An aliquot of serum from this baseline sample will be stored at -80°C for troponin I analysis at the end of the study.

#### **Blinded end-point blood samples**

After randomisation, up to 5mL of blood will be collected in an SST, processed immediately after collection, stored and transported as described in the PROACT laboratory manual. These samples will be taken within 72 hours prior to the intended start of chemotherapy at cycle 2, 3, 4, 5, 6 and at one month after the last epirubicin dose. These samples will be taken to coincide with standard pre-chemotherapy bloods, where possible. If the local processing laboratory finds that the samples collected are haemolysed, a repeat sample will be requested immediately. If chemotherapy is delayed by the clinical team, further study blood samples for troponin will not be required.

Troponin T will be batch-tested in a blinded manner for this trial and data will be entered into the eCRF by the central laboratory teams.

Troponin I will be batch-tested in a blinded manner at the end of the trial and the result entered into the eCRF by central teams.

Any remaining serum after analysis will be discarded.

The research team will not be made aware of the results of the troponin testing until the end of the trial. The results will not be available for the patients or treating clinicians.

A full chain of custody will be maintained for each sample throughout its lifecycle. The principal investigator at each study site will keep full traceability of collected samples while in storage at site until shipment or disposal and keep records of shipping for each sample. The receiver will acknowledge receipt of each sample and keep full traceability of the samples whilst in storage and during use until used or disposed of.

#### **13.2.9. Urea and Electrolytes (U&Es)**

U&Es (Urea, Na<sup>+</sup>, K<sup>+</sup> and Creatinine) will be assessed at baseline, at each dose evaluation visit (enalapril arm only), and within 72 hours prior to the intended day 1 at the start of chemotherapy at cycle 2, 3, 4, 5, 6 and at one month after the last epirubicin dose.

Samples will be collected, processed and analysed in accordance with local hospital practice, with the results recorded in the eCRF. These blood samples are often taken and tested routinely, if this is the case, and they fit within the windows for the trial, repeat tests specifically for the trial are not needed.

If serum creatinine levels increase by 30 µmol/L over 48-96 hours, or increases to >1.5 times the baseline value, the clinical judgement of the Principal Investigator should be sought, and/or the Chief Investigator, to confirm the action to be taken, which may require a temporary or permanent halt to enalapril (for those in the enalapril group).

#### **13.2.10. Estimated GFR**

Estimated GFR will be assessed at baseline. The recommended method for calculating eGFR is the Modification of Diet in Renal Disease (MDRD) GFR equation. eGFR must be ≥30 mL/min/1.73m<sup>2</sup> at baseline for the patient to be eligible to enter the trial.

#### **13.2.11. Pregnancy Test**

A pregnancy test (urine or blood) must be performed in all female patients of childbearing potential, between the ages of 18 and 50 in the 7 days prior to randomisation. The test must confirm that the patient is not pregnant.

#### **13.2.12. Echocardiogram**

Cardiac function will be assessed via transthoracic echocardiography (TTE) at baseline, and 4 weeks following the last epirubicin dose.

All echocardiograms will be assessed by a Core Laboratory, led by Dr Mike Stewart, and Dr Richard Graham at The James Cook University Hospital. Images will be transferred from the study centre to the Core laboratory in accordance to the PROACT Echocardiogram Manual. Dr Stewart, Dr Graham, and their team, will be blinded to the arm of the study to which patients are allocated.

Local reporting of the TTEs will be as per local hospital practice; the data reported by the Core laboratory (including GLS and LVEF) will be recorded in the eCRF and will be analysed as part of the secondary outcomes for the trial.

The PROACT Echocardiogram Manual provides further guidance to all centres involved in the study, detailing the number, quality and types of images to be acquired, and details of how to send these to the Core Laboratory. Heart rate and sinus rhythm will also be recorded at the time of the echocardiograms.

#### **13.2.13. Swabs**

If consent is given, buccal swabs will be taken at baseline. The samples will be processed into lysis buffer and stored at -20°C for up to one month. The sample will then be transported according to the laboratory manual to Newcastle University where DNA will be extracted. DNA samples will be stored at -80°C until analysis for a maximum period of 15 years following the last patient's last visit (LPLV) in the study, after which time they will be destroyed. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

A full chain of custody will be maintained for each sample throughout its lifecycle. The principal investigator at each study site will keep full traceability of collected samples while in storage at site until shipment or disposal and keep records of shipping for each sample. The receiver will acknowledge receipt of each sample and keep full traceability of the samples whilst in storage and during use until used or disposed of.

#### **13.2.14. Blood sampling for further research**

If consent is given, blood samples for further research will be collected in one SST (up to 5mL) and one EDTA tube (up to 5mL) at the following visits throughout the study: baseline, and within 72 hours prior to intended day 1 at the start of chemotherapy at cycle 3, 5 and at one month after the last epirubicin dose. These should be processed immediately at the local site, divided into four aliquots, stored at -20 °C and transported according to the laboratory manual.

These samples will be stored at Newcastle Laboratories at -80°C until analysis for a maximum period of 15 years following the last patient's last visit (LPLV) in the study, after which time they will be destroyed. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

A full chain of custody will be maintained for each sample throughout its lifecycle. The principal investigator at each study site will keep full traceability of collected samples while in storage at site until shipment or disposal and keep records of shipping for each sample. The receiver will acknowledge receipt of each sample and keep full traceability of the samples whilst in storage and during use until used or disposed of.

#### **13.2.15. Assessment of the acceptability of trial interventions**

At the start of cycle 4 and at the end of study visit (1 month after the last chemotherapy treatment), the patient will be asked to complete a short questionnaire.

#### **13.3. Eligibility Check and Randomisation**

Following all baseline assessments, eligibility must be confirmed per section 10. and 11., prior to randomisation, per section 11.

## **14. Trial Intervention**

### **14.1. Description of the Investigational Medicinal Product**

Enalapril is an Angiotensin Converting Enzyme (ACE) inhibitor which suppresses the renin-angiotensin-aldosterone system resulting in increased plasma renin activity and decreased aldosterone secretion. This trial aims to investigate the prevention of cardiac damage in patients treated for breast cancer using the pharmaceutical actions of enalapril.

This trial will use enalapril at doses from 2.5mg to 10mg twice daily using dose escalation depending upon the response and maximum tolerated doses in this patient group. Any brand of enalapril 2.5mg, 5mg, or 10mg tablets may be used during this trial. Further details relating to the properties of enalapril can be found in the summary of product characteristics (SmPC).

### **14.2. Manufacture of Enalapril**

Product licensed packs of enalapril tablets will be purchased by Nottingham University Hospitals NHS Trust (NUH), pharmacy production unit. As this is an open-label study, there is no blinding of the product required and therefore the product will remain within its original primary packaging as a minimum. The Qualified Person (QP) who will release the final packed products will be a member of the NUH quality team who is authorised to release investigational medicinal products (IMPs) and named on the MIA(IMP) licence.

### **14.3. Packaging and labelling of Enalapril**

NUH Pharmacy Production Units (MIA(IMP) 19162) will supply enalapril in pack sizes of 10 and 28 tablets. For those strengths of enalapril (2.5mg and 5mg) which will be supplied in packs of 10, the product will remain within the original sealed blister strip which will be assembled into plain white cardboard cartons each containing 10 tablets. The pack sizes of 28 tablets (2.5mg, 5mg, 10mg) will remain within the original primary and secondary packaging as supplied by the manufacturer. As a result of the primary packaging being retained intact, the product will maintain the original product shelf life and no further stability studies will be undertaken.

Each pack, 10 tablets or 28 tablets, will be labelled in accordance with EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use, Annex 13, Investigational Medicinal Products and the Clinical Trials Directive 2001/20/EC. Each label will state the product name, batch number, expiry date, storage conditions and a space to allow the patient's name to be completed at the point of dispensing. All other details will be compliant with the annex 13 labelling requirements.

### **14.4. Storage, dispensing and return**

The packs of enalapril will be stored in the designated clinical trials pharmacy at participating centres which are secure departments with temperature controls and continuous temperature monitoring. The

storage conditions for the IMP will be at or below 25°C with a warning that the product must not be refrigerated or frozen. A supply of IMP will be made for a patient upon presentation of a trial specific prescription to the clinical trials pharmacy at participating centres. The prescription may be written by a clinician or persons trained and qualified to do so (e.g., prescribing pharmacist or nurse), prescribers must be recorded on the study delegation log. Upon receipt of a trial specific prescription, pharmacy will dispense the corresponding strength of IMP to the patient. At the point of dispensing, pharmacy will complete the dispensing labels and accountability logs to allow the products to be traced.

Any unused IMP will be returned to the clinical trials pharmacy at the end of the treatment period to allow for final accountability and destruction of the product in accordance with local policy.

#### **14.5. Known side effects**

Very common side effects related to treatment with enalapril include: cough, dizziness, nausea, asthenia, blurred vision, and hyperkalaemia. Common and severe side effects include angioedema and renal impairment. More detailed information relating to the side effects of enalapril can be found in the SmPC for the product. See Appendix 1.

#### **14.6. Administration of Enalapril**

Following randomisation, patients randomised to receive Enalapril may begin taking the drug. The patient needs to have received at least 5 days of enalapril prior to their first dose of epirubicin-based adjuvant chemotherapy.

The trial aims to have all patients in the enalapril arm on a dose of 10mg BD, however clinical judgement alongside clinical assessments will be used to determine the maximum tolerated dose (MTD) for the patient, up to a maximum of 10mg BD. Dose titration and evaluation visits are described below. Chemotherapy will not be delayed by taking part in the trial.

##### **14.6.1. Dosing visit day 1**

Patients will be dispensed 2.5mg enalapril BD as their starting dose to begin taking that day.

##### **14.6.2. Dose evaluation visit 1**

Two to five days after the start of enalapril, the patient should return for a dose evaluation visit. Blood pressure and U&Es should be measured and the patient should be assessed for side effects.

If the patient has systolic BP  $\geq$ 100 mmHg, normal serum potassium (potassium  $<$ 5.5 mmol/L), and stable renal function (serum creatinine  $<$ 30  $\mu$ mol/L increase from baseline over 48-96 hours) then the enalapril dose should be up-titrated to 5mg BD.

If the patient is, in the clinical opinion of the investigator, unlikely to tolerate a higher dose at this point then the dose should remain the same. At the discretion of the investigator, a further assessment at

dose evaluation visit 2 could be made to consider up-titration of enalapril to 5mg BD using the same criteria as above.

If the patient has a  $\geq 30$   $\mu\text{mol/L}$  increase in serum creatinine levels since the last assessment compared to baseline, new hyperkalaemia (potassium  $\geq 5.5\text{mmol/L}$ ), or symptomatic hypotension (SBP  $< 100\text{mmHg}$ ) then enalapril should be permanently discontinued and the patient withdrawn from the study. The patient should be seen again within 7 days to ensure the reasons for withdrawal have resolved to the satisfaction of the investigator.

#### **14.6.3. Dose evaluation visit 2**

Two to five days after dose evaluation visit 1, if the dose of enalapril was increased, the patient should return for a second dose evaluation visit. Blood pressure and U&Es should be measured and the patient should be assessed for side effects.

If the patient has systolic BP  $\geq 100$  mmHg, normal serum potassium (potassium  $< 5.5$  mmol/L), and stable renal function (serum creatinine  $< 30$   $\mu\text{mol/L}$  increase since last assessment, or a  $< 1.5$  times increase from baseline) then the enalapril dose should be up-titrated to 10mg BD.

If the patient is, in the clinical opinion of the investigator, unlikely to tolerate a higher dose, then the dose should remain the same.

If the patient has a  $\geq 30$   $\mu\text{mol/L}$  increase in serum creatinine levels since the last assessment, or a  $\geq 1.5$  times increase from baseline, potassium  $\geq 5.5\text{mmol/L}$ , or symptomatic hypotension (SBP  $< 100\text{mmHg}$ ) then reduce back to previously tolerated dose and recheck blood pressure, and U&Es two to five days later.

#### **14.6.4. Dose evaluation visit 3**

If the dose was increased at titration visit 2, the patient should return two to five days later, to have their blood pressure and U&Es rechecked to confirm that they are tolerating the enalapril.

If the patient has a  $\geq 30$   $\mu\text{mol/L}$  increase in serum creatinine levels since the last assessment, a  $\geq 1.5$  times increase from baseline, potassium  $\geq 5.5\text{mmol/L}$ , or symptomatic hypotension (SBP  $< 100\text{mmHg}$ ) then reduce back to previously tolerated dose and recheck blood pressure, and U&Es two to four days later.

If the patient is, in the clinical opinion of the investigator, tolerating the dose, then the dose should remain the same. If not, then the dose of enalapril should be reduced to the previously tolerated dose.

#### **14.6.5. Continuation of treatment with enalapril**

Once the patient is on their maximum tolerated dose of enalapril they should receive this dose daily throughout the trial (including on chemotherapy treatment days). There may be instances where a patient has side effects to their cancer, chemotherapy or to enalapril that require a temporary halt to

taking enalapril. Temporary halts of up to 7 days (14 doses) will be allowed within the trial. These should be noted and explained. Where this due to an intolerance of enalapril, only one temporary halt will be allowed. Where the intolerance has manifested as angioedema, then treatment with enalapril should be withdrawn.

Re-introduction of enalapril may be at the discretion of the local clinician. It is recommended that where temporary halts are due to chemotherapy-related toxicities, then reintroduction at the established MTD is acceptable. Where temporary halts have been due to renal instability then reintroduction at a dose lower than the MTD is recommended.

Dose reductions of enalapril in routine use would not be expected; in this study they will be allowed and at the discretion of the investigator.

Any re-introduction or dose adjustment of enalapril must be followed 2-5 days after the re-introduction/adjustment to assess blood pressure and U&Es.

At each attendance prior to the start of a new cycle of chemotherapy, patients will be asked about how much enalapril they have left and a new prescription dispensed if required.

#### **14.6.6. End of treatment with enalapril**

Enalapril will be continued during chemotherapy and stopped three weeks following the last epirubicin dose. Any unused drug will be returned to the clinical research team who will return this to Pharmacy for reconciliation.

#### **14.7. Adherence to enalapril**

Patients on the enalapril arm will be asked to record their intake of enalapril and any reasons for not taking the drug using the PROACT enalapril adherence pro-forma. Patients will be asked to return unused drug when they:

- Change dose
- Withdraw
- Discontinue enalapril per protocol at the end of the trial

## **15. Adjuvant Chemotherapy**

All randomised patients will receive their planned 6 cycles of chemotherapy according to usual practice within the recruiting centre. This includes all concomitant medication and procedures for the safe administration of cytotoxic chemotherapy.

### **15.1. Permitted Chemotherapy Regimens**

Two 6-cycle epirubicin-based chemotherapy regimens will be permitted within this trial. Patients with HER2 positive breast cancer will be permitted as long as they are planned to receive one of these regimens, and Trastuzumab is not planned to start within 4-weeks of the final epirubicin dose.

#### **Regimen 1) 5-Fluorouracil, Epirubicin, Cyclophosphamide (FEC 75)**

Six cycles of epirubicin, dose 75mg/m<sup>2</sup> per cycle, given 3 weeks apart.

#### **Regimen 2) Epirubicin, Cyclophosphamide (EC 90)**

Six cycles of epirubicin dose 90mg/m<sup>2</sup> per cycle, given 3 weeks apart

### **15.2. Dose Modifications and Dose Delays to chemotherapy**

Dose reductions and dose modifications for adjuvant chemotherapy will be at the discretion of the treating oncologist. These will be recorded in the CRF.

## 16. Pharmacovigilance

### 16.1. Definitions

#### 16.1.1. Adverse Events

Adverse Events (AEs) are defined as **any** new medical occurrence, or worsening of a pre-existing medical condition in a patient who has been randomised as part of the trial, which does not necessarily have to have a causal relationship to enalapril (Investigational Medicinal Product (IMP)) or trial-related procedures. Medical conditions, symptoms or diseases present at baseline will only be considered adverse events if they worsen after randomisation. Adverse events that are unequivocally due to disease progressions should not be reported as an AE during the trial.

#### 16.1.2. Adverse Reaction

Any untoward and unintended response in a patient to enalapril (IMP) which is related to any dose administered to the patient. All Adverse Events considered as having a causal relationship to the IMP will be considered an Adverse Reaction (AR).

#### 16.1.3. Unexpected Adverse Reaction:

Any Adverse Reaction, the nature and severity of which is not consistent with the information about enalapril maleate in the SmPC.

#### 16.1.4. Serious Adverse Events (SAE) or Serious Adverse Reaction (SAR)

Any untoward or unexpected medical occurrence (Adverse Event, Adverse Reaction, or Unexpected Adverse Reaction) that:

- Results in death,
- Is life-threatening\*,
- Requires hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity,
- Is a congenital anomaly or birth defect,
- Any other important medical condition which, although not included in the above, may require medical or surgical intervention to prevent one of the outcomes listed.

\* life-threatening refers to an event in which the patient 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.

#### 16.1.5. Suspected, Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature and severity of which is not consistent with the information about the IMP in question set out in the RSI.

### 16.1.6. Causality

The relationship of each adverse event must be determined by a medically qualified individual who is on the delegation log for the trial. If any doubt about the causality exists, the local Principal Investigator should inform the Chief Investigator. The following definitions should be used to determine causality:

Unrelated	The event is not considered to be related to enalapril.
Unlikely to be related	The event is considered unlikely to be related to enalapril; there is little evidence to suggest a causal relationship or there is another reasonable explanation for the event.
Possibly related	Although the relationship to enalapril, cannot be ruled out, the nature of the event, the underlying disease, concomitant medications or temporal relationship make other explanations plausible.
Probably related	The temporal relationship and an absence of a more likely explanation suggest that enalapril is the most likely cause.
Definitely related	The known effects of enalapril indicate this to be the most likely cause and other contributing factors can be ruled out.

### 16.1.7. Severity

The severity of each adverse event must be determined by a medically qualified individual who is on the delegation log for the trial. The following definitions should be when determining severity:

Grade 1	Minor adverse event, not requiring medical intervention. May be asymptomatic and is likely to be a clinical or diagnostic observation only; or may be a symptomatic but minor, or transient event, with no necessity for medical intervention. This might include asymptomatic laboratory or radiographic findings. A minor adverse event is likely to have only marginal clinical relevance.
Grade 2	An adverse event which may require some medical intervention (local/non-invasive) and which is symptomatic to patient. May affect activities of daily living.
Grade 3	Significant symptoms reported, requiring medical intervention and possibly requiring hospitalisation. Medically significant and likely to be significantly affecting activities of daily living.
Grade 4	An adverse event that requires urgent intervention or may have life-threatening consequences.
Grade 5	Death related to the adverse event.

## 16.2. Foreseeable Adverse Events

Foreseeable adverse events are those which are foreseen in the patient population and as a result of the routine care of patients. If a foreseeable adverse event occurs, and this also fulfils the criteria for an SAE it will not need an SAE report to be submitted for this trial, but will need recording on the CRF as an adverse event. These will not be considered as SUSARs unless the severity of the event was considered to be unexpected.

Foreseeable adverse events are:

- Infection
- Anaemia
- Thrombocytopenia
- Neutropenia
- Nausea
- Vomiting
- Fatigue
- Alopecia
- Diarrhoea
- Stomatitis
- Loss of appetite
- Palmar-plantar syndrome
- Taste changes
- Bladder irritation
- Headache
- Skin changes
- Thrombosis
- Sepsis
- Neutropenic sepsis

## 16.3. Pregnancy

Where a patient becomes pregnant during their involvement in the trial, this must be reported to NCTU using the appropriate form, within 24 hours of the research team become aware of the situation. The pregnancy must be followed until the outcome is known, to determine if an SAE should be reported. Patients who become pregnant should be withdrawn from the trial and, if they are in the intervention arm, have their enalapril stopped immediately. Decisions regarding all other care, including continuation of chemotherapy, rest with the patient's clinical team.

## 16.4. Overdose

Patients who take a deliberate overdose of enalapril should be referred for an emergency assessment and withdrawn from the trial.

Accidental overdose will be defined as accidental ingestion of greater than the planned daily dose of enalapril. Enalapril is not usually dangerous in overdose, although most commonly causes hypotension. Patients who are asymptomatic, without hypotension at 5 hours are unlikely to have significant toxicity. In the trial population, medical assessment is recommended for overdose in the following patients who are treatment naïve or have taken more than their daily therapeutic dose:

- Patients aged over 65 years (who are more at risk of complications)
- Patients who are known to have renal impairment
- Patients on treatment with azathioprine, lithium or potassium
- Patients who have ingested >0.7mg/kg

After accidental overdose, the patient should not take further enalapril until discussion with the trial team at the earliest opportunity. The safety and appropriateness of restarting enalapril, including timing, will be considered at the discretion of the PI. A maximum of 7 days interruption will be permitted.

All overdoses will be recorded in the eCRF and noted in the deviation log. Where an overdose fulfils an SAE, then it will be fully described in the SAE report form and follow SAE reporting guidelines (see section 16.5).

## 16.5. Adverse Event Reporting

All AEs will be recorded in the patients' medical notes and on electronic case report forms. AEs will be recorded from the day of randomisation until the last visit or until withdrawal, with the exception of adverse events considered related to enalapril, which will be followed until resolution, a stable outcome or death.

All AEs will be assessed for severity, causality, and seriousness and expectedness by an Investigator. All events will be reviewed by the Independent Data Monitoring and Ethics Committee (IDMEC) as part of their ongoing assessment of safety.

Patients should be asked about any adverse events at each visit.

Where an AE fulfils the criteria for a reportable SAE as part of this trial, this will be reported immediately to NCTU (within 24 hours of the research team becoming aware of the event) who will inform the Sponsor and Chief Investigator. Should the SAE form be incomplete at the time of the initial report, follow-up information should be provided as it becomes available. The relationship to the IMP should be assessed by the Investigator at the site, and they will also assess expectedness in relation to the approved RSI.

Exceptions for SAE reporting include hospitalisation for:

- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
- Treatment which was elective or pre-planned, for a pre-existing condition not associated with any deterioration in condition
- Any admission to hospital or other institution for general care where there was no deterioration in condition

In the event that a SUSAR is fatal or life-threatening, the sponsor will inform the MHRA and the REC within 7 days. In the event that a SUSAR is non-life-threatening, the sponsor will inform the MHRA and the REC within 15 days.

All Principal Investigators will be informed of all SUSARs throughout the trial, as they occur.

SAEs and SUSARs should be reported to NCTU within 24 hours

[NCTU@durham.ac.uk](mailto:NCTU@durham.ac.uk)

#### **16.6. Foreseeable Adverse Event Reporting**

Foreseeable adverse events should be recorded as adverse events within the trial CRF, but do not require reporting as Serious Adverse Events for this trial.

#### **16.7. Notification of deaths**

Only deaths that are assessed to be caused by the IMP will be reported to the sponsor. This report will be immediate.

#### **16.8. Urgent safety measures**

If any urgent safety measures are taken, the CI/sponsor or NCTU shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice (in the form of a substantial amendment) to the MHRA and the REC of the measures taken and the circumstances giving rise to those measures.

## 17. Statistics

### 17.1. Sample Size

Audit data from 36 patients and 143 samples, showed a positive troponin T in 47% of patients who received  $>300\text{mg/m}^2$  of anthracycline in a six-cycle regimen. As a sensitive marker of cardiac cell death, we expect troponin to be “turned off” if enalapril is effective. There are other potential causes of an elevated troponin during chemotherapy that are accounted for in the sample size calculation. There is clinical consensus that a rate of 20% in elevated troponin would fully account for other causes such as infection.

Assuming alpha of 5%, and 90% power, 140 patients are needed to detect a reduction in the proportion of patients with cardiac troponin T present from 47% to 20% using a two-sided Fisher's exact test.

There is consensus within the clinical community that, a large effect size will be necessary to convince the clinical community to change the pathway of care for these patients.

Allowing for attrition, the trial will recruit and randomise 170 patients.

### 17.1. Statistical Analysis

Data cleaning and analysis will be provided by staff within NCTU and Durham University. Primary analysis will follow intention to treat principles with patient data analysed according to randomisation and irrespective of intervention received; other analysis groups such as per-protocol may be considered subsequently. Every effort will be made to retain and include all patients who are part of the trial.

A full statistical analysis plan (SAP) will be developed for the outcome measures and agreed with the IDMEC and Chief Investigator prior to any analysis being undertaken.

Outcome data will be analysed at the end of the study, no interim analyses is planned.

The primary analysis of presence or absence of cardiac troponin T will be assessed using Fisher's exact test. Analysis of the secondary endpoints will be dependent upon the nature of the specific endpoint and data structure; global longitudinal strain (GLS) and left ventricular ejection fraction (LVEF) will be analysed as a change from baseline using a t-test to compare intervention and control groups.

Cardiac troponin I data will also be analysed using Fisher's exact test. Changes in cardiac troponin T and I will also be analysed as a continuous variable. Additional analysis of the primary endpoint will be performed using logistic regression to account for baseline factors (regimen and HER2 status). Adverse events data will be analysed using cross-tabulation. Sensitivity analysis will also be performed for adherence to the protocol.

## **18. Structure and Duration of the Trial**

The total duration of this trial is anticipated to be 30 months; this comprises recruitment ending 20 months after the start of the grant. Patients will be followed for a minimum of 6 months following the start of their adjuvant chemotherapy. The trial will randomise 170 patients from participating centres in England. The final 4 months will comprise final data cleaning, analysis, report writing and dissemination of research findings.

The duration of trial participation for individual patients will be from the day of consent until the last follow-up assessment following adjuvant chemotherapy or withdrawal. Where a patient withdraws, but there is a study related adverse event, this will be followed until resolution, a state of persistence or permanence, or death. All participants will be asked to consent to longer-term follow up using routine data.

### **18.1. Definition of the end of the trial**

The end of the trial will be defined as the last assessment for the last patient at one month following the last epirubicin dose in the trial.

### **18.2. Early Trial Cessation**

If the Sponsor, Chief Investigator, NCTU, IDMEC, TSC, or TMG discover conditions arising during the trial that indicate the trial should be stopped, this action may be taken. The TSC carries the responsibility for deciding if the trial should be stopped early. Conditions likely to warrant study termination include, but are not limited to:

- Futility: the trial has no prospect of reaching its recruitment within the given time frame
- There is a substantial change in understanding/scientific advancement meaning that continuation of the trial is inappropriate
- Safety: overwhelming evidence for harm makes continuation non-viable

### **18.3. Remuneration**

No financial or material incentives will be given to participants, however reasonable travel expenses will be given for participants who return to the hospital for visits that are additional to standard care but required per the protocol.

## **19. Quality Control and Assurance**

### **19.1. Risk Assessment**

NCTU, in collaboration with the Sponsor, has assessed the risk of this trial and will review the risk level regularly throughout the trial.

### **19.2. Trial Registration**

This trial will be registered with the International Standard Randomised Controlled Trial Number (ISRCTN) database and on the European clinical trials database (EudraCT).

### **19.3. Site Initiation and Training**

Site Initiation Visits (SIV) at each participating centre will be performed by the Chief Investigator or his delegate and by representatives from NCTU. SIVs should be conducted once appropriate approvals are in place, but may occur earlier if required. Recruitment must not start until all appropriate approvals are in place.

Specific training will be given to centre staff on use of the randomisation system, eCRF system and other trial related processes as appropriate.

### **19.4. Centre Monitoring and Auditing**

The trial will be monitored by Newcastle Clinical Trials Unit (NCTU) and representatives from NCTU will visit the centres periodically, and in accordance with a trial-specific monitoring plan. NCTU representatives will review the quality of the data to confirm that the trial is being run in accordance with the protocol.

NCTU representatives will review the Case Report Forms of patients who are randomised for this study, and will compare these directly to the medical notes and source data (a process known as source data verification (SDV)). SDV of consent and full SDV of all data fields will occur for a proportion of patients who enter the trial, chosen at random. All signed consent forms will also be reviewed.

At monitoring visits NCTU staff will also discuss the conduct of the trial with the local trial team and review the Investigator Site File.

In addition, the study may be evaluated by an auditor or government inspector, who will also be allowed access to all case report forms, source documents, study files and all study facilities.

Protocol compliance will be monitored by NCTU. Prospective, planned deviations or waivers to this protocol are not allowed. Any accidental protocol deviations will be documented on the relevant CRFs and reported to NCTU as soon as possible. Frequent and repeated protocol deviations are unacceptable and potentially constitute a serious breach.

### **19.5. Blinded Endpoint Review**

This trial has blinded endpoint analysis of the primary outcome measure (troponin T) and of the echocardiogram and troponin I secondary outcome measures.

Central laboratories in Newcastle upon Tyne and Teesside will analyse the troponin T and I, respectively. Laboratory staff will be blinded to trial allocation.

All echocardiograms will be sent securely to the Core laboratory, based at The James Cook University Hospital for review and reporting. The Core laboratory team will be blinded to trial allocation.

### **19.6. Serious Breaches**

A serious breach will be reported to the Sponsor as soon as it is identified. The sponsor will notify the MHRA and REC within 7 days of becoming aware of the serious breach. Serious breaches are defined as a breach of the protocol which is likely to affect to a significant degree the safety or physical or mental integrity of a trial patient or the scientific value of the trial.

### **19.7. Ethics and Regulatory Compliance**

#### **19.7.1. Good Clinical Practice**

The trial will be run according to the conditions and principles of ICH GCP, and in accordance with relevant UK legislation and the protocol.

#### **19.7.2. Approvals**

The trial will not start until a favourable opinion has been given by an NHS REC, and both MHRA and HRA approval has been granted.

### **19.8. Information Governance and Confidentiality**

The information collected as part of this trial will be stored securely both electronically and on paper and kept confidential. Data will be used according to the provision of the 1998 Data Protection Act, and applicable new regulations, and individuals will not be identifiable through any reports or publications that result from the trial.

Patients will be assigned a unique trial identifier at screening. All paper study files and documents, including personal data and each patient's consent form will be retained at the participating NHS Trust in a locked office prior to secure archiving at the end of the study. Electronic trial records will be kept on secure NHS servers with access restricted to the study team; these will be securely archived at the end of the trial. Research data will be transferred to Newcastle Clinical Trials Unit, Durham University, and to Newcastle University for analysis in collaboration with the clinical trial team.

Data will be entered onto an electronic case report form for each patient. The data will be validated as defined in the study-specific data management SOP. Data will be stored on secure servers that are external to both the sponsoring NHS Trust and to Newcastle and Durham Universities. Personal identifiable data on these servers will be encrypted and all data will have access restricted to authorised personnel and be password protected. Data extracted for review during the course of the trial, and for archiving at the end of the trial, will be stored securely in restricted access areas of the Newcastle and Durham University server systems. This data will be accessible to the full research team and to Newcastle Clinical Trials Unit, Durham University, and Newcastle University staff, as well as in summary form to members of the TSC, IDMEC, and TMG. There may be occasions when TSC or IDMEC members may need unique study ID, age, gender and ethnicity when reviewing data; where possible data will be aggregated or fully anonymised.

The data stored electronically in the database will contain the month and year of birth, gender, and ethnicity, and assigned trial number for each patient, but no other personal identifiable data.

Echocardiograms for each patient will be sent to the Echo Core Laboratory for review in a blinded manner. These data will be included in the final research data set for analysis.

Blood samples collected during the trial may be analysed by local and central laboratories. Additional samples will be taken and stored for use in further research.

Consent from individual patients will enable scan data, along with their other trial research data, and sample data, to be used in future research following the end of PROACT.

Patients who withdraw from the trial will have all data collected up until the point of withdrawal included in the study, except where withdrawal is due to a trial related AE. In this event the patient will be followed until a stable outcome is achieved. Where a patient who has withdrawn agrees, data to answer the primary endpoint of the study can be collected; this will be recorded and the data included in the trial analysis.

An auditor or regulatory inspector may access trial data as required.

### **19.9. Retention of Personal Data**

Personal data will be needed to enable follow-up of patients, and to disseminate details of the trial and trial findings to patients.

Personal data will be held securely and confidentially, and will be kept beyond the end of this trial. Follow-on funding may be sought to continue to follow patients. As such, personal data will be kept for 15 years after the last data collection point for all patients, even if this last data point rests beyond the end of this trial, before being confidentially destroyed.

## 19.10. Archiving

The responsibility for the archiving of clinical study data and documents rest with the sponsor; however, the management and arrangements for this will be delegated to NCTU. Archiving of local study files and data will rest with the PI. Essential documents will be archived as soon as practicable after the completion of the study. All essential documents, as defined by ICH-GCP guidelines, will be retained for a minimum of 5 years after completion of the trial and according to the timelines in the sponsor's SOPs.

## 19.11. Amendments

Changes to this study after favourable ethical opinion and MHRA authorisation has been obtained should follow the guidance outlined below. All amendments will be documented in the Trial Master File (TMF) and in study document tracking logs.

### 19.11.1. Non-substantial amendments

Examples of non-substantial amendments are:

- minor changes to the protocol or other study documentation, e.g., correcting errors, updating contact points, minor clarifications;
- changes to the research teams (other than appointment of a new principal investigator in a CTIMP);
- changes in the documentation used by the research team for recording study data;
- changes in the logistical arrangements for storing or transporting samples;
- extension of the study beyond the period specified in the application form.

Where non-substantial amendments are required, NCTU will notify all the relevant bodies.

### 19.11.2. Substantial amendments

A substantial amendment is defined as an amendment to the terms of the application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree: the safety or physical or mental integrity of the subjects of the study; the scientific value of the study; the conduct or management of the study; or the quality or safety of any investigational medicinal product used in the trial.

Substantial amendments must be approved by the HRA and the MHRA. The responsibility for deciding whether an amendment is substantial rests with the sponsor, and will be based on the advice of the CI and the research team. Notification/application for the amendment is also the responsibility of the sponsor but will be delegated to NCTU. NCTU will complete the EU Notification of Substantial Amendment form and follow the appropriate HRA/MHRA processes.

### **19.12. Funding**

This trial has been funded by the National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) Programme.

### **19.13. Insurance**

NHS Indemnity is in place to cover all aspects of clinical treatment and care provided as part of this trial.

Newcastle University has insurance to cover Newcastle Clinical Trials Unit's contributions to the Trial.

## **20. Trial Governance**

### **20.1. Centre Research and Development Approval**

Recruitment at each centre will only begin following all applicable approvals.

### **20.2. Trial Sponsor**

South Tees Hospitals NHS Foundation Trust is the trial Sponsor.

### **20.3. Co-ordinating Centre**

The trial will be co-ordinated by Newcastle Clinical Trials Unit, Newcastle University, where the Trial Manager will be based.

NCTU will be responsible for the trial database, randomisation, trial management, data management. The statistical analyses will be conducted by Durham University in collaboration with NCTU. The Chief Investigator and the research teams at each centre will manage the day-to-day running of the trial including recruitment at centres, and in collaboration with NCTU, the training of staff. NCTU will service the trial related committees and the expert panel.

### **20.4. Trial Management Group (TMG)**

The day-to-day supervision of the trial will be the responsibility of the Trial Management Group, who will report to the Trial Steering Committee. The TMG will meet regularly throughout the trial.

The TMG will consist of:

- The Chief Investigator
- The CTU co-Investigators
- The Trial Manager

The Data Manager, lead Research Nurse, lead statistician, and other members of the co-applicant team may attend TMG meetings as required.

### **20.5. Trial Steering Committee (TSC)**

NCTU, in collaboration with the Chief Investigator, will organise a trial steering committee (TSC) consisting of an independent chair, other independent members, at least one of which will be a patient who is not a trial participant, and the Chief Investigator. Independence will be defined as not employed by any organisation directly involved in trial conduct.

The TSC will be joined by non-voting members including the Sponsor, the NCTU co-Investigators, the Trial Manager, and other co-applicants as appropriate..

The TSC will meet at 6 monthly intervals. The TSC will report to the Sponsor and TMG, and to the Funder as required.

The TSC will provide overall supervision of the trial, and will monitor progress, conduct and advise on the trial. The TSC will consider the recommendations of the IDMEC, and act where required. The TSC carries the responsibility for deciding if the trial should be stopped early. Terms of reference for the TSC will be agreed at the first meeting.

#### **20.6. Independent Data Monitoring and Ethics Committee (IDMEC)**

NCTU, in collaboration with the Chief Investigator will organise an independent data monitoring and ethics committee (IDMEC). The IDMEC will meet at 6 monthly intervals and will run in accordance with a trial specific DAMOCLES charter<sup>41</sup> which will be agreed at its first meeting.

The IDMEC will report to the TSC and will provide advice on the ongoing conduct and safety of the trial. The IDMEC will review trial outcomes, including adverse events and serious adverse events.

## 21. Study report/Publications

The trial will be published in peer-reviewed journals following the end of the trial, and the data will be presented national and international meetings.

Results of the trial will also be reported to the Funder, Sponsor, and the REC within one year after the end of the trial.

Trial participants will be informed about the trial results at the end of the trial, including in a lay summary.

The data will be the property of the Sponsor at the end of the trial.

### 21.1. Data sharing

We are committed to sharing de-identified individual level data, where a rigorous research question may be answered by the data. The research team including the CTU and Chief Investigator will consider proposals from researchers as long as there is no constraint due to:

- Ethical approval and informed consent
- The NIHR contract
- The request does not require the data prior to publication of the main trial findings
- The request for data does not extend beyond that which is needed to answer the specific research question.

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