

**Strain sUrveillance during Chemotherapy for improving Cardiovascular OUtcomes**

**(SUCCOUR Study)**

**PROTOCOL**

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# FUNDING

Support is being sought from multiple sources including GE Medical Systems and National Health and Medical Research Council of Australia (NHMRC).

# CLINICAL TRIAL REGISTRATION

The SUCCOUR Study will been registered with the publically accessible Australian New Zealand Clinical Trials Registry (ANZCTR) and an Australian New Zealand Clinical Trials Registry Number (ANZCTRN) is ACTRN12614000341628 (Date Registered: 31/March/2014).

# 

# ethics and good clinical practice statement

The SUCCOUR Study has been designed and will be performed according to the principles of the International Conference on Harmonisation (ICH) and the guidelines of Good Clinical Practice (GCP) enunciated within the Declaration of Helsinki. Specifically, this study will follow the *National Statement on Ethical Conduct in Research Involving Humans* written by the National Health and Medical Research Council (NHMRC) and the *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)* produced by the Therapeutic Goods Administration (TGA), both of which are the Australian ethical standards against which all research involving humans, including clinical trials, are reviewed.

The study will not commence without written approval from appropriate Human Research Ethics Committees (HRECs) that comply with the NHMRC National Statement. Primary ethics approval will be sought and obtained from each participating site. All participants will provide written informed consent prior to study commencement. The Protocol and Participant Information and Consent Form will be reviewed and approved by a properly constituted HREC before study start as acknowledged by a signed and dated Ethics Approval Certificate.

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# 1. background

Anthracycline drugs are widely used in the treatment of hematologic malignancy, sarcoma and breast cancer. The latter is the most common cancer in women, and the chance of developing invasive breast cancer during a woman's lifetime is approximately 1 in 7, with a mortality of about 1/33 (1). As cancer therapies and survival have improved, millions of patients treated with cardiotoxic therapy are now cancer survivors (2). Prolongation of survival resulting from cancer treatment allows patients to live long enough for cardiac toxicity to become the main determinant of quality of life, and in some cases premature mortality – in fact, for early stage breast cancer, a patient is more likely to die from heart disease than cancer. **Our preliminary work from the SEER-Medicare database in the USA showed a cohort treated from 2002-7 to have a 5 year incidence of heart failure of 18%.**

Not only anthracyclines but also multiple therapies used in cancer treatment are cardiotoxic. For example, trastuzumab (Herceptin) is a very effective therapy often used in conjunction with anthracyclines in the particularly aggressive cancers over expressing the growth factor receptor gene HER2 (HER2+ cancers). Trastuzumab increases the cardiotoxicity of anthracyclines; left ventricular (LV) dysfunction is noted in 19-41% of patients in studies administering trastuzumab after anthracycline-based chemotherapy. Anthracycline-induced cardiomyopathy has been associated with an especially poor prognosis, with a 2 year mortality of up to 60%.

As late-stage heart failure has such an adverse prognosis, attention has been directed towards recognition of Stage B heart failure - defined in patients with structural disease but without signs and symptoms of heart failure. This group of patients benefits from treatment with b-blockers and ACE inhibitors. While stage B heart failure is readily defined in a patient with a scar after myocardial infarction, its recognition in a patients with diffuse disease is more challenging.

Left ventricular ejection fraction (LVEF), most commonly assessed by echocardiography, is an important predictor of outcome, and is widely used to monitor cardiac systolic function after chemotherapy. Recent guidelines suggest that a reduction of LVEF >5% to <55% with symptoms of heart failure or an asymptomatic reduction of LVEF of >10% to <55% constitute cardiotoxicity. However, the measurement of LVEF presents a number of challenges related to image quality, assumption of left ventricular geometry and expertise. The 95% confidence intervals of measured LVEF are ±11%, so this method fails to detect subtle alterations in LV function. In addition, LVEF is dependent on hemodynamic conditions.

Two-dimensional strain (AFI) is an automated and quantitative technique for the measurement of global long-axis function from gray-scale images. 2D based strain may help the clinician recognize the chemotherapy patient that has evidence of abnormal function, and has been incorporated in international guidelines as a standard approach to assessing cardiac function responses to chemotherapy (Plana JC, J Am Soc Echocardiogr 2014;27:911-39). Different sites use strain and ejection fraction as part of routine practice, and this study will help to define which of these strategies provides the best outcomes. Our previous work has shown that **GLS correlates with LVEF, and GLS is a superior predictor of outcome to EF.** Recent work by our and other groups has shown that changes in tissue deformation, assessed by myocardial strain, identify LV dysfunction earlier than conventional echocardiographic measures in patients treated with chemotherapy. **However, these observational data are insufficient to justify a change from EF to strain for surveillance of these patients – first because the data are non-randomized and second because there is no evidence that the identification of subclinical dysfunction will change the outcome of these patients.** The applicants have initiated this process - in an observational study, we have shown beta-blockade to lead to improvement in patients where reduction of strain was documented.

# 2. STUDY Rationale

The purpose of this application is to perform a randomized study which will define the value of strain in patient management, by identification of subclinical LV dysfunction, which will be used to guide cardioprotective therapy.

# 3. study hypotheses & study endpoints

## 3.1 Hypothesis

The **Strain sUrveillance during Chemotherapy for improving Cardiovascular OUtcomes (SUCCOUR) Study** will test the following hypothesis:

Information from strain imaging leads to the use of adjunctive therapy that will limit:

* the development of LV dysfunction
* interruptions to planned chemotherapy
* development of heart failure in follow-up

The primary objective of this study is to show that information from strain imaging leads to the use of adjunctive therapy that will limit the development of reduced ejection fraction at a maximum of 3 years (see Section 3.3).

## 3.2 Primary End-Point

Consistent with the study hypothesis, the primary study end-point is change in 3D ejection fraction from baseline to up to three years,as determined by a blinded core laboratory and analyzed on an intention-to-treat basis according to random study group allocation.

## 3.3 Secondary End-Points

Secondary endpoints (from baseline to up to three years) will be:

* Development of cardiotoxicity – ie a categorical analysis of reduced LVEF concordant with the recent guidelines (reduction of LVEF of more than 5% to less than 55% with symptoms of heart failure, or an asymptomatic reduction of LVEF of more than 10% to less than 55%).
* Comparison of the rate of completion of the planned chemotherapy among groups.
* Comparison of the rate of heart failure among groups.

# 4. METHODOLOGY

## 4.1 Study Design

The study hypotheses will be examined via a multi-center randomized controlled trial (PROBE design) of strain in patients undergoing cardiotoxic chemotherapy, comparing a surveillance strategy using strain from conventional surveillance based on EF. Patients coming to the echo lab for echo surveillance of LV function will be randomized to provision of global strain (GLS) and ejection fraction (EF) or receive standard EF alone. If strain decreases, this will be reported to the treating physician and a recommended regimen and titration of beta blockers and ACE inhibitors will be initiated.

This study will be based on the CONSORT guidelines for the practice and reporting of randomised trials. **Figure 1** shows the overall design of the ***SUCCOUR Study***.

## 

## 4.2 Study Centres

In this multicenter study, participants will be recruited from three regions:

* Australia/Asia – Menzies Research Institute Tasmania: responsible site investigator Professor Tom Marwick
* North America – University of Toronto: responsible site investigator A/Prof Dinesh Thavendiranathan
* Europe – to be determined

The coordinating site will be Menzies Research Institute, with responsibility for study randomisation, data management and core imaging laboratory for primary endpoint determination.

## 4.3 Participants

This study will be conducted in patients undergoing chemotherapy at increased risk of cardiotoxicity (see below). Individuals can participate in the study if they fulfil inclusion criteria i-iii and fulfil none of the exclusion criteria as described below.

**Inclusion Criteria:**

1. Patients actively undergoing chemotherapy at increased risk of cardiotoxicity;

use of anthracycline WITH current (but not necessarily concurrent)

trastuzumab (Herceptin) in breast-cancer with the *HER2* mutation OR

tyrosine kinase inhibitors (eg sunitinib) OR

cumulative anthracycline dose >450g/m2 of doxorubicin, or equivalent other anthracycline cumulative dose (eg for epirubicin >900g/m2).OR

increased risk of HF (any two of age >65y, type 2 diabetes mellitus, hypertension, previous cardiac injury eg. myocardial infarction)

1. Live within a geographically accessible area for follow-up
2. Are able and willing to provide written informed consent to participate in the study (this includes the ability to communicate fluently with the investigator and that the patient is mentally competent)

**Exclusion Criteria:**

* Unable to provide written informed consent to participate in this study
* Participating in another clinical research trial where randomized treatment would be unacceptable
* Valvular stenosis or regurgitation of >moderate severity
* History of previous heart failure (baseline NYHA >2)
* Systolic BP <110mmHg
* Pulse <60/minute
* Inability to acquire interpretable images (identified from baseline echo)
* Contraindications/Intolerance to beta blockers or ACE inhibitors
* Existing therapy with both beta blockers and ACE inhibitors
* Oncologic (or other) life expectancy <12 months or any other medical condition (including pregnancy) that results in the belief (deemed by the Chief Investigators) that it is not appropriate for the patient to participate in this trial

## 4.4 Study Power

Assumptions (see figure)–

1) cutoff for strain = 11% decrement (Negishi JASE in press)

2) cutoff for EF = 10% asympt drop to <55% (Seidman AD, JCO 2002)

3) reduction in EF in at risk patients at 3m = 21% (Sawaya, AJC 2011)

4) response to medical Rx in patients with reduced EF=40% (from Cardinale).

5) development of HF in 41% at 3y (from Chen, JACC 2013).

6) reduction in strain in at risk patients = 34% (from submitted “3 toxic regimen” paper by Negishi, using 11% reduction strain).

7) response to therapy based on strain = 90% (from submitted “3 toxic regimen” paper by Negishi, based on 11% reduction strain).% (unpublished observation).

8) Reduction in EF of patients with reduced strain = 14% (from prelim data).

Calculations –The primary outcome is the change of EF in the usual care and strain surveillance groups. Based on a 9.7±5% reduction in usual care and a 5±5% reduction in the strain surveillance group, we would have an 80% power to identify a difference at p<0.05 using an intention-to-treat approach. To allow for drop-outs we will recruit 320 patients.

The secondary outcome is based on the development of cardiotoxicity. Assuming 40 (29%) and 24 (17%) patients developing cardiotoxicity (symptomatic fall >5% or asymptomatic fall >10%), a study of 138 patients/group would give 80% power to identify a difference at p<0.05 using an intention-to-treat approach.

## 4.5 Screening and Recruitment Procedures

Based on profiling patients undergoing chemotherapy for those at increased risk of cardiotoxicity, we seek 320 patients who will be subject to the following screening and recruitment process:

**STEP 1: Identification of potentially eligible participants**

At each study site, a range of recruitment strategies targeting potentially eligible subjects will be applied. These reflect the different institutional settings and will include:

* Detailing of oncology teams
* Posters and information brochures for patients and relatives being treated for cancer at the health care facilities attached to each centre

Once a patient is identified as being potentially eligible, the rationale for the study and other aspects of the patient information and consent document will be discussed in a face-to-face conversation with one of the investigators.

**STEP 2: Initial risk profiling of at risk individuals (Eligibility Visit)**

Baseline imaging will be used to identify whether image quality is suitable for enrolment. Suitable patients will proceed to randomization.

## 4.6 Measurement of LV function

A key feature of this study is on-site strain (GLS) measurement to further delineate risk of cardiotoxicity. It is important that this occurs at the site, as that is how the test will be used in practice. A standardised training and accreditation program will be coordinated through GE Medical Systems to ensure that each lab undertaking “point-of-care” GLS measurement will obtain accurate images.

Patients will undergo an echocardiogram at baseline (defined by start of anthracycline with other risk factors, anthracycline with previous course, or Herceptin). Testing will be repeated according to the study procedures in Table 1, using standard ASE measurements as follows:

* M-mode assessment of LV mass
* 2D echo assessment of LV volumes and EF, with contrast used if necessary. If contrast is used at baseline, it should be used at all other visits. Contrast use should ONLY be performed after acquisition of all other measures especially LV strain
* 3D echocardiography assessment of LVEF will be performed by acquiring a full- volume dataset using a matrix array transducer. Using offline analysis software (the same software should be used for each visit), this dataset will be manipulated to derive conventional 4-chamber, 2 chamber and short axis views. After selection of annular and apical reference points, a 3-dimensional endocardial shell will be constructed using semi-automated contour tracing. The resultant end-diastolic and end-systolic volumes will be used to calculate 3D- LVEF (EchoPAC 3DLVQ).
* Transmitral flow will be measured using pulsed-wave Doppler at the leaflet tips, aligned with the direction of LV filling. Mitral E and A waves, and medial and lateral mitral annular velocities (e’) will be measured. The class of diastolic dysfunction was determined using the E/e’, LA size and age-predicted normal range for E wave deceleration time as follows: class I – delayed relaxation; class II – pseudonormal filling (normal deceleration time for age in the presence of LA enlargement); and class III – restrictive filling (short deceleration time).
* Left atrial volume will be calculated from the apical 4- and 2-chamber views using the Simpson’s rule method.
* In addition to standard echocardiography, the three apical views will be acquired at increased frame-rate (50-70frames/second). Cine-loops of 5 cardiac cycles will be saved digitally and analyzed offline, to allow Doppler-independent strain and strain rate to be assessed using offline semi-automated speckle tracking techniques (Echopac, GE Medical Systems). Timing of the aortic valve opening and closure will be obtained using single-gated pulsed wave Doppler traces. The three apical views will be used to obtain an average global peak systolic longitudinal strain and peak systolic longitudinal strain rate, with systole manually defined by aortic valve closure. After initial tracing of the endocardial border and software processing, the operator will confirm adequate tissue tracking. Segments unable to be adequately tracked will be excluded.

The calculation of mean strain will be derived from model of the entire LV. All measures will be made in a blinded fashion by a single observer at each site. Images will also be collected on a secure server at the core laboratory.

If an individual shows evidence of cardiotoxicity (as usually defined by 5% symptomatic or 10% asymptomatic fall of EF to <55%), cardioprotective therapy will be initiated - this will be analogous in all patients. In some circumstances, this will lead to discontinuation of chemotherapy – if this occurs, LV measurements will be taken.

All baseline and final 3D images will be subsequently sent to the core laboratory at Menzies Research Institute for independent blinded measurement. In addition, a random 10% of strain images will be quantified at the core lab for verification of on-site measurements.

In order to complete study enrolment over 18 months from 2014-15, each site is expected to recruit ~10-15 patients per year.

## 

## 4.7 Baseline Profiling

Prior to study randomisation, the following baseline data will be collected by participant self-report and verified by personal interviews with the individual if required:

* ***Demographic profile***: age, sex, marital status, social support, income, education, ethnicity and language;
* ***Chemotherapy*** and radiotherapy treatment
* ***Treatment(s)***: existing prescribed medications (if any) and type of non-pharmacologic treatments (if any). The following should be archived on the CRF;

Permanent pacemaker

Diuretics

Anticoagulants

Antiarrhythmic drugs

ACE inhibitors

Statins

Antidiabetics or other drugs known to cause provoke fluid retention (eg NSAIDs)

* ***Clinical profile***: this includes a physical assessment to measure height, weight, waist and hip circumference, blood pressure, vital signs and past/concurrent cardiac and non-cardiac disease states including history of cardiovascular risk factors (DM, Hx smoking, total cholesterol), known CAD, valvular heart disease, NYHA class.
* ***Functional/general and mental health status****:* Health-related quality of life (EQ-5D)
* ***Neoplastic history*** *– type of cancer*
* ***Pathology*** renal function, glucose level, TnI, BNP;
* ***ECG***- arrhythmia assessment, conduction abnormalities

## 4.8 Clinical Safety

Safety evaluations will be performed by recording adverse events (AEs), serious adverse events (SAEs), and by monitoring laboratory parameters, physical examinations, ECGs and vital signs.

The following cardiac events will be considered:

1) sudden death;

2) death resulting from a cardiac cause;

3) acute pulmonary edema;

4) overt HF requiring hospitalization;

5) life-threatening arrhythmias requiring treatment; and

6) conduction disturbances requiring a permanent pacemaker implantation.

## 4.09 Randomisation

Consenting individuals will be centrally randomised using a computerized protocol at a ratio of 1:1 strain vs usual care. Block randomisation for the participating centres will be applied.

Conventional imaging: If there is a symptomatic drop of more than 5% of ejection fraction, or a 10% asymptomatic drop of ejection fraction to EF <55%, the patient will be referred for initiation and titration of heart failure therapy (see below)

Advanced cardiac imaging: If there is a reduction of global longitudinal strain by >12% in any of the follow-up echocardiograms (3,6,9,12), as compared to baseline, the patient will be referred for initiation and titration of heart failure therapy (see below).

## 4.10 HF Intervention

The intervention is based on the combination of both ACE inhibition and beta blockade. Internationally, not all sites have access to the same two agents. Therefore this protocol is indicative. Patients will be initially treated with ACE inhibition – eg. ramipril at a dose of 1.25 or 2.5 mg (according to baseline systemic arterial pressure), once or twice a day, and gradually up-titrated to 10 mg/day, or to the maximal-tolerated dose. An alternative ACE inhibitor or ARB at equivalent dose is acceptable. In patients receiving low dose ACE inhibition (eg. at least 2.5 mg/day of ramipril, or equivalent), carvedilol will be started at an initial dose of 6.25 (3.125 mg twice a day) and progressively up-titrated to the maximal dose of 50 mg/day. An alternative beta blocker at equivalent dose is acceptable. Additional heart failure therapy (diuretics, anticoagulants or antiarrhythmic drugs) can be given at the discretion of the cardiologist.

Titration schedule

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Weeks since starting therapy | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 |
| Ramipril (mg/d)\* | 1.25 | 2.5 |  |  |  |  |  | 5 | 10 |
| Carvedilol (mg/d)# |  |  | 6.25 | 12.5 | 25 | 37.5 | 50 |  |  |

Patients will be seen every 2 weeks during the uptitration phase. At each of these visits, symptom status (fatigue, dizziness), BP and HR will be obtained. If patients complain of side-effects or the HR is <50/minute, the dose should be reduced to that prior to the last increment.

\*In countries where ramipril or carvedilol are unavailable for this indication, perindopril or metoprolol will be used.

*Discontinuation criteria;* Patients with intolerable side-effects of therapy (eg. severe fatigue), may discontinue therapy but will remain in the study on an intention-to-treat basis.

As indicated above, the process of randomization will involve imaging strategy rather than therapy – all patients with LV dysfunction will be given the same therapy – the difference will relate to as what level of LV impairment this is administered.

## 4.11 Study Timelines and Follow-up

Participant recruitment utilising this current protocol is planned to commence in Q4 of 2013 and conclude at end 2018 (5 years in total). Outcome data will be censored 24 months following the recruitment of the last patients (end 2020).

## 4.12 Data Collection and Management

Consistent with the study schema in **Table 1**, assessments will be undertaken at a series of mandatory time-points and will include completion of a standardised set of easy to use Case Report Forms ([CRFs] designed and managed by MRIT). A permissible window of one month either side of the scheduled study visit will allow for scheduling flexibility. Appointment cards and reminder phone calls and/or letters will be utilised to reduce the loss to follow-up. Study participants will be reminded of the need to adhere to the study schedule. Completed CRFs for additional visits will also be required.

Study data capture, analyses and archiving will be coordinated via MRIT using well established resources (including electronic capture of paper-based CRFs). Investigators and/or Research Nurses will enter the information required by the protocol into the MRIT CRFs. Non-obvious errors or omissions will be recorded on Data Query Forms which will be returned to the investigational site for resolution. Study monitors will verify randomly selected study data against source documents via a systematic auditing program.

## 4.13 Statistical Analyses

Primary data analysis will compare the outcomes of patients will be compared with a t-test (change in EF) or survival analysis (heart failure and cessation of treatment). Multivariable models (respectively linear and Cox regression) will be developed to identify effect size, and will be extremely important if groups are mismatched despite randomization. All analyses will be performed on an intention to treat basis. Subsequent analyses will include the same methods to compare differences in the secondary end-points.

The data from all participating investigational sites will be pooled and summarised with respect to demographic and baseline characteristics. Exploratory data analyses will be performed using descriptive statistics. Data will be presented for the complete intent-to-treat (ITT) population (all patients having taken part in a significant proportion of the study but did not complete follow-up data collection and/or had major protocol deviations) as well as the per-protocol population (ITT patients who completed the study).

Survival curves will be constructed using time-dependent, all-cause survival and event-free survival data for all patients on an ITT basis followed by log-rank and Breslow tests to determine differences between groups with respect to the number and/or timing of events. To examine the interactions between risk factors and treatment mode and other potential correlates of event-free survival and all-cause mortality during study follow-up we will construct Cox-Proportional Hazards Models with calculation of relative risk (RR) and 95% confidence interval. Multiple logistic regressions will be used to determine independent correlates of clinical events at fixed time-points.

A *Clinical Safety and Efficacy Committee* (CSEC) led by an experienced clinician will review the safety findings at the end of each year and the efficacy findings after 2 years. All endpoints will be blindly adjudicated (including determination of probable causality). The CSEC will use the Haybittle-Peto stopping rule at a p=0.001 level of significance (which is unlikely).

**Table 1. Study procedures**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study Procedures | Screening/ Baseline | Week 1-2 | Month 3 | Month 6 | Month 9 | Month 12 | Month 24 | Month 36 | Early Discontinuation Visit |
| Informed Consent | X |  |  |  |  |  |  |  |  |
| Medical History a | X |  |  |  |  |  |  |  |  |
| Physical Exam | X |  |  |  |  |  |  |  | X |
| 12 Lead ECG b | X |  |  |  |  |  |  |  | X |
| Echocardiogram | X |  | X | X | X | X | X | X | X |
| Vital Signs (BP, HR, RR) | X | X | X | X | X | X | X | X | X |
| Usual care labs (including high-sensitivity troponin I [hsTnI], N-terminal pro–B-type natriuretic peptide [NT-proBNP, Chem Panel, Creatinine Clearance) as per local practice | X | X | X | X | X | X |  |  | X |
| Quality of life (EQ5D) | X | X | X | X | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X |
| AE/SAE Assessment | X | X | X | X | X | X | X | X | X |
| Heart Failure Assessment (NYHA-HF)-see attachment 1 | X | X | X | X | X | X | X | X | X |
| Chemotherapy Regimen & Review c | X | X | X | X | X | X |  |  | X |
| Reinforce dispensing cardioprotective drug |  | X | X | X | X | X |  |  |  |
| Medication Compliance (pill counts) | X | X | X | X | X | X |  |  |  |

a- History of cardiovascular risk factors, known CAD, valvular heart disease; BMI, side of breast cancer, Hx DM, Hx smoking, total cholesterol

b- 12 lead ECG with arrhythmia assessment, conduction abnormalities

c- Time from chemotherapy completion to HF symptoms; Interruptions in planned chemotherapy; completion or discontinuation of chemotherapy

**Figure 1. Patient allocation and study design**

