An Integrated Consent Model Study to Compare Two Standard of Care schedules for monitoring cardiac function in patients receiving Trastuzumab for early stage breast cancer: REaCT-EF

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PROTOCOL SIGNATURE PAGE

My signature below confirms that I have reviewed and approved this protocol, and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and all applicable local regulations

_____

Qualified Investigator (Please Print)

_____

Qualified Investigator Signature

_____

Date

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1 BACKGROUND

Approximately 20-25% of breast cancer tumours over-express Her2-neu, a pro-oncogenic surface receptor of the epidermal growth factor receptor family (1). Her2-neu amplification is a positive predictor for response to trastuzumab, an antibody which inhibits Her2-neu growth signalling. Several large adjuvant trastuzumab trials have demonstrated improved overall survival, in patients with early stage breast cancer, with a 33% decrease in risk of death (2). However, retrospective analyses of patient outcomes in these trials have demonstrated increased risk of cardiotoxicity (i.e. damage to the heart) in a small number of patients (4-8% in NASBP B-31) (3). According to the American College of Echocardiology recommendations, cancer therapeutics-related cardiac dysfunction is defined as a decrease of at least 10% in left ventricular ejection fraction (LVEF) to below a threshold of 53% (4). Left ventricular ejection fraction, has traditionally been used to assess cardiac function in patients receiving potentially cardiotoxic systemic therapy.

At this time, we are unable to predict which patients are at increased risk of cardiac-related treatment complications. Currently all patients receive regular cardiac imaging throughout their one year of trastuzumab treatment. A number of imaging strategies (which measure LVEF) are used to screen and monitor for cancer treatment-induced cardiotoxicity, including transthoracic echocardiography (ECHO) and multiple gated acquisition scan (MUGA) (4)). However, the vast majority of patients, who are at low risk of cardiac complications, may not require such frequent monitoring. Imaging significantly increases cost to the health care system and can reduce the patient's quality of life. At this time, the optimal monitoring schedule for trastuzumab-related cardiotoxicity remains unknown, and several published consensus guidelines are currently in use as "standard of care". The UK National Cancer Research Institute Breast Clinical Studies group recommends cardiac imaging every 4 months while receiving adjuvant trastuzumab therapy (5), while both the European Society of Medical Oncology and the National Comprehensive Cancer Network (NCCN) guidelines suggest cardiac monitoring every 3 months (6, 7). All published guidelines acknowledge a lack of evidence supporting a defined cardiac monitoring schedule. Interestingly, a recent SEER study from the USA showed that only 36% of older patients treated with trastuzumab received cardiac monitoring according to the NCCN guidelines (8).

This state of clinical equipoise is demonstrated by breast oncologists within our own institution where some oncologists order cardiac scans every 3 months, and others every 4 months. Therefore, at this time, it is not known which standard monitoring schedule is optimal. To our knowledge, no published clinical trial has ever prospectively compared these two standards of care. All cardiac monitoring schedules are funded in Ontario, and there is little incentive for physicians to identify the best strategy. When multiple standards of care exist, clinicians often choose their approach based on those of other colleagues, or purely on personal preference. Despite this, determining the optimal treatment remains an important medical issue for patients, physicians and society. Defining an optimal and uniform cardiac monitoring schedule will streamline the management of patients receiving potentially cardiotoxic therapy, improve quality of life for patients, and potentially reduce cost to the health care system without compromising safety or efficacy of cancer treatment.

As demonstrated by variations in practice, physicians do not know the "best" cardiac monitoring schedule for their patients and therefore, genuine uncertainty ("clinical equipoise") exists. A novel method to allow comparison of established standards of care is needed as part of an increasing internationally mandated incentive to perform more pragmatic clinic trials. Pragmatic clinical trials which commonly incorporate comparative effectiveness research – that is, comparing the safety and effectiveness of diagnostic, therapeutic or delivery systems – can help overcome these challenges of deciding optimal cardiac monitoring schedules, when multiple choices exist and are in common use. These studies, in addition to the ability to leverage patient data from electronic health records to increase sample size of trials at much lower costs, is enabling major national and international initiatives to generate the data needed to improve care (9).

This study will use a novel method to allow comparisons of established standard of care for cardiac monitoring using the "integrated consent model" as part of a pragmatic clinical trial (10). By integrating medical and clinical practices, physicians will be able to inform their patients about the RCT, akin to a typical conversation between the physician and patient, without written informed consent. This clinical interaction would then be documented, as ordinarily done in clinical practice. This study is similar in design to the ongoing React-TC (20140380-01H) and React-G (20150316-01H, OCBRE #14-059) studies at the Ottawa Hospital Cancer Centre, and

extends the concept of integrated consent to the provision of cardiac monitoring. As of January 1st 2016 these ongoing REaCT trials have accrued over 150 cancer patients with excellent patient and physician endorsement.

We will explore whether the integrated consent model is feasible with regards to ordering routine cardiac imaging; whether it can be used to increase the number of physicians and patients who take part in clinical trials, and address the critical issue around optimal cardiac monitoring in patients receiving trastuzumab therapy for early stage breast cancer.

2 OBJECTIVES

2.1 Primary objective

To demonstrate that cardiac monitoring (echocardiogram/MUGA) every 4 months is not inferior to every 3 months in the detection of cardiac dysfunction (as defined as a decrease of at least 10% in LVEF to below a threshold of 53%) in patients receiving trastuzumab-based therapy for early breast cancer.

Secondary objectives

1) To compare the two study arms for: 1) changes in left ventricular ejection fraction (LVEF); 2) delay or discontinuation of trastuzumab therapy; 3) referrals to cardiology; and 4) health-related quality of life.

2) To determine feasibility of study physicians using an integrated consent model to enter participants on this study. Feasibility will be reflected through a combination of endpoints including physician engagement, accrual rates, and physician compliance.

3 STUDY DESIGN

This will be a multi-center unblinded randomized trial**.** This trial will accrue participants at multiple sites across Ontario including the Ottawa Hospital Cancer Centre.

4 METHODS

Investigators will approach potentially eligible patients with early stage breast cancer (stage I to III) scheduled to receive trastuzumab-based therapy. The physician will inform their patient about the RCT study, akin to a typical conversation between the physician and patient. Patients will be asked to provide oral consent to be randomized to cardiac investigations every 3 months, or every 4 months while receiving trastuzumab therapy. An oral consent script will be given to the patient (see below). Written informed consent will not be sought as the integrated consent model is ethically acceptable as the only prominent change to the standard of care treatment is the randomization process. Eligible and consented patients will be randomized using a permuted block design developed by The Ottawa Hospital's Methods Centre to receive cardiac evaluation (by either transthoracic echocardiography or MUGA) every 3 months, or every 4 months while on treatment. The physician can randomize a patient either through a secure web-based randomization system on the clinic desktop or mobile device, or through the designated site study CRA. The CRA will ensure that the dictated consent process has taken place.

Patients will be asked to complete a health questionnaire and the EQ-5D 5L quality of life questionnaire (11) before starting chemotherapy, at the time of the first cardiac scan and at the end of 1 year follow up. To enhance the ability of patients being able to complete the questionnaire, depending on the patient's preference, the questionnaire may be emailed (from secured TOH e-mail address) or mailed from the CRA.

5 CONSENT SCRIPT

In this study the investigator will obtain oral consent using the following prepared REB approved script.

An Integrated Consent Model to Compare Two Standard of Care Schedules for Monitoring Cardiac Function in Patients Receiving Trastuzumab for Early Stage Breast Cancer: REaCT-EF

Principal Investigator: Dr. Susan Dent of the Ottawa Hospital Cancer Centre (613-737-7700, ext. 70167)

Our discussion today is a new approach of informing and consenting patients to participate in this study. The traditional approach is to provide a paper copy of the detailed information sheet and consent form for you to sign. Using this integrated model for consenting we will have a discussion and you may give a verbal consent to participate or not to participate. I will document our discussion and your decision in your progress notes that are part of your health records.

As we've talked about, you will be receiving trastuzumab as part of your breast cancer therapy. Because this medication can cause a reduction in your heart function, we will monitor your heart with routine scans throughout treatment. At this time, we do not know the best schedule for monitoring your heart. However, we do know that unnecessary scans are an inconvenience to patients, and considerably increase health care costs. Some physicians order heart scans every three months while on therapy and others order scans every four months. There are published guidelines which support both schedules; however they have never been compared directly. Because we really don't know if one is better than the other, we are conducting this study to answer this question. Study participants will be randomly (like a flip of a coin, so that we can obtain an unbiased answer) assigned to either an every three month or every four month scanning schedule, and then we will compare the results over a period of 1 year. We are also looking at how feasible it is for study doctors to enter participants on this study using this integrated consent model. If you choose to participate there won't be any special procedures or visits required of you. Your verbal consent would simply allow us to randomly assign you to the three month scanning schedule or the four month scanning schedule and then collect the results of those scans for 1 year.

You will be asked to complete a health questionnaire about your quality of life and health while you are receiving treatment at 3 different timepoints. The timepoints of the questionnaire will be before starting chemotherapy, at the time of your first scan and at the end of the 1 year follow up period. As this study does not involve any additional visits to the cancer clinical beyond your usual visits, if you wish we can email or mail you the questionnaires. If you agree, we will obtain your email or mail address. Your email or mail address will be stored in a de-identified electronic file on the secure hospital network and will only be accessible by the study coordinator. The questionnaires will take you approximately 5-10 minutes. You do not have to answer any questions that make you uncomfortable.

Your medical records will be consulted in order for us to conduct a cost-effectiveness analysis from the perspective of the health care system.

If you choose to participate and then change your mind later, we can discuss together how to proceed; likely this would mean switching to the preferred follow up schedule of your treating oncologist.

Your participation in this study is voluntary. If you choose not to participate, your decision will not affect the care you receive at this institution at this time, or in the future. You will not have any penalty or loss of benefits to which you are otherwise entitled to.

All research-related records will be kept for 10 years after termination of the study. No identifiable information will leave this institution. On all study related documentation, you will be identified with an independent study code rather than your name or other personal identifying information. The Ottawa Health Science Network Research Ethics Board (OHSN-REB) and the Ottawa Hospital Research Institute may review your original medical records and relevant study records for audit purposes, under the supervision of Dr. Dent.

If you have any questions about this study please contact one of the study investigators, Dr. Susan Dent (613-737-8899, ext. 70167) at TOHCC.

The OHSN-REB has reviewed this protocol. The Board considers the ethical aspects of all research studies involving human participants at the Ottawa Hospital Cancer Centre. If you have any questions about your rights as a study participant, you may contact the Chairperson at 613-798-5555, extension 16719.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Do you have any questions?

You will receive a copy of this document for your reference.

If the patient agrees to participate the physician will dictate in the progress note they have had the above conversation with the patient. There will be no need for the patient to sign an informed consent form.

6 ELIGIBILITY

6.1 Inclusion Criteria

- Histologically confirmed early stage HER2-positive breast cancer
- Planned trastuzumab therapy for early stage breast cancer
- ≥18 years of age
- Able to provide verbal consent
- Normal LVEF (>53%) before trastuzumab therapy

6.2 Exclusion Criteria

- Contraindication to transthoracic echocardiography or MUGA

7 RANDOMIZATION

We will randomize participants using a web-based system developed by the Methods Centre at The Ottawa Hospital. Each site investigator will have the web-based randomization system short-cut uploaded to their device in order to randomize participants. The physician must dictate that the verbal consent and eligibility review has taken place prior to randomization. The investigators will then forward the randomization confirmation email indicating the selected cardiac monitoring schedule to the local study CRA. Stratification will be performed for anthracycline and non-anthracycline-based chemotherapy. Screening and randomization logs will be kept on file.

8 DATA COLLECTION

Once the patient has been randomized, the study CRA will collect participant information on LVEF, delay/discontinuation of trastuzumab therapy, referral to cardiology, or rates of hospitalization, all recorded in real-time via electronic health records. To facilitate timely data collection, the treating physician will automatically receive an email (generated at the time of randomization) at the time of the next patient clinic visit. This email will ask for details of any cardiac complications the patient may have had since the last clinic visit. From a study standpoint only the CRA will access this information. Data not available at the time of visit will be collected from the dictated physician note. CRAs will complete the paper case report forms (CRF). The data will then be transcribed onto case report forms.

Participant data to be collected over the treatment period:

- Date of birth (month, year)
- Past medical history (history of cardio-vascular co-morbities)
- Body mass and height to calculate body mass index (kg/m^2) (cardio-vascular co-morbidity)
- Type and dose of current or new cardiac medications

- Chemotherapy treatment received
- Type of cardiac monitoring - echocardiography or MUGA
- Schedule of cardiac monitoring (3 vs. 4 months)
- Baseline and follow-up LVEF (%)
- Rate of treatment delay/discontinuation
- Referral to cardiology
- Estrogen and progesterone receptor status
- Hospitalisations or visits to the emergency room and reason while on study
- Changes to chemotherapy, trastuzumab or cardiac medications while on study
- Health related quality of life at baseline, the first cardiac monitoring (3 or 4 month) and the end of the follow-up using the EQ-5D-5L questionnaire
- Health related questionnaire at baseline, , the first cardiac monitoring (3 or 4 month) and the end of the follow-up
- To assess physician engagement (i.e. the proportion of patients who enter the study) pharmacy records will be assessed in order to calculate the number of patients receiving trastuzumab on the study and off the study
- To assess Percentage of medical oncologists who attend the site initiation visit and have agreed to participate in the trial compared to the percentage of medical oncologists that actually approached patients regarding the trial log of initiation visit will be collected.

If the patient is randomized and either the patient or physician refuses the randomization selection, reasons for this will be recorded. If physicians choose to break the protocol, they must inform the patient and investigative team as to why the allocated selection should not be used from the randomization process. We will monitor the charts to ensure that this reason has been recorded.

9 OUTCOMES

9.1 Primary Clinical Outcome

1. Changes in LVEF (by echocardiography or MUGA) throughout the course of trastuzumab based therapy

9.2 Secondary Clinical Outcomes

1. Rates of trastuzumab delay/discontinuation

2. Referral to cardiology

3. Rate of cardiac events

4. Health system cost analysis and quality of life adjusted years measured by EQ-5D-5L questionnaire (11)

9.3 Secondary Feasibility Outcomes

Feasibility of performing this study will be measured with combination of endpoints:

1. Percentage of patients who receive trastuzumab therapy for early stage breast cancer compared to the number of participants who agree to randomization. The total number of patients receiving adjuvant trastuzumab at each site will be provided by pharmacy.

2. Percentage of participants who complete their assigned cardiac monitoring schedule compared to the percentage who discontinue their cardiac monitoring schedule while on study (compliance) will be calculated using the medical record.

3. Percentage of medical oncologists who attend the site initiation visit and have agreed to participate in the trial compared to the percentage of medical oncologists that actually approached patients regarding the trial. At the Ottawa Hospital Cancer Centre, patients are assigned to a primary medical oncologist. Therefore, all approached patients with have their primary oncologist documented on the medical record, which will be compared to the list of all oncologists agreeing to participate in the trial.

10 RISKS

There are no risks associated with this study as both arms are standard of care schedules.

11 SAFETY REPORTING

For the purpose of this feasibility study SAE reporting is not required. Adverse events specific to the secondary outcome will be captured on the CRFs. However, as with all investigator-initiated trials in Ottawa a regular meeting of study staff will take place every 6-8 weeks.

12 MONITORING

Monitoring will be performed remotely by Nancy Page at The Ottawa Hospital Cancer Centre. The de-identified source documents and CRFs will be reviewed according to the approved monitoring plan.

13 CRITERIA FOR FEASABILITY SUCCESS

The following criteria were established a priori and needed to be met to deem this feasibility trial successful:

1) over 50% of appropriate patients approached agree to participate in the RCT,

2) over 50% of physicians who agree at study commencement to participate in the study do indeed approach patients for the study. Prior to study commencement and at study closure, all of the medical oncologists who treat breast cancer patients will be sent an email requesting feedback on their enthusiasm for the study and how they feel optimal methods of patient accrual can be incorporated into the feasibility of this study.

14 PREMATURE WITHDRAWAL

Participants have the right to withdraw from the study treatment at any time for any reason

Investigator has the right and obligation to withdraw subjects from the study treatment in the event of:

- Intercurrent illnesses which would, in the judgment of the investigator, affect assessment of clinical status to a significant degree, and require discontinuation of the assigned cardiac monitoring schedule
- Any toxicity that would produce further harm if continued on the protocol
- Request by the participant or of their legally authorized representative (consent withdrawal)
- Non-compliance to the study protocol or logistic consideration
- Participant is lost to follow-up

15 SAMPLE SIZE AND STATISTICAL ANALYSIS

As per protocol one of the outcome points will be change in LVEF (by ECHO or MUGA) throughout the course of trastuzumab-based therapy (%) in both groups. It is known, that normal LVEF is >53% (average – 61% with standard deviation 8%). In adjuvant clinical trials. the majority of patients during trastuzumab treatment experienced reversible decrease in LVEF of between 4-6%. As a criteria of non-inferiority the Mean of last measured LVEF while on trastuzumab treatment can be used to prove the same safety and sensitivity of both schedules. Our non-inferiority margin between groups is 4% ($\mathbf{M}_{LVEF_{3m}}$-$\mathbf{M}_{LVEF_{4m}}$<±4%) with a standard deviation of the mean change of 8%. To demonstrate non-inferiority of 4 versus 3 monthly monitoring mean LVEF in two independent groups with **t tests (**Means: Difference between two independent means) and our non-inferiority margin of 4%, we require 87 patients in each group – total 174 +10% (drop rate) = 200. We assumed a significance level α=0.05, power *(1-β)* of 95%, and effect size d = 0.5 (G*Power 3.1.9.2.).

Analysis:

Descriptive analysis: Baseline characteristics and management data will be presented with means (continuous measures) or proportions (categorical or ordinal data) with 95% confidence intervals.

Intention-to-treat analysis: In both studies, all statistical analyses of the data will be based on an intention-to-treat approach (based on subjects who underwent randomization). In addition, a treatment received as per protocol analysis of the primary outcome measure will be conducted.

Analysis of the primary outcome (LVEF): The primary outcome (LVEF) will be measured at baseline and every 3 or 4 months with the primary (and common) time point measure at 1 year. As the primary outcome is a continuous variable, the mean difference between both treatment groups at one year of follow up and the last measured LVEF while on trastuzumab treatment will be assessed using repeated-measures analysis of variance, which control for study sites (random effect) and eventually control for differences in confounding variables, should any arise despite randomization. The purpose of our model is not inferential, but rather to estimate the expected

change in treatment effect and confidence interval i.e. whether or not the 4 monthly group is found to be inferior by non-inferiority by a margin of 4%.

Analysis of secondary feasibility and clinical outcomes: Secondary feasibility outcomes will be reported using descriptive statistics. Protocol adherence will be reported as a proportion. Dichotomous clinical outcomes will be compared using a one-sided Z-test while continuous variables will be compared using a one-sided t-test in an analogous manner. Relative risk (dichotomous) and mean differences (continuous) along with their 95% confidence intervals will also be calculated and presented.

Compliance and loss to follow-up: Secondary analyses will be considered to better understand the influence of compliance, and losses to follow-up on the robustness of the intention-to-treat analysis. The general approaches will include an analysis of primary and secondary outcomes including only participants who completed the study as per their assigned diagnostic schedule protocol.

Economic analysis. We will use a decision analytic model to compare total health system cost and quality-adjusted life years (QALYs) among patients receiving 4 versus 3 monthly cardiac monitoring. We will obtain health resource use, relative efficacy of 4 versus 3 monthly cardiac monitoring and health utility values from the trial. Aggregate and individual average costs of hospital and emergency visits among patients with and without cardiac events will be obtained from the Ottawa Hospital Data Warehouse Database (Ottawa site only). Unit costs of physician visit will be based on the Ontario's Schedule of Benefits for Physician Services (12), while the costs of outpatient medications will be sought from the Ontario Drug Benefit Formulary. QALYs will be estimated for each patient within the clinical trial using the total area under the curve method (13). We will calculate an incremental cost per QALYs gained and an incremental cost per one unit change in LVEF. We will perform a series of one-way and probability sensitivity analyses to assess the robustness of the study findings. Results from the probabilistic sensitivity analysis will also be used to create cost-effectiveness acceptability curves, which link the probability of the intervention being cost-effective to a range of potential threshold values that the health system may be willing to pay for an additional unit of effect. All analyses will be performed in Microsoft Excel. All patients will be asked to complete a baseline health questionnaire about any cardiac risk factors (i.e. diabetes, smoking status, prior heart health

history) and current cardiac medications. Patients in the 3-monthly arm will be asked 3 months after their first trastuzumab if in the previous 3 months; number of visits to ER, number of night at the hospital, type, changes to any cardiac medications. Patients in the 4-montly group will be asked 4 months after their first trastuzumab the same questions relating to the previous 4 months. Both groups will be asked the same question at the 12 month time point. At screening visits physicians will document any hospitalizations, ER visits, changes in chemotherapy, trastuzumab or cardiac medications, any drop in LVEF and referrals to cardiology.

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