To: CTEP Protocol and Information Office

Date: 2022-SEP-22

Re: **CCTG MA.39**: "**Tailor RT: A Randomized Trial of Regional Radiotherapy in Biomarker Low Risk Node Positive and T3N0 Breast Cancer**"

NCI/Local Protocol #: CCTG MA.39

NCI Protocol Version Date: **Amendment #2 – September 19, 2022**

PI/Lead Organization: Timothy Whelan / Canadian Cancer Trials Group (CCTG)

Protocol updates are as follows:

The primary reason for this amendment is to make several administrative corrections and updates throughout the protocol. The main updates include:

(1) Clarification added that as of 2022Aug02 the CCTG MA.39 trial has completed accrual to the following:
- the optional questionnaire component of the trial (i.e., 736 eligible English or French-speaking patients who were randomized (to STEP 2) and agreed to optional questionnaire completion). Thus, completion of questionnaires for patients enrolled (randomized) after this date is not applicable.
- for the Resource Utilization Assessment (RUA) component of the trial. Thus, patients randomized after this date do not require reporting of RUA data (i.e., for hospitalizations, institutional log, and outpatient visits and procedures).

(2) Changed company name 'Genomic Health' to Exact Sciences' throughout protocol and screening consent (note that Exact Sciences acquired Genomic Health, and will perform the Oncotype DX testing for the CCTG MA39 trial)

(3) Corrections to accrual estimates for Screening, in both the domestic table and the international table.

Consent form changes - are specified in the consent documents (Screening and Main)

Accrual will continue during the approval process.

I. Comments - submission to CTEP on 2022SEP22

The following sections of the protocol were updated:

#	Section	Comments
1.	Global	• The protocol version date has been updated in the document header/footer
2.	Cover Page	• Document history table was updated to include Amendment #2

#	Section	Comments
3.	Table of Contents	• Table of contents updated to accommodate Amendment #2 changes
4.	Section 1.0 – Objectives	• Section 1.2, page 3 – Clarification that as of 2022Aug02 the CCTG MA.39 trial has completed accrual to: o the optional questionnaire component of the trial (i.e., 736 eligible English or French-speaking patients who were randomized (to STEP 2) and agreed to optional questionnaire completion). o for the Resource Utilization Assessment (RUA) component of the trial.
5.	Section 2.3 - Quality of Life, Patient Reported Outcomes and Toxicity	• Section 2.3.2, page 9 – Clarification that as of 2022Aug02 the CCTG MA.39 trial has completed accrual to the optional questionnaire component of the trial (i.e., 736 eligible English or French-speaking patients who were randomized (to STEP 2) and agreed to optional questionnaire completion).
6.	Section 2.4 – Economic Evaluation	• Section 2.4 – page 11 - Clarification that as of 2022Aug02 the CCTG MA.39 trial has completed accrual to the optional questionnaire component of the trial (i.e., 736 eligible English or French-speaking patients who were randomized (to STEP 2) and agreed to optional questionnaire completion).
7.	Section 3.1 – Eligibility Criteria	• Section 3.1.8, page 16 – Administrative change to company name from 'Genomic Health' to Exact Sciences' (note that Exact Sciences acquired Genomic Health, and will perform the Oncotype DX testing for the CCTG MA39 trial). • Section 3.1.13, page 16 - Clarification to eligibility criterion to change 'administered' to 'started' • Section 3.1.16, page 16 – Clarification that as of 2022Aug02 the CCTG MA.39 trial has completed accrual to the optional questionnaire component of the trial (i.e., 736 eligible English or French-speaking patients who were randomized (to STEP 2) and agreed to optional questionnaire completion).
8.	Section 4.0 – Patient Evaluation Flowsheet – Pre-Treatment, On Study, and After Treatment	• Section 4.0, page 20 - Footnote 5 – Correction • Section 4.0, page 20 - Footnote 6 – Update to clarify that as of 2022Aug02 the CCTG MA.39 trial has completed accrual to the optional questionnaire component of the trial (i.e., 736 eligible English or French-speaking patients who were randomized (to STEP 2) and agreed to optional questionnaire completion). Thus, completion of questionnaires for patients enrolled (randomized) after this date is not applicable. • Section 4.0, page 20 - Footnote 7 - Update to clarify that as of 2022Aug02 the CCTG MA.39 trial has completed accrual for the Resource Utilization Assessment (RUA) component of the trial. Thus, patients randomized after this date do not require reporting of RUA data (i.e., for hospitalizations, institutional log, and outpatient visits and procedures).

#	Section	Comments
9.	Section 5.1 – Entry Procedures	• Section 5.1.2, page 23 - Administrative change to company name from 'Genomic Health' to Exact Sciences' (note that Exact Sciences acquired Genomic Health, and will perform the Oncotype DX testing for the CCTG MA39 trial).
10.	Section 6.0 – Treatment Plan	• Section 6.1, page 25 – administrative – corrections as per changes made to eligibility criterion 3.1.13 as per the previous Amendment #1.
11.	Section 7.0 – Radiation Oncology Facility Credentialing and Quality Assurance	• Section 7.4, page 40 – administrative – correction as per changes made to section 6.7 made with the previous Amendment #1.
12.	Section 13 – Statistical Considerations	• Section 13.3, page 53 – administrative – updates to accrual estimates for Screening, in both the domestic table and the international table. • Section 13.6, page 55 – Clarification that as of 2022Aug02 the CCTG MA.39 trial has completed accrual to the optional questionnaire component of the trial (i.e., 736 eligible English or French-speaking patients who were randomized (to STEP 2) and agreed to optional questionnaire completion).
13.	Appendix II – Documentation for Study	• Addition of Minimal Follow-Up Report • Footnote * - updated with generic template language • Footnote **** - added for clarification of the aim of the Minimal Follow-Up Report
14.	Appendix IV – Quality of Life Assessment	• Clarification that as of 2022Aug02, the CCTG MA.39 trial has completed accrual to the optional questionnaire component of the trial (i.e., 736 eligible English or French-speaking patients who were randomized (to STEP 2) and agreed to optional questionnaire completion).
15.	Appendix V – Health Utilities Assessment	• Clarification that as of 2022Aug02, the CCTG MA.39 trial has completed accrual to the optional questionnaire component of the trial (i.e., 736 eligible English or French-speaking patients who were randomized (to STEP 2) and agreed to optional questionnaire completion).
16.	Appendix VI – Lost Productivity Questionnaire	• Clarification that as of 2022Aug02, the CCTG MA.39 trial has completed accrual to the optional questionnaire component of the trial (i.e., 736 eligible English or French-speaking patients who were randomized (to STEP 2) and agreed to optional questionnaire completion).
17.	List of Contacts (Final pages)	• Section updated for personnel changes and corrections to the 'mailto' hyperlinks of some email addresses.

INITIAL PROTOCOL: 2018-APR-04
NCI U.S. SUBMISSION: 2017-SEP-20
AMENDMENT #1: 2021-MAR-23

CANADIAN CANCER TRIALS GROUP (CCTG)

TAILOR RT: A RANDOMIZED TRIAL OF REGIONAL RADIOTHERAPY IN BIOMARKER LOW RISK NODE POSITIVE AND T3N0 BREAST CANCER

CCTG Protocol Number: **MA.39**

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Document History

Modification	Version Date
Amendment #2	September 19, 2022
Amendment #1	March 23, 2021
Initial Protocol	April 4, 2018

CONFIDENTIALITY STATEMENT

This protocol contains information that is confidential and proprietary. The contents of this protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial may not be used for any other purpose and may not be disclosed to any other person or entity without the prior written permission of CCTG (and other applicable parties as designated by CCTG).

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol and any supplementary information that may be added to this document, contains information that is confidential and proprietary, and must be kept in confidence.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, in accordance with any modifications that may occur over the duration of the study, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by CCTG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to CCTG of any such disclosure.

I understand that I may terminate or suspend enrollment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however, I will give prompt notice to CCTG. The study may be terminated at any time by CCTG with or without cause.

_____ _____

Qualified Investigator
(printed name and signature)

Date

Protocol Number: CCTG MA.39

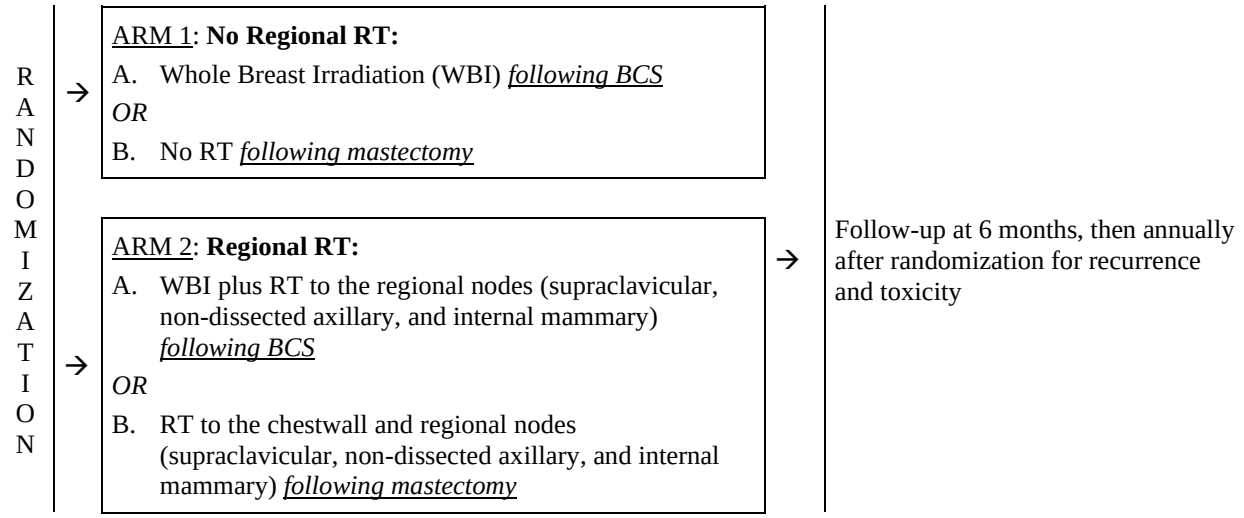
CENTRE: _____

TREATMENT SCHEMA

This is an international multi-centre, randomized, non-inferiority phase III trial evaluating regional radiotherapy (RT) [defined as RT to regional nodes following breast conserving surgery (BCS) or RT to the chestwall and regional nodes following mastectomy] in patients with ER +ve biomarker low risk breast cancer (BC) [defined as Oncotype DX recurrence score≤ 25] and limited nodal disease or T3N0 that have had BCS, or mastectomy and will receive endocrine therapy for 5 years. Patients treated by axillary dissection may have 1-3 positive axillary nodes (macrometastases, > 2 mm) regardless of type of surgery (BCS or mastectomy). Patients treated by sentinel lymph node biopsy (SLNB) alone may have 1-2 positive nodes (macrometastases, > 2mm). Patients with disease limited to nodal micrometastases are eligible.

Stratification

- Surgery type (BCS or mastectomy)
- Axillary dissection (yes or no)
- Adjuvant chemotherapy (yes or no)
- Lymphovascular invasion (yes or no)
- Oncotype DX score (0–10, 11-17, or 18-25)



N = 2140 patients

1.0 OBJECTIVES

1.1 Primary Objective

To compare the breast cancer recurrence-free interval (BCRFI) between patients that received regional RT or not, defined as time from randomization to time of invasive recurrent disease in the ipsilateral chestwall, breast, regional nodes, distant sites or death due to BC.

1.2 Secondary Objectives

- To compare the invasive disease-free survival (DFS) between patients that received regional RT or not.
- To compare the breast cancer mortality between patients that received regional RT or not.
- To compare the overall survival (OS) between patients that received regional RT or not.
- To compare the locoregional recurrence-free interval (LRRFI) between patients that received regional RT or not.
- To compare the distant recurrence-free interval (DRFI) between patients that received regional RT or not.
- To compare the toxicity between patients that received regional RT or not.
- To compare arm volume and mobility measurements between patients that received regional RT or not.
- To compare patient reported outcomes (PROs) and the quality of life (QOL) between patients that received regional RT or not (enrollment completed 2022AUG02).
- To compare the cost effectiveness between patients that received regional RT or not (enrollment completed 2022AUG02).

1.3 Tertiary Objectives

- To establish a comprehensive tumour bank linked to a clinical database for the further study of predictive and prognostic biomarkers in breast cancer.
- To evaluate the ability of intrinsic subtype measured by immunohistochemistry (IHC) to predict BCRFI, LRRFI, DRFI and the effect of regional RT on these outcomes.
- To evaluate other radiation sensitivity signatures to prognosticate and predict effect of regional RT.
- To describe the prevalence of detectable baseline ctDNA in node positive low risk ER positive breast cancer and evaluate its prognostic ability.

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Node Positive Breast Cancer and Biomarker Low Risk

In 2015, it was estimated there were approximately 110,000 new cases of node positive breast cancer in North America *[American Cancer Society]*. Most are treated with surgery, chemotherapy, endocrine therapy, and RT. BCS is now performed in about 2/3 of women with node positive breast cancer. WBI is given after BCS. The MA.20 trial (n=1832, 85% with 1-3 +ve axillary nodes) demonstrated that RT to regional nodes in addition to WBI improved disease-free survival (DFS) from 77 to 82% [hazard ratio (HR)=0.76, 95% confidence interval (CI)=0.61-0.94, p=0.01] with an increase in locoregional DFS (92.2% to 95.2% respectively, HR=0.59, 95% CI=0.39-0.88, p=0.009) and distant disease-free survival (DDFS) (from 82.4% to 86.3%, HR=0.76, 95% CI=0.60-0.97, p=0.03) *[Whelan 2015]*. Another larger randomized trial the EORTC 22922 (n=4004) demonstrated very similar findings with an improvement in DFS (69.1% to 72.1%, HR=0.89, 95% CI=0.80-1.00, p=0.04) and DDFS (from 75.0% to 78.0%, HR=0.86, 95% CI=0.76-0.98, p=0.02) and a reduction in breast cancer mortality from 14.4% to 12.5% (HR=0.82, 95% CI=0.70-0.97, p=0.02) *[Poortmans 2015]*. Based on these results, RT to the regional nodes is increasingly used in women with node positive breast cancer following BCS.

Changes in surgical practice have also contributed to the increased use of RT to the regional nodes. SLNB is now the standard method of assessing breast cancer spread to axillary lymph nodes. Recently the practice of omitting a completion axillary node dissection when 1-2 sentinel nodes are positive has been adopted based on results of ACOSOG Z11, AMAROS (NCT00014612) and other trials *[Giuliano 2011; Donker 2014; Galimberti 2018]*. In the AMAROS trial all patients with a SNLB were treated with regional RT and in ACOSOG Z11 a significant proportion of patients treated with SNLB were estimated to receive some regional nodal RT *[Jagsi 2014]*. Accordingly, radiation oncologists are being asked to provide regional RT to such patients given a concern for remaining residual disease in the lymph nodes *[Haffty 2011]*. Despite variability in practice, regional RT appears to be increasingly used. At the ASTRO 2016 Annual Meeting radiation oncologists (n=212) were presented cases for discussion and feedback about current practice. For 1-3 node positive lower risk cases (T_1, ER/PR+ve, HER2–ve, grades 1-2) treated with BCS and SLNB or axillary dissection, regional RT was used 60-87% of the time *[Harris 2016]*.

Regional RT to the chestwall and surrounding lymph nodes following mastectomy for patients with 1-3 positive nodes is also increasingly considered based on the recent meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) which demonstrated this treatment reduced breast cancer recurrence by 32% (p<0.001) and breast cancer mortality by 20% (p=0.01) *[EBCTCG 2014]*. A study of the National Cancer Database performed before the publication of these results demonstrated that post-mastectomy RT for patients with 1-3 positive nodes increased from 23.9% in 2003 to 36.4% in 2011 with an annual percent increase of 6.2% (p<0.001) *[Yao 2015]*. As a result of the publication of the meta-analysis *[EBCTCG 2014]*, the use of post-mastectomy RT is expected to have increased further since then. At the same ASTRO meeting described above, regional RT post-mastectomy was recommended 75% of the time for a lower risk case (T_1, ER/PR+ve, HER2–ve, grades 1) with 1 of 2 positive sentinel nodes *[Harris 2016]*.

Regional RT is associated with significant acute side effects e.g. skin irritation, pain, and fatigue, and long-term adverse effects e.g. radiation pneumonitis, limited arm/shoulder mobility, lymphedema and poor cosmetic outcomes secondary to soft tissue fibrosis and skin telangiectasia *[Lind 2002; Powell 2003; Olsen 1993]*. The latter is particularly relevant for women after mastectomy who have breast reconstruction, which is increasingly performed. In addition, there remains a concern of increased risk of cardiac disease and induction of second cancers with regional RT *[Darby 2013]*.

Genomic studies have shown that breast cancer is composed of four major intrinsic subtypes: luminal A, which overexpresses estrogen pathway genes and is non-proliferative; luminal B, which overexpresses estrogen pathway and proliferation genes; HER2 enriched, which is ER-ve and overexpresses genes from the HER2 amplicon; and basal, which are ER-ve and overexpresses abnormal cell cycle control and DNA repair genes *[Perou 2000; Sorlie 2003]*. Luminal A subtype has the lowest risk of recurrence and is less responsive to chemotherapy *[Sorlie 2001]*. Currently the majority of women with ER+ve breast cancer will receive adjuvant endocrine therapy and a number will also receive adjuvant chemotherapy to reduce the risk of recurrence. It is not clear that additional regional RT is necessary for all patients.

A pre-planned subgroup analysis of the MA.20 trial demonstrated for DFS that patients with ER positive disease compared to ER negative disease were less likely to benefit from regional RT (p for interaction = 0.04) *[Whelan 2015]*. A further exploratory analysis showed that for luminal A-like breast cancer defined by ER positivity, PR positivity, HER2 negativity, and grades I or II, there was no measureable effect of treatment (HR=1.09, 95% CI=0.75-1.57); in contrast to luminal B-like breast cancers defined as ER or PR positive, and HER2 positive or grade III (HR=0.66, 95% CI=0.46-0.94); and HER2 enriched or basal-like cancers defined as ER-ve and PR-ve, HER2-ve or +ve (HR=0.59, 95% CI=0.40-0.86, p for interaction=0.05). The lack of treatment effect in node positive luminal A-like breast cancer likely reflects the low risk of locoregional recurrence (LRR) resulting from effective systemic therapy and potentially a decreased response to RT. Other studies have supported a low risk of LRR following BCS and mastectomy in luminal A *[Voduc 2010]* or low Oncotype DX score disease *[Mamounas 2010]*. A recent randomized trial of WBI also suggests that RT may be less effective in luminal breast cancer *[Liu 2015]*.

Mamounas et al. evaluated the ability of Oncotype DX Recurrence Score (RS) to predict risk of LRR in node positive breast cancer *[Mamounas 2017]*. Investigators studied 1065 patients treated on a NSABP-B28 randomized trial comparing adriamycin and cyclophosphamide to adriamycin and cyclophosphamide plus paclitaxel. In this study, it was recommended that patients treated by BCS receive WBI only and patients treated by mastectomy not receive RT. A multivariable analysis adjusting for systemic therapy and type of surgery, demonstrated the RS was an independent predictor of LRR (HR=2.86, 95% CI=1.51-5.31) for a 50 point, p=0.008). The 10 year cumulative incidence for locoregional recurrence was 3.3%, 7.2%, and 12.2% for low (RS 0 to 18), intermediate (18-30) and high (> 31) RS, respectively. Rates of locoregional recurrence were for lower for patients with 1-3 positive nodes vs. > 4 positive nodes (p<.006) and were similar for patients after lumpectomy or mastectomy. The majority of recurrences for patients with 1-3 positive nodes with low or intermediate RS were local rather than regional especially after lumpectomy and whole breast irradiation and would be less likely affected by omitting regional radiotherapy. A study reported by Woodward et al. evaluated the ability of RS to predict risk of LRR for patients post-mastectomy treated on SWOG S8814 where patients with node positive breast cancer were randomized to tamoxifen alone vs. tamoxifen plus cyclophosphamide, adriamycin, and fluorouracil *[Woodward 2020]*. On multivariate analysis RS independently predicted risk of LRR (p=.04).

We further reviewed data from B-28 regarding the risk of locoregional recurrence and any recurrence (locoregional or distant) based on the RS for patients with 1-3 positive nodes looking at different cut-offs for the RS score (see Table) *[Mamounas 2020]*. Rates of locoregional recurrence at 10 years for patients treated with lumpectomy or mastectomy remained low (3.7%, 95% CI 2.1% to 5.8%) for cut-offs up to RS≤25. Rates of any recurrence also remained low (13.3%, 95% CI 10.2-16.7) for an RS score ≤25 and were consistent with a low risk population.

Recent data from the RxPonder trial (evaluating the role of adjuvant chemotherapy in 1-3 positive node patients with RS≤25 also support low risks of locoregional and distant failure at 5 years *[Kalinsky 2020]*.

TABLE: B28 Recurrence Score data-set *[Mamounas 2020]* – see below:

Ten-year cumulative incidence function (CIF) in percent for loco-regional recurrence or any recurrence (loco-regional plus distant) among B28 patients with 1-3 positive nodes (N=722) treated by lumpectomy and mastectomy by different cut offs for Recurrence Score (RS).

		Loco-regional		Recurrence (loco-regional+ DM)	
Groups	Sub-total	# Events	10-year CIF (95% CI)	# Events	10-year CIF (95% CI)
RS≤18	284	13	3.8 (1.9, 6.6)	34	9.2 (6.2, 13.1)
RS≤20	338	14	3.5 (1.8, 5.9)	42	10.2 (7.2, 13.8)
RS≤22	383	16	3.6 (2.0, 5.9)	52	11.4 (8.4, 14.9)
RS≤25	436	18	3.7 (2.1, 5.8)	68	13.3 (10.2, 16.7)
RS≤30	512	23	4.2 (2.6, 6.2)	89	15.4 (12.4, 18.7)
RS>31	210	17	7.7 (4.6, 11.9)	69	32.4 (26.1, 38.9)

Based on these considerations, patients with 1-3 positive nodes that are ER +ve and low risk by biomarker testing may not benefit from regional RT. Other data are not consistent with this premise. In the original Danish trial, which demonstrated the impact of regional RT following mastectomy investigators found that luminal A patients were the only group to benefit in terms of OS compared to luminal B, HER2, or triple negative *[Kyndi 2008]*. Also, in the recent EORTC 22922 trial of regional RT following BCS or mastectomy, patients who received some hormonal therapy (i.e. ER positive) either alone or in combination with chemotherapy were more likely to benefit in terms of OS compared to patients treated with chemotherapy alone (ER negative) *[Poortmans 2015]*. It has been hypothesized that lower risk ER positive cases are more likely to have distant metastases controlled by systemic therapy so that the impact of regional RT is more evident. These conflicting data have created uncertainty and support the need for a trial to determine if regional RT can be safely omitted in patients with biomarker low risk node positive breast cancer.

In this proposal, patients with 1-3 node positive ER+ve breast cancer who undergo BCS or mastectomy will be tested for low risk biomarker status (defined as Oncotype DX RS≤ 25). Patients with low risk biomarker status treated with adjuvant systemic therapy (endocrine with or without chemotherapy) will be randomized to regional RT (defined as RT to the regional nodes following BCS or RT to the chestwall and regional nodes following mastectomy) or no regional RT. Our hypothesis is that the risk of recurrence in patients where regional RT is omitted will not be inferior to the risk of recurrence in patients treated with regional RT.

2.2 Rationale for Current Study

Presently there is substantial confusion regarding the optimal locoregional management of patients with node positive breast cancer. Studies support that SLNB alone is equivalent to SLNB and completion axillary node dissection *[Giuliano 2011; Donker 2014]*. As a result, patients following BCS or mastectomy are often treated with SLNB alone when SLN is positive. Recent RT trials indicate that patients with 1-3 positive axillary lymph nodes benefit from regional RT [*Whelan 2015; Poortmans 2015*]. As a result, such patients are often discussed at tumour boards and increasingly less aggressive surgery is being replaced with regional RT when it may not be needed at all, particularly for some subgroups. The goal of this study is to reduce over treatment of breast cancer. The proposed study will use molecular biomarkers to identify a group of patients that may not require regional RT. The study could have important consequences on quality of life, avoiding RT to the regional nodes for women after BCS and avoiding any RT for women post-mastectomy leading to reduced acute toxicity and late risks of lymphedema, arm/shoulder limitations, and worse cosmesis associated with treatment. A positive study would support omitting regional RT in 1-3 node positive biomarker low risk breast cancer estimated to be as many as 30,000 women per year in North America and would result in substantial health care savings. Conversely, a negative study would support use of regional RT in all 1-3 node positive patients.

In patients presenting with early breast cancer, there is interest in tailoring adjuvant treatments to those with tumours at risk of recurrence and those with tumours most likely to benefit from therapy. Adjuvant chemotherapy and RT can be associated with significant short and long-term side effects. Gene array studies have identified intrinsic breast cancer subgroups that more accurately predict risk of recurrence and response to treatment than classic clinico-pathological factors *[Perou 2000; Sorlie 2001]*. To date, although gene signatures are being used to tailor adjuvant chemotherapy, little research has been done on using biomarkers to predict response to adjuvant RT *[Paik 2007; van de Vijver 2002; Parker 2009]*.

The goal of this proposal is to use molecular biomarkers to identify a subgroup of 1-3 axillary node positive breast cancer patients who could be spared regional RT. Patients with ER+ve biomarker low risk breast cancer (Oncotype DX RS$\leq$ 25) will be randomized to regional RT or not. The objective is to determine if omitting regional RT following BCS or mastectomy is non-inferior to its use in these women.

2.3 Quality of Life, Patient Reported Outcomes and Toxicity

2.3.1 *Background*

Regional RT can be associated with increased acute toxicities including: radiation dermatitis, pneumonitis, and fatigue; and late toxicities such as lymphedema, brachial plexopathy and limited arm and shoulder movement *[Lind, 2002; Powell 2003; Olsen 1993]*. Patients treated by regional RT may also experience greater time off work and increased health costs, both from the additional treatment and the associated side effects. Most of this information is a result of retrospective studies and rarely from randomized controlled trials. In addition, there is very limited data about the impact of regional RT using modern techniques on PROs and QOL. In 1997 Ragaz et al. reported the results of the British Columbia randomized trial (n=318) of RT to the chest wall and regional lymph nodes compared to no RT after modified radical mastectomy *[Ragaz, 1997]*. Lymphedema was increased from 3.2% to 9.1% at 12.5 years. Radiation pneumonitis was reported in only 0.6% of patients treated with regional RT. PROs or QOL were not reported. In the MA.20 trial (n=1832), regional RT after BCS and axillary dissection was associated with an increased risk of grade 2 or greater pneumonitis from 0.2% to 1.2%, radiation dermatitis from 40 to 50%, and lymphedema from 4.5 to 8.4% *[Whelan 2015]*. QOL has yet to be reported in this trial, but it is important to note that in both the British Columbia trial and the MA.20 trial RT was delivered with older wide field RT techniques.

In MA.39, RT will be delivered using more modern conformal approaches. All targeted areas (breast/chest wall and regional nodes) will be contoured and RT will be delivered using 3D conformal RT or IMRT, thereby significantly minimizing radiation to the adjacent normal tissues. These techniques have been shown to reduce toxicity associated with RT for breast cancer and other disease sites *[Pignol 2008; Donovan 2007; Chun 2017]*. Such conformal approaches have yet to be evaluated in the context of delivering regional RT. In addition, since the previous trials of regional RT were performed, surgical treatment of breast cancer has dramatically changed and the majority of patients treated with BCS are now treated with SLNB alone where a limited number of lymph nodes are removed. It is expected that additional regional RT may result in less symptoms in this situation. In a recent cohort study from the Massachusetts General Hospital (n=1476) the risk of lymphedema at 2 years following axillary dissection was 7.3% and with additional regional RT increased to 23.9%. In patients treated with SLNB alone the risk of lymphedema was 2.8%, which increased to 7.1% with additional regional RT *[Warren 2014]*.

MA.39 is a unique opportunity to evaluate the impact of regional RT delivered with modern conformal techniques in a randomized trial on patient-reported outcomes and QOL following BCS and mastectomy. The trial is evaluating whether omitting regional RT is not inferior in patients with node positive breast cancer. Should the trial demonstrate that omitting RT does not result in higher rates of recurrence, PRO and QOL data will inform the benefits women receive by avoiding this treatment both for those treated by BCS or mastectomy. Should the trial demonstrate higher rates of recurrence with omission of regional RT, PRO and QOL data will be very helpful in informing physicians and patients about the negative impact of regional RT from the patient perspective and will be very valuable in informing treatment decision making. As a randomized trial, PRO and QOL data will also be very useful for physicians and patients with higher risk disease not eligible for the trial who will be making decisions regarding regional RT delivered using modern RT approaches. In this trial, patients treated with BCS will be randomized to WBI alone or WBI plus regional RT. It is estimated that a vast majority of these patients will be treated with SLNB. Patients treated by mastectomy will be randomized to no RT or RT to the chest wall and regional nodes. It is estimated that the majority of these patients will be treated by axillary dissection. The trial will provide important information about the impact of modern regional RT following both BCS and mastectomy.

PROs and QOL from randomized trials of SLNB alone vs. additional axillary dissection have provided important information about the impact of surgical interventions to the axillary nodes. In the NSABP B32 study investigators observed a decrease in arm symptoms (tenderness, swelling, pain, numbness, sensitivity, tightness, and weakness) of 1.9 (SD 5.7) on a scale from 0 to 28, when comparing SLNB alone vs. additional axillary dissection at 6 months post-surgery *[Land 2010]*. This was associated with an important reduction in arm symptoms such as swelling from 13% to 4%, pain from 20% to 11%, and numbness from 19% to 8%. There was also a reduction in breast/chest symptoms, but this did not reach statistical significance. Overall QOL was improved in patients treated by SLNB alone, but only in the first few weeks after surgery. Arm symptoms decreased over time and fewer differences were observed between patients treated by SLNB alone vs. additional axillary dissection after 1 year.

We are particularly interested in the negative effects to the arm associated with regional RT which will be common both to the patients treated with BCS and mastectomy. Regional RT both after BCS and mastectomy would be expected to increase arm and shoulder symptoms and possibly breast/chest symptoms. These effects are expected to be less after BCS and SLNB. For patients treated by mastectomy and axillary dissection the effects of regional RT on arm symptoms are expected to be greater. These effects may impair overall QOL in the short-term, but are not expected to continue long-term (beyond 3 years).

Patients will be administered the NSABP Arm and Breast Symptom Questionnaire used in previous studies and the EORTC QLQ-C30 and relevant items from the EORTC QLQ-BR23 Breast Cancer Module. These questionnaires have been studied extensively and validated in women with breast cancer *[Aaronson 1993; Sprangers 1996; Land 2010]*. Questionnaires will be administered at baseline and the last day of RT or 2 months post-randomization for those not receiving RT and at 6 months, 1, 3, and 5 years post-randomization.

2.3.2 *Quality of Life Objectives and Hypotheses*

The primary objective is to determine the effect of regional RT on arm symptoms for patients treated by BCS or mastectomy. The secondary objectives are: (1) to determine the effect of regional RT on arm symptoms for patients treated by BCS; (2) to determine the effects of regional RT on arm symptoms for patients treated by mastectomy; (3) to determine the effects of regional RT on overall QOL; and (4) to determine the effects of regional RT on breast symptoms, skin symptoms, and fatigue.

Our specific hypotheses are: (1) that arm symptoms will be less severe in patients where regional RT is omitted after BCS or mastectomy and that the effect will be greater for those treated by mastectomy. The NSABP Questionnaire will be used.; (2) overall QOL will be improved in patients were regional RT is omitted at least in the short-term (< 1 year) The EORTC QLQ-C30 scale will be used; and (3) breast/chest symptoms, skin symptoms, and fatigue will be less in patients treated with regional RT and that these effects will be greater for patients treated by mastectomy compared to those treated by BCS. The NSABP Questionnaire and the EORTC QLQ-BR23 Breast Cancer Module will be used. Quality of life evaluations will be restricted to the first 736 English or French-speaking patients who agree to completion of optional questionnaires. (Note: enrollment completed 2022AUG02.)

2.3.3 *Toxicity*

Toxicities will be graded using the current CTCAE version 5.0 at each follow up.

The following CTCAE version 5.0 adverse events are considered of interest for the intervention under consideration, and their presence/absence should be assessed, and severity graded, at each protocol visit.

Baseline	**Follow-up**
Fatigue	Breast pain
Lymphedema – ipsilateral arm	Chest pain – cardiac
Joint function – ipsilateral shoulder	Chest wall pain
Breast pain	Fatigue
Chest wall pain	Localized edema (breast)
	Lymphedema (arm)
	Myocardial Infarction
	Pericarditis
	Pneumonitis
	Telangieactasia
	Joint range of motion decreased
	Skin induration
	Dermatitis radiation
	Brachial plexopathy

Arm measurements for lymphedema will be performed at baseline, 6 months, 1, 3 and 5 years. Circumference measurement of lymph volume will be performed of both the ipsilateral and contralateral arms. A recommended method for arm measurement is the following: Patients will be seated in a chair beside a bedside table that is raised to the level of the axilla, with the short site of table lateral to the patient. The patient should be positioned with arm extended (abduction) and palms down, fingers together, relaxed and as straight as possible. Measurements with a standard plastic seamstress tape will be performed in centimetres at the wrist, half way between the wrist and the antecubital fossa, at the antecubital fossa, half way between the antecubital fossa and the axilla, and at the axilla. The plane of the tape around the arm will be held perpendicular to the long axis of the arm. The tape will be held snugly about the arm without indenting the skin or compressing subcutaneous tissue. For Canadian sites, see the MA.39 website https://www.ctg.queensu.ca/trials/breast/ma39 and for US sites, see the CTSU website for the CCTG MA.39 trial for further details regarding arm circumference measurement. The standard formula for a cylindrical cone will be utilized to calculate arm volume from the circumferences and arm length. The patient will be considered to have developed arm edema if there is a 10% or greater increase in the volume of the ipsilateral arm compared to the contralateral arm.

Arm mobility will also be measured at the same time points measuring the straight lateral abduction for both the ipsilateral and contralateral arm using a standard orthopedic goniometer to determine the angle between the lateral chestwall and the humerus. For Canadian sites, see the MA.39 website https://www.ctg.queensu.ca/trials/breast/ma39 and for US sites, see the CTSU website for the CCTG MA.39 trial for further details regarding arm mobility measurement. Arm abduction deficit will be defined as a difference in arm abduction of 10% or greater in the comparison of the ipsilateral to the contralateral arm.

2.4 Economic Evaluation

Because determining health care value is critical to the adoption of new technologies and procedures in the health system and society, we will embed an economic evaluation nested within the trial framework. Value is calculated by determining the incremental costs and benefits across the two treatment arms from two perspectives, a health system and a societal perspective.

For the cost portion of the value assessment, we will determine both the health system and societal resources utilized by subjects in the trial and direct cost information will not be collected. Health system resources will be identified as, but not limited to, clinic visits, treatments (radiation, surgery, medication), physician encounters, hospitalizations or emergent visits related to treatment and complications. The health system resources will be based on the trial protocol and data collected during the trial itself. Societal resources will be identified as, but not limited to, lost productivity related to treatment (e.g. time off work, change in status), and any significant out-of-pocket subject expenses (e.g. travel, parking). Societal resources will be based on patient specific data collected alongside the quality of life portion of the study. Health system and societal resources will be quantified over the course of the trial to generate utilization information by patient in each study arm. Once quantified and depending on the country where patients were enrolled, resources will be valued using public available or peer-reviewed unit cost data. For the United States, we will use Medicaid/Medicare unit costs and costs from other published economic analyses. For Canada, we will leverage publicly available costs, such as the Ontario-specific public funded costs (Ontario Health Insurance Plan, drug formula costs). It will generate an average cost per study subject by treatment arm for an overall mean cost per study arm.

For the benefit portion of the value assessment, if the efficacy results are different between the two treatment arms, we will conduct a cost effectiveness analysis, evaluating both incremental costs and clinical outcomes (e.g. recurrence). If there is no significant clinical benefit, we anticipate that there will be differences in quality of life between the two treatment arms and will conduct a cost-utility analysis. As such, we will determine the health preference of study subjects to calculate a quality adjusted life year (QALY) by marrying the health preference value and the time frame in which one experiences that health state. Health preference will be measured with the EQ-5D-5L. The EQ-5D-5L is a well-used and standardized measure of health status for economic analyses (https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf). Patient time off work will be measured using the Lost Productivity Questionnaire (LPQ), which we have used previously. The EQ-5D-5L and the LPQ will be collected alongside the study QOL instrument. The economic evaluations will be restricted to the first 736 English or French-speaking patients who agree to completion of optional questionnaires. (Note: enrollment completed 2022AUG02.) Sensitivity analyses, variation in benefit, resources and costs, will be conducted to test the robustness of the incremental ratios calculated. Time off work and lost productivity due to regional RT will be reported.

2.5 Correlative Science

2.5.1 *Correlative Science Rationale and Hypotheses*

Although genetic signatures such as Oncotype DX can classify breast cancer into different risk groups, they are costly and not universally available. Nielsen and colleagues have demonstrated that IHC analysis of a limited number of expressed protein markers can classify breast cancer into intrinsic subtypes that predict distant and LRR similar to genetic signatures. It has been demonstrated that intrinsic subtype measured by IHC using 6 molecular biomarkers (ER, PR, HER2, Ki67, CK5/6, and EGFR) can predict risk of distant recurrence *[Cheang 2009; Prat 2013]*. Recently studies have also shown that intrinsic subtype can also predict the risk of LRR. Voduc et al. reported on 2985 patients with node negative or node positive breast cancer treated by BCS or mastectomy with a median follow-up of 12 years *[Voduc 2010]*. Those with luminal A tumours (defined as ER or PR positive, HER2 negative, Ki67 < 14%) had the best prognosis with the lowest rate of LRR compared to luminal B (ER and PR positive, HER2 negative, Ki67 ≥ 14%), luminal – HER2 (ER and PR positive and HER2 positive), HER2 enriched (ER and PR negative and HER2 positive) or basal subtype (ER and PR negative, HER2 negative and CK5/6 or EGFR positive). We also evaluated the ability of intrinsic subtype to predict risk of local recurrence in two trials of radiation therapy following BCS. Intrinsic subtype was found to predict local recurrence in the hypofractionation trial which compared whole breast hypofractionation to convention fractionation *[Bane 2014]*. Luminal A had the lowest risk of local recurrence compared to other subtypes (p=<0.01). In the British Columbia/Toronto Trial patients were randomized to WBI vs. no RT after BCS and Tamoxifen. The risk of local recurrence using IHC was lowest for the luminal A subtype compared to others *[Liu 2015]*. In addition luminal subtypes appeared to gain less benefit from RT (luminal A HR=0.40; luminal B HR=0.51 and high risk subtypes HR=0.17). However, the subtype treatment interaction did not reach statistical significance (p=0.26).

The primary goal of this proposal is to evaluate intrinsic subtype using IHC and in particular Ki67 in the MA.39 trial. We hypothesize that intrinsic subtype will predict risk of locoregional and distant recurrence and the effect of regional RT on these outcomes. The reliability of IHC assessment for Ki67 is reported to be variable *[Dowsett 2011]*. Nielsen and colleagues have developed a more reliable method to assess Ki67 using full cut sections and systematic guidelines for staining, sampling and a digital interface for quantitating Ki67 *[Polley 2015]* which will be used in this study. Identification of an IHC-based assay that can identify patients who do not benefit from regional RT could allow for more widespread application, for example, in community hospitals or lower-resource international environments with better access to IHC than to genomic testing.

More recently a number of radiation specific signatures have been developed to predict response to RT in breast cancer such as the Danish Breast Cancer Group Radiotherapy (DBCG-RT) profile, the Radiosensitivity Index (RSI) and the Breast Cancer Radiation Sensitivity Signature (RSS). Tramm and Overgaard have developed a radiation sensitivity signature based on DBCG post-mastectomy RT trials 82B and C *[Tramm 2014]*. Their 4 gene signature (IGKC, RGS1, ADH1B, DNALI1) was shown to predict risk of LRR post-mastectomy. Patients categorized as high risk using this signature had a reduction in LRR with RT (57% to 12% at 20 years (p=0.001, HR=0.17) whereas for patients at low risk no improvement in local control was demonstrated (8% vs. 9% at 20 years, p=0.97, HR=1.13). Torres-Roca and colleagues have developed a radiosensitivity molecular signature based on surviving fraction at 2 Gy in 48 different cancer cell lines *[Torres-Roca 2005]*. Their 10 gene signature (AR, cJun, STAT, PKC, RelA, cABL, SUMO1, PAK2, HDAC, and IRF1) has been shown to predict relapse-free survival for breast cancers treated with RT compared to those who did not receive radiation treatment *[Eschrich 2012]*. Speers et al. have also developed a breast cancer radiosensitivity specific signature based on 16 breast cancer cell lines. This signature has been shown to predict risk of local recurrence in patients treated with RT and is currently being further validated *[Speers 2015]*. A secondary goal of this correlative study will be to evaluate the ability of a number of of these signatures to predict risk of recurrence and response to regional RT in the MA.39 trial.

Genomic assays continue to be the most widely used method to predict risk of recurrence and potential need for adjuvant therapy. Since the 1970s it has been known that cell free DNA can be detected in the circulation, but only since methods were developed to effectively detect somatic mutations has there been the ability to quantify and describe DNA from tumour. Circulating tumour DNA (ctDNA) has been shown to provide a non-invasive genomic description of an individual's metastatic tumour with demonstrated prognostic significance and suggestive clinical utility in metastatic breast cancer. ctDNA is an accurate and dynamic biomarker with good concordance to the genomic phenotype of the metastatic deposit. For example, identification of ESR 1 mutations in the ligand binding domain from the ctDNA has been suggestive of primary resistance to aromatase inhibitors *[Fribbens 2016]*. In addition, identification of PIK3CA mutations from ctDNA has also been shown to identify a cohort of patients with metastatic breast cancer that are more likely to benefit from a PI3K inhibitor *[Baselga 2017]*. Limited but evolving evidence is now emerging regarding the potential prognostic role of ctDNA in early stage disease. A study of 55 patients with stage II-III breast cancer treated with neoadjuvant chemotherapy and subsequent surgery collected plasma post-operatively and in serial follow-up *[Garcia-Muillas 2015]*. Detectable ctDNA post-operatively predicted subsequent metastatic relapse with a hazard ratio of 25.1 (95% CI: 1.08-130.5). Detectable ctDNA was able to predict 12 of 15 relapses observed. In a smaller retrospective study of 20 patients diagnosed with predominantly stage IIA-III breast cancer, positive post-surgical levels of ctDNA predicted relapse with a sensitivity of 93% *[Olsson 2015]*. No recurrence was detected in patients who had no detectable ctDNA post-operatively. We propose to collect a baseline plasma sample on all patients enrolled on MA.39 to investigate the prognostic significance of detectable post-operative ctDNA in node positive low risk ER positive breast cancer. Our hypothesis is that detectable ctDNA can predict recurrent disease as an independent factor. An exploratory analysis will assess if specific mutational features (specific genes, number and type of mutations) have additional prognostic significance.

2.5.2 *Correlative Science Methods*

Formalin-fixed paraffin-embedded (FFPE) samples will be collected as part of the trial protocol. Intrinsic subtype measured by IHC will be performed using two approaches. For the first approach: tissue microarrays (TMAs) will be constructed and tumours will be classified by molecular subtype as luminal A or luminal B using a 4 IHC biomarker panel (ER, PR, HER2, and Ki67) using the previously published methods *[Cheang 2009; Prat 2013].* Since ER –ve and HER2 +ve patient are excluded for the trial HER2 enriched and basal subtypes will not be tested for. For the second approach we will use the clinical ER, PR, and HER2 data provided with the accrued case data as measured in clinical practice. Ki67 will be measured on open face whole sections using the method developed by Nielsen, Bane and colleagues to improve reliability, incorporating systematic guidelines for staining, sampling and utilizing a digital interface for quantitating Ki67 *[Polley 2015]*. The whole slide will be imaged using APERIO Scanoscope XT. A computer program developed by Dr. Nielsen's group will be used to identify five random areas on the whole mount slide for Ki67. A minimum of 500 nuclei (100 from each area) will be counted using a keystroke counting data capture software. This method has been successfully applied in the Canadian LUMINA trial of WBI de-escalation in low risk cases. For testing gene expression signatures, mRNA will be extracted from FFPE sections and gene expression will be measured using quantitative reverse transcription polymerase chain reaction (qRT-PCR) as recommended for each radiation sensitivity signature (i.e. using the methods employed in their signature validation experiments).

Baseline blood post-consent and confirmation of eligibility for randomization will be collected in two x 9 ml Cell-free DNA® BCT plastic Streck tubes. The timing of the blood collection is before the commencement of radiotherapy. For patients who will not receive radiotherapy on trial, blood collection must occur within 6 weeks post-randomization. Tubes must be shipped at room air no longer than 3 working days post draw to CCTG Central Office Biorepository (Kingston, ON). Plasma and lymphocytes (for germline DNA) will be separated out and frozen within 2 working days of receipt of Streck tubes. Plasma will subsequently be subjected to a digital droplet PCR assay with the specific common alleles (p53 hotspots, PIK3CA alleles, GATA3 alleles, ESR1 resistance mutations) prevalent in primary ER positive breast cancers. A multiplex amplicon panel assay inclusive of over 200 genes commonly altered in solid malignancies will also be performed.

A detailed analytical and statistical plan will be developed for use of samples collected for MA.39 for all biomarker assays described and will be submitted as an amendment for approval by CTEP in accordance with the National Clinical Trials Network (NCTN).

3.0 STUDY POPULATION

The study population consists of women with newly diagnosed biomarker low risk node positive and T3N0 breast cancer with no evidence of metastases that have been treated by mastectomy or BCS.

3.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of registration or randomization. Questions about eligibility criteria should be addressed prior to enrollment.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfil the following criteria to be eligible for admission to the study:

3.1.1 Patients must be women with newly diagnosed histologically proven invasive carcinoma of the breast with no evidence of metastases, staged as per site standard of care.

3.1.2 Patients must have been treated by BCS or mastectomy with clear margins of excision*.

* Patients treated by BCS with focally positive margins for invasive breast cancer or DCIS (involving ≤ 3 high power fields) are eligible if additional surgery is not possible, e.g. posterior margin positive and deep resection margin abuts the chest wall or anterior margin positive and superficial resection margin abuts the skin. Boost radiotherapy must be administered for positive margins as described above.

Post-mastectomy positive margins for invasive breast cancer and/or DCIS is not allowed.

Multifocal disease (i.e. the presence of two or more foci of breast cancer within the same breast quadrant) and multicentric disease (i.e. the presence of two or more foci of breast cancer in different quadrants of the same breast) are allowed.

3.1.3 Patients with T3N0 disease are eligible.

3.1.4 Patients with disease limited to nodal micrometastases are eligible.

3.1.5 Patients with nodal *macrometastases (> 2 mm*) treated by axillary dissection must have 1-3 positive axillary nodes *(macrometastases, > 2 mm)*.*

3.1.6 Patients with nodal *macrometastases (> 2 mm*) treated by SLNB alone must have only 1-2 positive axillary nodes *(macrometastases, > 2 mm)*.*

* *Note patients with additional nodal micrometastases (> 0.2-2mm) or isolated tumour cells (≤ 0.2 mm) are eligible.*

3.1.7 Patients must be ER ≥ 1% and HER2 negative on local testing

3.1.8 Patients must have an Oncotype DX recurrence score ≤ 25 obtained from testing of breast tumour tissue from a core biopsy or from the surgical specimen.**, ***

** *If the patient does not already have Oncotype DX recurrence score, specimen (unstained blocks or slides) must be sent to the Exact Sciences centralized laboratory in Redwood City, California. For Canadian sites, see the MA.39 website https://www.ctg.queensu.ca/trials/breast/ma39 and for US sites, see the CTSU website for the CCTG MA.39 trial for instructions on ordering Oncotype DX test.*

*** *Oncotype DX testing must be performed on a core biopsy PRIOR to commencement of neoadjuvant endocrine therapy. See ineligibility criterion 3.2.8 for further details on the duration of neoadjuvant endocrine therapy.*

3.1.9 Patient must consent to provision of, and investigator(s) must agree to submit to the CCTG Central Tumour Bank, a representative formalin fixed paraffin block of tumour tissue in order that the specific correlative marker assays described in the protocol may be conducted. Where tissue exists but local centre regulations prohibit submission of blocks of tumour tissue, the approval of the CCTG must be sought prior to randomization of the first patient to allow cores (two 2 mm cores of tumour from the block) and slides (20 x 5 micron thick unstained slides) of representative tumour tissue to be substituted. Where tumour tissue is available, failure to submit any tissue samples will result in the patient being considered ineligible.

3.1.10 Patient must consent to provision of samples of blood in order that the specific correlative marker assays described in the protocol may be conducted.

3.1.11 Patients must have had endocrine therapy initiated or planned for ≥ 5 years. Premenopausal women will receive ovarian ablation plus aromatase inhibitor therapy or tamoxifen if adjuvant chemotherapy was not administered. For all patients, endocrine therapy can be given concurrently or following RT.

3.1.12 Patients may or may not have had adjuvant chemotherapy.

3.1.13 RT must commence within 16 weeks of definitive surgery if the patient is not treated with chemotherapy. If adjuvant chemotherapy is given, RT must begin within 12 weeks after the last dose. (Note: adjuvant chemotherapy may be ongoing at the time of randomization).

Note: Definitive surgery is defined as the last breast cancer-related surgery.

3.1.14 Patient's ECOG performance status must be 0, 1 or 2.

3.1.15 Patient's age must be ≥ 35 years.

3.1.16 <u>For the first 736 eligible English or French-speaking subjects who have agreed to optional questionnaire completion (note: enrollment completed 2022AUG02)</u>: Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life, health utilities and lost productivity questionnaires in either English or French. The baseline assessment must be completed within required timelines, prior to registration/randomization. Inability (lack of comprehension in English or French, or other equivalent reason such as cognitive issues or lack of competency) or refusal to complete the questionnaires will not make the patient ineligible for the study. Participation in questionnaire completion is mandatory for centres, but optional for patients.

3.1.17 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate.

A similar process must be followed for sites outside of Canada as per their respective cooperative group's procedures.

3.1.18 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

3.1.19 In accordance with CCTG policy, protocol treatment is to begin within 6 weeks of patient randomization.

3.1.20 Women of childbearing potential must have agreed to use an effective contraceptive method. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, she is responsible for beginning contraceptive measures.

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Section 4.0); this may include an ultrasound to rule-out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin is high and partner is vasectomized, it may be associated with tumour production of hCG, as seen with some cancers. Patient will be considered eligible if an ultrasound is negative for pregnancy.

3.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

3.2.1 Patients with nodal disease limited to isolated tumour cells ($pN0_{i+}$ < 0.2 mm).

3.2.2 Patients with pT3N1 and pT4 disease (Note: patients with T3N0 are eligible).

3.2.3 Any prior history, not including the index cancer, of ipsilateral invasive breast cancer or ipsilateral DCIS treated with radiation therapy. (Patients with synchronous or previous ipsilateral LCIS are eligible.)

3.2.4 Synchronous or previous contralateral invasive breast cancer. (Patients with contralateral DCIS are eligible unless previously treated with radiation.)

3.2.5 History of non-breast malignancies except adequately treated non-melanoma skin cancers, in situ cancers treated by local excision or other cancers curatively treated with no evidence of disease for ≥ 5 years.

3.2.6 Patients who are pregnant.

3.2.7 Patients that have had prior ipsilateral chestwall/thoracic radiation.

3.2.8 Patients treated with chemo or endocrine therapy administered in the neoadjuvant setting for breast cancer. Endocrine therapy exposure 12 weeks or less prior to surgery is permitted.

3.2.9 Patients with serious non-malignant disease (e.g. cardiovascular, scleroderma etc.) which would preclude RT.

3.2.10 Patients with any serious active or co-morbid medical conditions, laboratory abnormality, psychiatric illness, active or uncontrolled infections, or serious illnesses or medical conditions that would prevent the patient from participating or to be managed according to the protocol (according to investigator's decision).

4.0 PATIENT EVALUATION FLOWSHEET: PRE-TREATMENT, ON STUDY, AND AFTER TREATMENT

All patients entered on study must be evaluated according to the schedule outlined below with documentation submitted according to the schedule in Appendix II.

Required Investigations	Pre-study prior to randomization	Last week of RT **(if receiving RT)**	2 months after randomization **(if <u>not</u> receiving RT)**	6 months after randomization	12 months after randomization, then annually
History and Physical Exam[1]					
Including breast cancer history, height, menopausal status and smoking status	Within 14 days				
Arm volume and mobility measurements	Within 14 days			X	1, 3, and 5 years
Weight and ECOG performance status	Within 14 days	X	X	X	X
Clinical assessment of recurrence				X[2]	X[2]
Radiology					
Bilateral mammogram or breast MRI	Within 18 months				X[1]
Other staging per standard of care					
Complete staging including CT thorax (including supraclavicular, axillary or internal mammary nodes) and abdomen/ pelvis		At the time of local-regional recurrence			
Complete staging and assessment of local-regional recurrence, including CT of thorax (including supraclavicular, axillary or internal mammary nodes)		At the time of distant recurrence			
Other Investigations					
Pregnancy test[3]	Within 14 days				
Oncotype DX test[4]	X				
Correlative Studies					
Archival tissue sample collection (mandatory)[5]	X				
Whole blood collection for ctDNA (mandatory)[5]	Post-consent, prior to RT treatment, or within 6 weeks for patients not receiving RT treatment				
Adverse Events					
Adverse Event Assessment using NCI CTCAE version 5.0	Within 14 days	X	X	X	X
Patient Reported Outcomes[1,6]					
EORTC QLQ-C30 + QLQ-BR23 and Arm and Breast Symptom Questionnaire	Within 14 days	X	X	X	1, 3 and 5 years
EQ-5D					
Lost Productivity Questionnaire					
Trial Specific Economics Questions		X			
Health Economics[1,6]					
Resource Utilization Assessment[6,7]		X	X	X	X (*and at the time at recurrence*)

footnotes on next page …

1 Not required after recurrence.

2 After local-regional recurrence, patients should continue to be followed for distant recurrence.

3 Pregnancy test (in women of childbearing potential), as part of Pre-Study Evaluation, may include an ultrasound to rule- out pregnancy.

4 For patients that do not already have an Oncotype DX score. Must be done after registration and prior to randomization. For Canadian sites, see MA.39 website for further details https://www.ctg.queensu.ca/trials/breast/ma39 and for US sites, see the CTSU website for the CCTG MA.39 trial.

5 See Section 12 and the MA.39 Correlative Studies Laboratory Manual for details.

6 To be done in the first 736 English or French Speaking patients who agree to questionnaire completion. (Note: enrollment completed 2022AUG02) – for patients randomized after this date, completion of questionnaires is not applicable.)

7 The Resource Utilization Assessments (RUA) are the i-Medidata-EDC report forms for hospitalizations, institutional log, and outpatient visits and procedures (on the Radiotherapy Report and Follow-up Report folders). (Note: enrollment completed 2022AUG02 – patients randomized after this date do not require reporting of RUA data.)

4.1 Follow-up for Ineligible and Randomized Patients

The follow-up requirements for ineligible patients who have received no protocol therapy include submission of the Baseline Report plus an annual minimal follow-up form. Data submission for ineligible participants who have received at least one dose of protocol therapy should be according to the protocol to allow for treatment and adverse event assessment.

5.0 ENTRY/RANDOMIZATION PROCEDURES

5.1 Entry Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

5.1.1 *Local Activation Process*

Investigator and Research Associate Registration with CTEP:

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster;
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol PI on the IRB approval.

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR **Help Desk** by email at RCRHelpDesk@nih.gov .

Each clinical site must obtain IRB approval for this protocol before they can enroll patients. Study teams may check the status of their site by logging into the CTSU website, clicking the blue 'Regulatory' tab then clicking the beige 'Site Registration' tab then entering the CTEP site code and protocol number in the search boxes and clicking 'Go'.

Details of the local activation process are available by contacting CCTG, or by visiting the trial websites. Canadian sites should visit and use documentation posted to the CCTG website for MA39, while sites in the US should refer to the CTSU website.

Radiotherapy Credentialing:
Instructions for completing credentialing requirements are available on the IROC Houston's website at http://irochouston.mdanderson.org under "Credentialing". To determine if these requirements have already been met by your institution, select "Credentialing Status Inquiry."

For applicable NCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

Please refer to Section 7.2 for details of RT credentialing.

5.1.2 *Registration/Randomization Procedures*

Patient registration/randomization can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff will use the Oncology Patient Enrollment Network (OPEN) to enroll patients to this study. Each site will need to credit their existing affiliated Cooperative Group for the enrollment. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. All enrolled patients will be assigned a CCTG patient ID.

All data entry tasks, except for randomization, will be done through a web-based, password-operated Electronic Data Capture (EDC) system. Data must be submitted electronically using Medidata Rave® at the following url: https://login.imedidata.com/selectlogin

- If prompted, select the 'CTEP-IAM IdP' link.
- Enter your valid and active CTEP-IAM User ID and password. This is the same account used for the CTSU members website and OPEN.

You may also access Rave® via the CCTG MA.39 trial website for Canadian sites or via the CTSU website for US sites. If sites experience difficulties accessing the system and/or randomizing patients please contact the help desk or the MA.39 Study Coordinator.

Step 1 – Registration:

Patients who have not had previous Oncotype DX testing done:
A screening consent will be required. After patient consent, if the investigator believes patient is eligible according to all other criteria, patient must be registered using the OPEN system. An abbreviated eligibility checklist will be used for this purpose. Following registration, tissue must be sent to the Exact Sciences centralized laboratory for testing. Exact Sciences will cover the cost of the test for these cases. For Canadian sites, see the CCTG MA.39 trial specific website, and for US sites, see the CTSU website for instructions. Once the Oncotype DX test score is received, if the score is less than or equal to 25 and all other eligibility criteria are met the patient may be randomized (see Step 2). If Oncotype DX score is greater than 25, the patient is not eligible and cannot proceed to randomization. Follow up data will not be collected.

Patients that have had previous Oncotype DX testing done:
If the existing Oncotype DX score is less than or equal to 25 and all other eligibility criteria are met, the patient may be registered using the OPEN system and then immediately randomized (see Step 2).

Access Requirements for Oncology Patient Enrollment Network (OPEN):

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site. Additional information about obtaining a CTEP-IAM account can be found at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. Questions may be directed to the CTEP Associate Registration Help Desk by email at ctepreghelp@ctep.nci.nih.gov.
- To perform registrations/randomizations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations/randomizations on protocols for which you are a member of the Lead Group (CCTG), you must have an equivalent 'Registrar' role on the CCTG roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations/randomizations to trials accessed via the CTSU mechanism (i.e. non-Lead Group randomizations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

Note: *The OPEN system will provide the site with a printable confirmation of randomization and treatment information. Please print this confirmation for your records.*

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org . For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Step 2 – Randomization
Randomization will be provided electronically, using the OPEN system. Patients must be randomized prior to the initiation of treatment, and after baseline assessments are completed.

Note: *The validity of results of the trial depends on the authenticity of and the follow-up of all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.*

All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

All randomized patients are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required. The follow-up requirements for ineligible patients are outlined in Section 4.1.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG.

The following information will be required:

- trial code (CCTG MA.39)
- patient's initials (may be coded)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- tissue banking/optional consent version date
- confirmation of the requirements listed in Section 3.0
- height and weight
- stratification factors

5.2 Stratification

Subjects will be stratified by:

- Surgery type (BCS or mastectomy)
- Axillary dissection (yes or no)
- Adjuvant chemotherapy (yes or no)
- Presence of lympovascular invasion (Yes or no)
- Oncotype DX score (0–10, 11-17, or 18-25)
- Treatment centre

5.3 Inclusion of Women and Minorities

There are no exclusions based on race or ethnicity in this trial. In the Canadian Cancer Trials Group as a whole, 60% of patients have been female and 40% have been male. The female preponderance reflects the number of studies performed in breast cancer. Recruitment to trials for disease sites that involve both males and females has been approximately in proportion to the gender incidence *[Marlin 1996]*. Insufficient data has been collected to test a similar relationship for racial/ethnic groups. This study, however, will be presented to patients through the major cancer-treatment institutions of the Canadian provinces, to which all racial/ethnic groups have equal access. The intention, therefore, is to recruit subjects from racial/ethnic groups in close approximation to the incidence of the disease in these groups.

6.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with CCTG policy, protocol treatment is to begin within 6 weeks of patient randomization.

6.1 Radiation Therapy

RT will be administered within 16 weeks of surgery if the patient is not treated with chemotherapy. If adjuvant chemotherapy is given, RT should begin within 12 weeks after the last dose. Endocrine therapy can be given concurrently or following RT. Patients treated by BCS will be randomized to WBI alone or WBI plus RT to the regional nodes. Patients treated by mastectomy will be randomized to no RT or RT to the chestwall and regional lymph nodes.

6.2 Treatment Arms

6.2.1 *Arm 1*

Group 1A: patients treated with BCS will receive WBI with standard tangents with the intention to treat the breast at risk. **High tangents with the intention to treat additional level I and/or II axillary nodes are not permitted.** Conventional (50 Gy in 25 fractions of 2 Gy) and hypofractionation (42.56 Gy in 16 fractions of 2.66 Gy) are permitted. All fractions are delivered daily Monday to Friday. Boost RT to the lumpectomy cavity is optional and permitted as per local policy. Different dose schedules are permitted (for conventional fractionation: 10 Gy in 5 fractions or 14 Gy in 7 fractions; for hypofractionation: 10 Gy in 4 fractions or 12.5 Gy in 5 fractions).

Group 1B: patients treated by mastectomy will not receive RT.

6.2.2 *Arm 2*

Group 2A: for patients treated with BCS the intention is to treat the breast and regional lymph nodes (in the supraclavicular, un-dissected axilla and upper three intercostal internal mammary nodal areas). Conventional (50 Gy in 25 fractions of 2 Gy) and hypofractionation (42.56 Gy in 16 fractions of 2.66 Gy) are permitted. All fractions are delivered daily Monday to Friday. In patients treated with an axillary dissection the dose to the supraclavicular and axillary nodes can be reduced (for conventional fractionation: 45 Gy in 25 fractions; and for hypofractionation: 40 Gy in 16 fractions). Boost RT to the lumpectomy cavity is optional and permitted as per local policy. Different dose schedules are permitted (for conventional fractionation: 10 Gy in 5 fractions or 14 Gy in 7 fractions; for hypofractionation: 10 Gy in 4 fractions or 12.5 Gy in 5 fractions).

Group 2B: for patients treated with mastectomy the intention is to treat the chestwall and regional lymph nodes (in the supraclavicular, un-dissected axilla, and upper three intercostal internal mammary nodal areas). Conventional (50 Gy in 25 fractions of 2 Gy) and hypofractionation (42.56 Gy in 16 fractions of 2.66 Gy) are permitted. All fractions are delivered daily Monday to Friday. In patients treated with axillary dissection the dose to the supraclavicular and axillary nodes can be reduced (for conventional fractionation: 45 Gy in 25 fractions; and for hypofractionation: 40Gy in 16 fractions). Boost to the mastectomy scar is not encouraged, but may be used at the discretion of the investigator for special circumstances (e.g. close margins < 2 mm on the mastectomy specimen). Permitted boost doses are for conventional fractionation: 10 Gy in 5 fractions or 14 Gy in 7 fractions; and for hypofractionation: 10 Gy in 4 fractions or 12.5 Gy in 5 fractions.

6.3 Equipment and Treatment Delivery

6.3.1 Equipment

CT planning systems with capability for DICOM data transfer must be used. Treatment is to be delivered using 4-18 MV photons. Electron beam therapy is also permitted. Proton therapy is not permitted. MV, kV or CBCT imaging capabilities are required.

6.3.2 *Treatment Delivery*

Technique and field arrangement will be at the discretion of the treating physician. 3 dimensional conformal RT (3DCRT) or intensity modulated RT (IMRT) techniques are permitted. The latter can be done using static beam technique or rotational techniques including forward planning IMRT, inverse planning IMRT, volumetric arc therapy (VMAT), or tomotherapy. Field arrangements are at the discretion of the treating physician as long as the composite plan meets the dose-volume Compliance Criteria (Section 6.9), but the following field arrangements are recommended. For Group 1A standard breast tangents are recommended. In Group 2 the following beam arrangements are recommended: the modified wide tangent technique to include the upper three intercostal space internal mammary nodes, chestwall or breast, and an anterior or anterior and posterior field to include the supraclavicular and axillary nodes. Other field arrangements such as a direct mixed photon/electron field to treat the internal mammary nodes are permitted provided appropriate dosimetric coverage for the target structures and normal tissue restrictions are met.

6.4 Positioning, Immobilization and Localization/Simulation

6.4.1 *Positioning*

Simulation and treatment should be performed with the patient in the supine position. For patients post-lumpectomy in Arm 1/Group 1A the prone position is also permitted.

6.4.2 *Immobilization*

Patients should be optimally positioned with breast boards, wing boards and/or other methods of immobilization, alpha cradle casts, vac fix, at the discretion of the treatment physician. **For left sided cancer, methods to minimize cardiac exposure to RT such as deep inspiration breathhold (DIBH), gating or the use of a minimal heart shield are encouraged provided target volumes are adequately covered.**

6.4.3 *Localization Imaging/Simulation*

Treatment planning CT scan in the treatment position will be required to define clinical target volumes (CTV), planning target volumes (PTV), and Organs at Risk (OAR).

For post-lumpectomy (ARM 1/Group 1A and Arm 2/Group 2A) – Radio-opaque markers are recommended to be placed on the patients skin in the treatment position as external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify: 1) the lumpectomy incision; 2) the outline of the palpable breast tissue circumferentially at least from 2 o'clock to 10 o'clock; and 3) the superior border of the breast tissue at 12 o'clock based on palpation. Note for Arm 1/Group 1A this will identify the superior aspect of the breast CTV. For Arm 2/Group 2A the superior marker of the clinical extent of breast tissue can be at a different location than the match line between the breast and RNI fields. The use of bolus is not permitted.

For post-mastectomy (Arm 2/Group 2B) – Radio-opaque markers are to be placed on the patients skin in the treatment position as external landmarks at the acquisition of the CT scan to facilitate contouring segmentation of the CT data-set. These markers should identify: 1) the mastectomy scar; and 2) the clinical outline at least from 2 o'clock to 10 o'clock of the "at risk" chestwall representing where the breast previously was located. The use of bolus can be used at the discretion of the investigator.

For patients that have an expander in place post-mastectomy for reconstruction, the amount of expansion during radiation is per the investigator's discretion. The position of the expander, ranging from collapsed to fully expanded, that is present at the time of acquisition of the CT scan for treatment planning must remain stable until the completion of RT. In the setting of the contralateral mastectomy, with expander placement, contralateral expansion should not increase contralateral chestwall/reconstructed breast exposure to radiation. In this situation, it is recommended to at least partially deflate contralateral expander before CT simulation.

The CT scan should extend cephalad to start at or above the mandible and extend sufficiently caudally to the inframammary fold to encompass the entire lung volume. A CT scan image thickness of $\leq$ 0.5 cm should be used.

External skin localizing marks, which may include permanent tattoos, are recommended for daily radiation localization and set-up accuracy.

Use of IMRT (or VMAT) is allowed if credentialed (please see section below for IMRT guidelines). Calculations should take into account the effect of tissue heterogeneities. Left sided cancer methods to minimize cardiac exposure to RT such as breathhold, gating or minimal heart shield are encouraged provided target volumes are adequately covered.

6.5 Definition of Target Volume and Margins

All target volumes and normal tissues at risk (heart, both lungs, contralateral breast, thyroid, spinal cord, and trachea) will be contoured. Chestwall or breast, and regional nodal clinical target volumes (CTVs) will be based on definitions from the RTOG Breast Cancer Atlas *[RTOG]* with additional margins for planning target volumes (PTVs) as per conventional practice. Spinal cord, trachea and thyroid are contoured for reference with no trial specified dose constraints, the dose should be kept as low as reasonably possible consistent with the ALARA principle.

Table 1: Structures List (Right Breast)

Target Volumes	Description	Validation
CTV_WB_R	Breast CTV	Required Arm 1/1A and Arm 2/2A
PTV_WB_R	Breast PTV	Required Arm 1/1A and Arm 2/2A
PTV_WB_EVA_R	Breast PTV Eval	Required Arm 1/1A and Arm 2/2A
Lumpectomy_R	The excision cavity volume	Required Arm 1/1A and Arm 2/2A
CTV_Lump_R	Lumpectomy CTV	Required Arm 1/1A and Arm 2/2A
PTV_Lump_R	Lumpectomy PTV	Required Arm 1/1A and Arm 2/2A
PTV_Lump_EVA_R	Lumpectomy PTV Eval	Required Arm 1/1A and Arm 2/2A
CTV_CW_R	Chestwall CTV	Required Arm 2B
PTV_CW_R	Chestwall PTV	Required Arm 2B
PTV_CW_EVA_R	Chestwall PTV Eval	Required Arm 2B
Scar_R	Mastectomy Scar	Required Arm 2B
CTV_Scar_R	Mastectomy Scar CTV	Required Arm 2B
PTV_Scar_R	Mastectomy Scar PTV	Required Arm 2B
PTV_Scar_EVA_R	Mastectomy Scar PTV Eval	Required Arm 2B
CTVn_SCL_R	Supraclavicular CTV	Required Arm 2A and 2B
PTVn_SCL_R	Supraclavicular PTV	Required Arm 2A and 2B
CTVn_Ax_R	Axillary CTV	Required Arm 2A and 2B
PTVn_Ax_R	Axillary PTV	Required Arm 2A and 2B
CTVn_IMN_R	Internal mammary nodal CTV	Required Arm 2A and 2B
PTVn_IMN_R	Internal mammary nodal PTV	Required Arm 2A and 2B
Normal Tissue	Description	Validation
LUNG_R	Ipsilateral lung	Required Arm 1A, 2A and 2B
LUNG_L	Contralateral lung	Required Arm 1A, 2A and 2B
Heart	Heart	Required Arm 1A, 2A and 2B
Thyroid	Thyroid	Required Arm 1A, 2A and 2B
BREAST_L	Contralateral Breast	Required Arm 1A, 2A and 2B
External	External	Required Arm 1A, 2A and 2B

Table 2: Structures List (Left Breast)

Target Volumes	Description	Validation
CTV_WB_L	Breast CTV	Required Arm 1/1A and Arm 2/2A
PTV_WB_L	Breast PTV	Required Arm 1/1A and Arm 2/2A
PTV_WB_EVA_L	Breast PTV Eval	Required Arm 1/1A and Arm 2/2A
Lumpectomy_L	The excision cavity volume	Required Arm 1/1A and Arm 2/2A
CTV_Lump_L	Lumpectomy CTV	Required Arm 1/1A and Arm 2/2A
PTV_Lump_L	Lumpectomy PTV	Required Arm 1/1A and Arm 2/2A
PTV_Lump_EVA_L	Lumpectomy PTV Eval	Required Arm 1/1A and Arm 2/2A
CTV_CW_L	Chestwall CTV	Required Arm 2B
PTV_CW_L	Chestwall PTV	Required Arm 2B
PTV_CW_EVA_L	Chestwall PTV Eval	Required Arm 2B
Scar_L	Mastectomy Scar	Required Arm 2B

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CTV_Scar_L	Mastectomy Scar CTV	Required Arm 2B
PTV_Scar_L	Mastectomy Scar PTV	Required Arm 2B
PTV_Scar_EVA_L	Mastectomy Scar PTV Eval	Required Arm 2B
CTVn_SCL_L	Supraclavicular CTV	Required Arm 2A and 2B
PTVn_SCL_L	Supraclavicular PTV	Required Arm 2A and 2B
CTVn_Ax_L	Axillary CTV	Required Arm 2A and 2B
PTVn_Ax_L	Axillary PTV	Required Arm 2A and 2B
CTVn_IMN_L	Internal mammary nodal CTV	Required Arm 2A and 2B
PTVn_IMN_L	Internal mammary nodal PTV	Required Arm 2A and 2B
Normal Tissue	Description	Validation
LUNG_R	Contralateral lung	Required Arm 1A, 2A and 2B
LUNG_L	Ipsilateral lung	Required Arm 1A, 2A and 2B
Heart	Heart	Required Arm 1A, 2A and 2B
Thyroid	Thyroid	Required Arm 1A, 2A and 2B
BREAST_R	Contralateral Breast	Required Arm 1A, 2A and 2B
External	External	Required Arm 1A, 2A and 2B

6.5.1 *Breast Volumes (Arms 1/Group1A and Arm2/Group 2A)*

Breast CTV:
Includes the palpable breast tissue demarcated with radio-opaque markers at CT simulation (see Section 6.4.3) the apparent CT glandular and fatty breast tissue visualized by CT, consensus definitions of anatomical borders based on the RTOG Breast Cancer Atlas, and should include the lumpectomy CTV (see below). The Breast CTV is limited anteriorly within 5 mm from the skin and posteriorly to the anterior surface of the pectoralis, serratous anterior muscle excluding chestwall, boney thorax, and lung. In general, the pectoralis and/or serratous anterior muscles are excluded from the Breast CTV unless clinically warranted by the patient's pathology. MA.39 planning guidelines are available on the CCTG MA39 website for Canadian sites, while sites in the US should refer to the CTSU website.

Breast PTV:
Breast CTV + a minimum of 5-7 mm 3D expansion (excludes heart and does not cross midline).

Breast PTV Eval:
The Breast PTV Eval is intended to exclude the portion of the breast PTV that extends outside the patient or into the lung or boney thorax. The Breast PTV is copied to a Breast PTV Eval which is edited. This Breast PTV Eval is limited anteriorly to exclude the part outside the patient and the first 5 mm of tissue under the skin (in order to remove most of the build-up region for the dose volume histogram [DVH] analysis) and posteriorly to the anterior surface of the ribs (excludes boney thorax and lung). This Breast PTV Eval is the structure used for DVH constraints and analysis and not for beam aperture generation. **Contouring should not normally lead to extended fields; the medial border would be expected to be inside of or at the mid-sternal line and the lateral border would be expected to be medial to or at the mid-axillary line to cover the breast.**

Lumpectomy Gross Target Volume (GTV):
Contour surgical cavity using all available clinical and radiographic information, architectural distortion, lumpectomy scar, seroma and/or extent of surgical clips. If no visible lumpectomy and no boost required patient is still eligible.

Lumpectomy CTV:
Lumpectomy GTV + 1 cm 3D expansion. Limit the CTV posteriorly at the anterior surface of the pectoralis/serratous anterior muscles and/or chestwall; anterolaterally 5 mm from skin: and should not cross midline.

Lumpectomy Planning Target Volume (PTV):
Lumpectomy CTV + 5-7 mm 3D expansion (excludes heart).

Lumpectomy PTV Eval:
Lumpectomy PTV is copied to the lumpectomy PTV Eval, which is edited. Lumpectomy PTV Eval is limited to exclude the part outside the ipsilateral breast, the first 5 mm of tissue under the skin, the chestwall, pectoralis muscles and lung. The lumpectomy PTV should not cross midline. The lumpectomy PTV Eval is the structure used for DVH analysis.

6.5.2 *Chestwall Target Volumes Post-Mastectomy (Arm 2/Group 2B)*

Chestwall CTV:
Should include the radio-opaque markers at CT identifying clinical extent of chestwall, surgical changes visualized by CT, the mastectomy scar CTV (see below), and should take into account consensus definitions of anatomical borders of chestwall based on the RTOG Breast Cancer Atlas.

The Chestwall CTV is limited by the skin anteriorly, by rib-pleural interface posteriorly and excludes the heart and lung. Depending on the location of the Mastectomy Scar CTV, it should exclude the sternum medially and the axilla deep to the anterior surface of the pectoralis major muscle laterally. In general, the Chestwall CTV should not cross midline.

Expanders, implants, or autologous tissue present for reconstruction will be included in the Chestwall CTV. The degree of expander expansion is per the treating physician's discretion. The expander should remain at the same expansion through the course of treatment that is present for the CT simulation.

Chestwall PTV:
Chestwall CTV + a minimum of 5-7 mm 3D expansion (excludes heart and does not cross midline).

Chestwall PTV Eval:
As part of the Chestwall PTV often extends outside the patient, the Chestwall PTV is copied to a Chestwall PTV Eval which is edited. The Chestwall PTV Eval is limited anteriorly to exclude the part outside the patient and the first 3-5 mm of tissue under the skin (in order to remove most of the build-up region for the DVH analysis) and posteriorly is limited to no deeper than the posterior rib surface and excludes lung and heart. The Chestwall PTV Eval is used for DVH constraints and analysis and not for beam aperture generation. The use of bolus is permitted at the discretion of the investigator.

Mastectomy Scar GTV:
Mastectomy scar and surrounding vicinity is a common location for chestwall recurrences post-mastectomy. To ensure this area of chestwall is covered by post-mastectomy RT an initial target volume for the mastectomy scar will be created. The mastectomy scar will be contoured by delineating the radio-opaque wire placed over the scar at CT simulation and additionally including affected subcutaneous tissue visible on CT per investigator's discretion.

Mastectomy Scar CTV:
The mastectomy scar GTV + 1 cm 3D expansion. Limit the expansion posteriorly at the anterior surface of the ribs and limit anterolaterally 3-5 mm from skin and should not cross midline. In specific cases, it might be clinically indicated to cross midline to adequately cover the target volumes e.g. mastectomy scar. In these cases, it might be difficult to meet compliance criteria and the patient might be unsuitable for enrollment in this protocol.

Mastectomy scar PTV:
Mastectomy scar CTV + 5-7 mm 3D expansion (excluding heart).

Mastectomy scar PTV Eval:
Since a substantial part of the mastectomy PTV often extends outside the patient, a mastectomy scar PTV Eval is created. The mastectomy scar PTV Eval is limited to exclude the part that extends outside the body and the first 3-5 mm of tissue under the skin (to remove build-up region for the DVH) and posteriorly to exclude lung and heart. The mastectomy scar PTV Eval should not cross mid-line and should be contained within the borders of the chestwall PTV Eval. It is used for DVH analysis primarily.

6.5.3 *Regional Nodal Target Volumes (Arm 2/Groups 2A and 2B)*

Supraclavicular CTV:
Based on consensus definitions from the RTOG Breast Cancer Atlas, superior extent is typically below the level of the cricoid; medially excludes thyroid, trachea, and esophagus; extends laterally to the edge of the sternocleidomastoid muscle superiorly and the clavicle at its more inferior extent and the inferior border extends to the junction of the brachiocephalic and subclavian veins or the caudal aspect of the clavicular head, and posteriorly extends to the anterior aspect of the scalene muscle, excluding muscle.

Supraclavicular PTV:
Supraclavicular CTV + 5 mm margin in all directions except medially. The following structures should be excluded to minimize excess dose to normal tissues: ipsilateral thyroid, trachea, esophagus, ipsilateral lung, the vertebral body and 5 mm inside skin. The medial border of the supraclavicular PTV will be same as that of the supraclavicular CTV.

Axillary CTV:
The extent of the axilla to target for regional nodal irradiation (RNI) will depend on how much of the axilla has been dissected. The Axillary CTV consists of a portion of the axilla that remains un-dissected. When an axillary dissection has been done, the inferior border of the Axillary CTV will be the most cephalic extent of the dissection. Review of the operative report, clips post-operative changes on the planning CT, and discussion with the patient's surgeon can be used for determining the most cephalic extent of the dissection and inferior border of the Axillary CTV. Axillary dissection typically removes level 1–2 axillary nodes, so that the Axillary CTV in these cases is expected to include level 3 primarily and on occasion some of the level 2 axilla.

When a sentinel node procedure is done without complete axillary dissection, the Axillary CTV will then include all three levels of the axilla as all three levels that are "un-dissected". Note, that

most of level 1 will be covered by the breast or chestwall tangents and typically the lateral field border would not extend beyond the mid-axillary line to avoid high lung doses. The consensus definitions for anatomical borders of the axillary levels are based on the RTOG Breast Cancer Atlas. MA.39 planning guidelines are available on the MA.39 trial specific website https://www.ctg.queensu.ca/trials/breast/ma39 for Canadian sites and on the CTSU website for the CCTG MA.39 trial for US sites.

Axillary PTV:
Axillary CTV + 5 mm expansion. The ipsilateral lung should be excluded from the Axillary PTV, meaning that some or all of the medial border of the Axillary PTV can be the same as that of the Axillary CTV. Note that contouring should not normally lead to enlarged field sizes e.g. in patients treated with a SLNB, the lateral border of the anterior supraclavicular and axillary field should not normally extend beyond the lateral border of the humeral head. For patients who have been treated with an axillary dissection the lateral border should not normally extend beyond medial aspect of the humeral head. Typically the field or volume irradiated should not extend laterally into the axillary dissection area (beyond the coracoid process or medial border of the humeral head).

Internal Mammary Node (IMN) CTV:
Includes the internal mammary/thoracic vessels in the first three intercostal spaces.

Internal Mammary Node (IMN) PTV:
The IMN CTV + a minimum of 5 mm medially, laterally, superiorly, and inferiorly. The IMN PTV is limited medially not to extend to the sternum. In order to minimize excess normal tissue irradiation, no additional expansion into the lung or heart should be done for the IMN PTV. The deep (or posterior) edge for the IMN PTV will be the same for the IMN CTV. No anterior expansion of the CTV into the chestwall or breast volumes will be done.

6.5.4 *Normal Structures (Organs at Risk – OAR)*

The, "as low as reasonably achievable," (ALARA) principle is recommended for all OARs. Techniques to reduce the heart dose to as low as possible level are encouraged.

Ipsilateral and Contralateral Lung:
This may be contoured with auto-segmentation with manual verification.

Heart:
This is to be contoured for all cases – not just the left-sided. The heart is contoured beginning just inferior to the level in which the pulmonary trunk branches into the left and right pulmonary arteries (PA). Above the PA, none of the heart's 4 chambers are present. The heart should be contoured on every contiguous slice to its inferior most extent near the diaphragm. The following structures, if identified, should be excluded from the heart's contour: esophagus, great vessels (ascending and descending aorta, inferior vena cava and pericardial fat). Contouring along the pericardium itself is appropriate.

Thyroid:
The thyroid is easily visible on a non-contrast CT due to its preferential absorption of iodine, rendering it "brighter" or denser than the surrounding neck soft tissues. The left and right lobes of the thyroid are somewhat triangular in shape and often do not converge anteriorly at midline. All "bright" thyroid tissue should be contoured. For patients who

have undergone total thyroidectomy, there may not be thyroid tissue to contour.

Contralateral Breast:

The contralateral breast is at risk for exposure to inadvertent radiation and the volume includes the CT glandular breast tissue visualized by CT and consensus definitions of anatomical borders from RTOG Breast Atlas. In general, the borders are:

Posterior border: At the anterior surface of the pectoralis, serratous anterior muscles excluding chestwall, ribs, boney thorax, and lung/heart.

Medial border: The sternal-costal junction.

Lateral border: Varies based on the size of the breast, but typically is at the mid-axillary line and excludes the ipsilateral lattisimus dorsi muscle.

Cephalad border: First or second rib medially.

Caudal border: Inframammary fold.

Anterior border: Skin minus 5 mm to minimize inaccuracy of dose calculation at the skin surface.

6.6 Treatment Planning

CT-based planning with tissue inhomogeneity correction is required.

3DCRT or IMRT are permitted

The following definitions and conditions are applied concerning IMRT in this protocol:

1. The treatment plan will be considered IMRT for the purposes of this protocol if an inverse planned optimization is used to determine the beam weights to meet the target and critical structure dose volume constraints.
2. The plan generated by direct aperture optimization that employs an inverse planning algorithm is considered as IMRT when the target and critical structure dose volume constraints are met and at least 3 apertures for each beam direction are used.
3. If IMRT is combined with the standard open medial and lateral tangential fields for WBI, the IMRT beam as defined above should deliver > 50% of the total number of monitor units for the beam orientation.
4. If an IMRT plan is used with another IMRT plan, forward planning photon beams, and/or electron beam, a composite dose distribution and DVHs should be generated.
5. All standard IMRT planning and delivery systems using MLC (step-and-shoot, dynamic MLC, slide-and-shoot, VMAT, tomotherapy) are allowed and classified as IMRT so long as target and critical structure dose volume constraints are met.
6. IMRT planning and delivery systems using physical beam-intensity compensators designed by

an inverse algorithm to modulate beam intensity so that the required dose constraints are met are also accepted as IMRT.

7. A patient-specific pre-treatment QA measurement is required prior to the first treatment for an IMRT plan.

All plans that do not fit into the above definitions and conditions are classified as 3DCRT plans. Specifically:

- The plans generated using forward planning methods or segmental techniques such as "field-in-field" to meet dose volume constraints are considered as 3DCRT plans. These forward planned or segmental treatment techniques are intended to mainly improve the uniformity of the dose distribution but not to produce steep dose gradients to protect critical structures (e.g. heart or lung).
- The plans with the number of apertures < 3 for each beam direction are considered 3DCRT plans even if they were generated with inverse planning algorithms.

6.6.1 *Whole Breast +/- Boost Radiotherapy (Arm 1/Group 1A and Arm 2/Group 2A)*

Whole breast +/- boost irradiation alone is used in Arm 1/Group 1A and with regional nodal RT in Arm 2/Group 2A. The Breast PTV is used to generate beam apertures with additional margin into account penumbra. Fields should include all of the Breast PTV and Lumpectomy PTV. The aperture margin generally needed beyond the PTV is 5 mm. The goals of treatment planning are to encompass the Breast PTV and minimize an inclusion of heart, lung, and other normal tissues.

Field arrangements for 3DCRT and IMRT irradiation of the Breast PTV are at the discretion of the treating physician. Multiple beam arrangements may be designed during the treatment planning process to produce an optimal plan that meets the dose volume constraints on the Breast PTV and normal tissues outlined in Table 3 under Compliance Criteria (Section 6.9). Treatment planning may include the use of respiratory motion control such as gating or DIBH, as necessary.

A lumpectomy boost may be given by either electron beam or photon beams using either 3DCRT or IMRT. A composite dose distribution and DVHs that include the whole breast using IMRT or 3DCRT and lumpectomy cavity boost using electron beams, IMRT or 3DCRT should be completed and provided for review. Simultaneous integrated boost using IMRT is not allowed. Brachytherapy boost is not allowed.

Boost radiation should be planned from the initial CT for radiation planning. If boost is planned on a different CT-simulation, a combined dosimetry with a dose estimate for coverage and OAR must be provided.

6.6.2 *Chestwall With or Without Reconstruction Radiation Therapy (Arm 2/Group 2B)*

The goals of treatment planning are to encompass the Chestwall PTV and regional node targets and minimize inclusion of the heart, lung, and other normal tissues. Field arrangements for 3DCRT and IMRT are at the discretion of the treating physician. Multiple beam arrangements that use photons of various or mixed energies either alone or in combination with electrons are to be designed during the treatment planning process to produce an optimal plan that meets the dose volume constraints on the Chestwall PTV and normal tissues outlined in Table 3 under Compliance Criteria (Section 6.9). Treatment planning can include the use of respiratory motion control such as gating or DIBH, as necessary.

In cases where an expander is in place for purposes of breast reconstruction, there can be a metal port that will need to be taken into account in the radiation treatment planning.

For many cases, there will not be a boost to the chestwall post-mastectomy. For cases where the investigator decides to deliver a chestwall boost, a composite dose distribution and DVHs that include chestwall irradiation using either 3DCRT +/- electrons or IMRT should be completed and provided for review to evaluate adherence to Compliance Criteria (Sections 6.9). Simultaneous integrated boost using IMRT is not allowed. Brachytherapy is not allowed. Changes in patient positioning for the boost is not recommended.

6.6.3 *Regional Nodal RT (Arm 2/Group 2A and Arm 2/Group 2B)*

The goals of treatment planning are to encompass the supraclavicular, axillary, and internal mammary nodal targets along with the breast PTV Eval in Arm 2/Group 2A and with the Chestwall PTV Eval in Arm 2/Group 2B respectively and to minimize inclusion of the heart and lung. Field arrangements for 3D conformal or IMRT are at the discretion of the treating physician. When planning with IMRT, it is recommended to create an additional structure that includes the SCL PTV and the Axillary PTV for optimization. For these patients the following beam arrangements are recommended: the modified wide tangent technique to include the upper three intercostal space internal mammary nodes, chestwall or breast; and an anterior or anterior and posterior field to include the supraclavicular and axillary nodes. Other field arrangements such as a direct mixed photon /electron field to treat the internal mammary nodes are permitted. These and any other beam arrangements are permissible so long as the composite plan meets the compliance criteria in Section 6.9 for the supraclavicular, axillary, and internal mammary node PTVs with either the breast PTV (Arm 2/Group 2A) or the chestwall PTV (Arm 2/Group 2B), respectively; and normal tissue criteria as outlined in that section.

6.7 Required Dose Volume Histogram (DVH) Analysis

The composite treatment plan for whole breast with boost in Arm 1/Group 1A, whole breast with boost and regional nodal radiation in Arm 2/Group 2A, and chestwall and RNI in Arm 2/Group 2B must be done prior to the start of radiation. Plans will undergo quality assurance review as outlined in Section 7.0 and must meet the required dose volume constraints listed in Table 3 under Compliance Criteria (Section 6.9). The maximum doses are defined for 10cc's of PTV Eval and for maximum point doses defined as one dose calculation voxel (e.g. 3 mm x 3 mm x 3 mm or 0.03 cc).

For the pre-treatment review centres will be required to submit the first case treated with standard WBI with or without boost (Arm 1/Group 1A) and the first 2 cases for regional nodal RT plus breast or chest wall RT (first to Arm 2/Group 2A and first to 2B). See Section 7.4 for further details. Planned cases should be submitted at least 7 business days before treatment start date, allowing 3 business days for review completion.

Following pre-treatment review, all treatment plans should be submitted for review within 21 days of treatment initiation. All treatment plans will be reviewed; 33% of cases will be randomly selected for on-treatment review with feedback to centres within 21 days of receipt.

The institution will be notified when 3 plans on quality assurance review do not meet Compliance Criteria (defined in Section 6.9) and are labeled "Deviation Unacceptable. If three plans are labeled "Deviation Unacceptable" the institution will be notified of problems with radiation quality and may require further pre-treatment review.

6.8 Treatment Verification

Port film images for each 3DCRT beam and orthogonal pair for all patients must be obtained and approved by a physician before the third fraction of radiotherapy. For IMRT, orthogonal films or 3D images [cone beam CT (CBCT), MVCT, kV CT] are required to document the verification of isocentre. Images will be repeated until satisfactory and can be repeated as per local policy.

6.9 Compliance Criteria

The composite treatment plan for whole breast +/- boost in Arm 1/Group 1A, whole breast +/- boost and regional nodal irradiation in Arm 2/Group 2A, and chest wall and regional nodal irradiation in Arm 2/Group 2B should meet the following compliance criteria outlined below. Cases will be reviewed accordingly. Investigators should aim for protocol criteria described below in Table 3, but acceptable variation ("Variation Acceptable") is also outlined. Criteria not meeting "Variation Acceptable" will be deemed "Deviation Unacceptable". Note, in addition to these criteria, maximum doses for 10 cc target volume and maximum point doses (0.03 cc) are also required and will be reviewed for radiation quality. In addition to the criteria specified doses to normal tissues or organs at risk should be kept **as low as reasonably achievable** (ALARA) consistent with that principle.

Table 3: Compliance Criteria

Structure and Description	Protocol	Variation Acceptable	Maximum Dose*
Target Volumes			
Breast or Chestwall PTV_Eval (calculated without boost)	≥ 95% receives 95% of prescribed dose	≥ 90% receives 90% of prescribed dose	*Photons only*: < 10 cc receives 107% (up to 110%) < 0.03 cc receives 115% (up to 120%) *Photons and electrons*: < 10 cc receives 110% (up to 115%) < 0.03 cc receives 120% (up to 130%)
Lumpectomy Boost PTV_Eval and Mastectomy Scar PTV Eval (calculated only if boost used)	≥ 95% receives 95% of prescribed dose	≥ 90% receives 90% of prescribed dose	< 10 cc receives 110% < 0.03 cc receives 120%
Supraclavicular SCL_PTV	≥ 95% receives 95% of prescribed dose	≥ 90% receives 90% of prescribed dose	< 10 cc receives 105% < 0.03 cc receives 110%
Axillary PTV	≥ 95% receives 95% of prescribed dose	≥ 90% receives 90% of prescribed dose	< 10 cc receives 105% < 0.03 cc receives 110%
Internal Mammary IMN_PTV	≥ 95% receives 90% of prescribed dose	≥ 90% receives 80% of prescribed dose	< 10 cc receives 110% < 0.03 cc receives 115%

table continues on next page ...

Structure and Description	Protocol	Variation Acceptable	Maximum Dose*
Normal Tissue			
Ipsilateral Lung ***Arm 1/Group IA***	≤ 15% volume receives 20 Gy (17.5 Gy for hypofractionation)	≤ 17% volume receives 20 Gy (17.5 Gy for hypofractionation)	
Ipsilateral Lung ***Arm 2/Group 2A, 2B***	≤ 35% volume receives 20 Gy (17.5 Gy for hypofractionation)	≤ 40% volume receives 20 Gy (17.5 Gy for hypofractionation)	
	Recommended: ≤75% receives 5Gy		
Contralateral Lung ***Groups 1A, 2A, 2B***	≤ 10% volume receives 5 Gy	≤ 15% volume receives 5 Gy	
Contralateral Breast ***Groups 1A, 2A, 2B***	≤ 10% receives 3 Gy	≤ 10% receives 5 Gy	
Heart			
Left sided cancer	Mean dose ≤ 3 Gy and ≤ 10% receives 25 Gy	Mean dose ≤ 5 Gy or ≤ 10% receives 30 Gy	
Right sided cancer	Mean dose ≤ 2 Gy and ≤ 2% receives 25 Gy	Mean dose ≤ 5 Gy or ≤ 2% receives 30 Gy	

* These criteria are required and no variation is acceptable.

7.0 RADIATION ONCOLOGY FACILITY CREDENTIALING AND QUALITY ASSURANCE

7.1 Quality Assurance

To contain a high degree of compliance to the protocol, several quality assurance procedures will be incorporated which we and other cooperative groups have employed in previous studies. These methods have shown to improve and maintain compliance. They are: (1) centre credentialing (including a facility questionnaire, Benchmark case and phantom irradiation); (2) pre-treatment review; and (3) on-treatment review

7.2 Credentialing Requirements

To participate in MA.39, centres are required to be fully credentialed. The credentialing process includes the completion of a Facility Questionnaire, phantom irradiation (for IMRT only), a Benchmark case, and the completion of a Credentialing Status Inquiry Form (Table 4). Instructions for completing these requirements are available on the IROC Houston QA centre website. Visit: http://irochouston.mdanderson.org and select "Credentialing". The study will require each institution to submit a minimum of one Benchmark case for credentialing (Arm 2/Group 2A). **NOTE, if the institution has been previously credentialed for NRG NSABP protocol B-51-RTOG protocol 1304 or Alliance protocols A011202 or A221505, they will not be required to complete the benchmark case for MA.39. The facility questionnaire and Credentialing Status Inquiry Form must be completed by all centres regardless of previous credentialing.**

Table 4

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions http://irochouston.mdanderson.org		
	Treatment Modality		
	3D	IMRT	Key Information
Facility Questionnaire	x	x	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Phantom Irradiation		x	If credentialing for IMRT, an irradiation of the IROC Houston's IMRT phantom must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston website (http://irochouston.mdanderson.org).
Benchmark	x	x	Instructions for Benchmark credentialing may be found on the IROC Houston website (http://irochouston.mdanderson.org).
Credentialing Status Inquiry Form	x	x	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Credentialing Notification Issued to:			
Institution			Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and CCTG Headquarters that all desired credentialing requirements have been met.

If the institution is interested in treating patients using 3DCRT only, then only one Arm 2/Group 2A Benchmark case will need to be submitted. If the institution is interested in treating patients using 3DCRT and IMRT, then two Arm 2/Group 2A Benchmark cases will need to be submitted, one planned using 3DCRT and the other using IMRT. The Benchmark cases (Arm 2/Group 2A) are a treatment planning exercise. CT scans for the case will be made available for downloading from the IROC Houston Web site http://irochouston.mdanderson.org, and the institution is expected to use this dataset to demonstrate their ability to generate an acceptable dose distribution. The planning results will be submitted electronically via TRIAD (Section 7.3). The results of this planning exercise will be examined and approved by IROC Houston before the first patient can be enrolled from a particular institution. Upon successful completion and approval of the Benchmark case, the CCTG will notify the institution that they have completed this requirement.

In order to utilize either 3DCRT or IMRT on the study, the institution must have met specific technology requirements both for 3DCRT and IMRT, have provided appropriate baseline physics information and provided two Benchmark cases, one planned using 3DCRT and the other using IMRT. When an institution has been credentialed for one technique only, and in the course of the trial, decides to add the other technique, the institution must do one more Benchmark case (Arm 2/Group 2A) using the other technique. Approval of this case will allow the institution to be credentialed in the new technique.

7.3 Data Submission

In order to submit the benchmark credentialing case and all digital data for registered patients, the institution site staff will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user ID and password) used for the CTSU Members' Web site. To obtain an active CTEP-IAM account, go to https://ctepcore.nci.nih.gov/iam/index.jsp. Upon review and successful completion of all requirements, the CCTG Central Office (for Canadian sites) or CTSU (for US sites) will notify the institution that they are eligible to enroll patients on the MA.39 study.

The quality assurance (QA) program will cover the delivery of both 3DCRT and IMRT. Each case will be submitted digitally via TRIAD where it will be processed and made available for review by study chairs or designees, and the IROC Houston or IROC Philadelphia RT Dosimetry Group.

7.3.1 *CTEP Registration Procedures / CTEP-IAM Account*

Please refer to Section 5.1.1 for information regarding registration with CTEP and obtaining a CTEP-IAM account.

7.3.2 *Digital RT Data Submission to RTOG Using TRIAD*

TRIAD is the American College of Radiology's (ACR) image exchange application, and it is adopted for NCTN trials. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

7.3.3 *TRIAD Access Requirements*

Site physics staff who will submit images through TRIAD will need to be registered with CTEP and have a valid and active CTEP IAM account. Please see above for instructions on how to request a CTEP-IAM account.

To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. NRG Oncology users should contact their site Lead RA to be added to the site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.

7.3.4 *TRIAD Installations*

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

7.3.5 *Procedures for Data Submission via TRIAD*

Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan and dose files. This study uses TRIAD for RT data submission. Use of TRIAD requires several preliminary steps as described above. Additional information is available at: http://triadhelp.acr.org/ClinicalTrials/NCISponsoredTrials.aspx.

In the event that a site has not completed all steps required for TRIAD data submission in time to meet the timeline for review, data submitted via SFTP will also be accepted. See the instructions for submission of data via SFTP on the IROC Houston website under Digital Data.

7.4 Pre-Treatment Review

Centres that have previously enrolled patients in the NSABP-B-51, A011202 or A221505 trials are exempted from the pre-treatment review.

Centres will be required to submit the first case treated with standard WBI with or without boost (Arm 1/Group 1A) and the first case for regional nodal RT plus breast or chestwall RT (Arm 2/Group 2A and 2B). Planned cases should be submitted at least 7 business days before treatment start date, allowing 3 business days for review completion.

7.5 On-Treatment Review

All treated cases that do not have a pre-treatment review must be submitted via TRIAD within 21 days of treatment initiation. Cases will be reviewed within 21 days and feedback given to the submitting radiation oncology facility. Institutions that receive 3 or greater ‘variation unacceptable’ on quality assurance review, for any arm will be notified regarding their data quality and may require further pre-treatment review.

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

As breast cancer recurrence-free interval (BCRFI) is the primary endpoint in this study, it is vital that it be adequately and precisely documented.

8.1 Definitions

8.1.1 *Breast Cancer Recurrence-Free Interval (BCRFI)*

The primary outcome is BCRFI defined as time from randomization to time of invasive recurrent disease in the ipsilateral chestwall, breast, regional nodes, distant sites or death due to BC *[Hudis 2007]*.

8.1.2 *Invasive Disease Free Survival (DFS)*

Invasive DFS is defined as the time from randomization to the time of recurrent BC, new primary malignancy, or death.

8.1.3 *Breast Cancer Mortality*

Breast cancer mortality is defined as death due to BC.

8.1.4 *Overall Survival (OS)*

Overall survival is defined as the time from randomization to the time of death from any cause.

8.1.5 *Locoregional Recurrence-Free Interval (LRRFI)*

Locoregional RFI is defined as time from randomization to time of invasive recurrent disease in the ipsilateral chestwall, breast or regional nodes, or death to due to BC.

8.1.6 *Distant Recurrence-Free Interval (DRFI)*

Distant RFI is defined as time from randomization to time of invasive recurrent disease in distant sites or death due to BC.

8.1.7 *Adverse Events*

All patients will be evaluable for toxicity from the time of randomization. Toxicity will be scored using the National Cancer Institute Common Terminology.

Criteria for Adverse Events (NCI CTCAE) version 5.0 and will assess risks of acute radiation toxicity (dermatitis, fatigue, and pneumonitis and late radiation toxicity, (lymphedema, arm mobility and discomfort, brachial neuritis, and cardiac toxicity). Evidence of second cancers will also be collected.

8.1.8 *Arm Volume and Mobility*

All patients will have arm volume and mobility measurements performed. The patient will be considered to have developed arm edema if there is a 10% or greater increase in the volume of the ipsilateral arm compared to the contralateral arm. Arm abduction deficit will be defined as a difference in arm abduction of 10% or greater in the comparison of the ipsilateral to the contralateral arm.

8.1.9 *Quality of Life*

All patients who have completed the baseline quality of life instrument are evaluable for quality of life collected. Quality of life (QOL) and Patient Reported Outcomes (PROs) will be assessed with the EORTC QLQ-C30 and specific items from QLQ-BR23 BC Module and NSABP B-32 Arm and Breast Symptom Questionnaire.

8.1.10 *Economic Analysis*

Patient resources (direct and indirect) associated with RT and health service utilization (hospitalizations, complications and other treatments) will be collected.

8.2 Evidence of Disease Recurrence

8.2.1 *Local - Regional Sites*

Patients with local or regional recurrence should have CT thorax to rule out other regional disease, such as internal mammary nodal recurrence.

1. Definite - positive cytology, aspiration or biopsy.
2. Suspicious - a visible or palpable lesion.

8.2.2 *Distant Recurrence*

A) Bone Marrow

1. Definite - positive cytology, aspiration or biopsy.
2. Suspicious - leukoerythroblastic blood picture.

B) Lungs and Pleural

1. Definite -
   a) positive cytology, aspiration or biopsy, or;
   b) presence of multiple pulmonary nodules which are felt to be consistent with pulmonary metastases.

Note: If a solitary lung lesion is found and no other lesions are present on lung tomograms, further investigation, such as CT scan, biopsy or needle aspiration, should be performed.

C) Skeletal

1. Definite -
   a) X-ray evidence of lytic, blastic, or mixed lytic-blastic lesions on skeletal films with or without bone scan confirmation;
   b) Biopsy proof of bone metastases;
   c) Progressive bone scan changes over at least a four week period showing development of new lesions is necessary in asymptomatic patients with only bone scan abnormalities.

Note: In the absence of progressive disease by scan a biopsy is strongly recommended. Any positive bone scan in joints or in a recent area of trauma (surgical or otherwise) cannot be used as a criterion of treatment failure.

D) Ascites and Pleural Effusions

1. Definite - positive cytology.
2. Suspicious - roentgenographic or clinical evidence.

E) Liver

1. Definite -
   a) Liver enlargement, especially if the liver is nodular, with additional confirmation by an abnormal liver scan, ultrasound or CT scan demonstrating solid space occupying lesions.
   b) Liver biopsy confirmation of metastatic disease.

Note: If the liver scan, ultrasound or CT scan findings are not definitive a liver biopsy is mandatory.

F) Central Nervous System

1. Definite -
   a) Positive CT scan or MRI, usually in a patient with neurological symptoms.
   b) Biopsy or cytology (for a diagnosis of meningeal involvement).

8.3 Dating of First Recurrence

The dating of first recurrence should always be based on the onset of a sign but never on the onset of a symptom. The date of first detection of a palpable lesion is acceptable only when the diagnosis of tumour involvement is subsequently established.

The diagnosis of recurrent disease by radiographs or scans should be dated from the date of the first positive record, even if this is determined in retrospect.

Initial recording of dates of first recurrence and death should be made as they occur by those who are responsible for the care of the patient. Dates that are based on suspicion alone will be reviewed by the CCTG coordinating office in order to establish their accuracy through subsequent behaviour. In addition, the case records of those patients not reported as having recurrent disease will be scrutinized regularly to check that review is continuing and to ensure consistent recording.

8.4 Management Following Recurrence

Patient management following local breast, regional nodal, or distant recurrence is at the discretion of the investigator.

8.5 Contralateral Breast Cancer

A lesion in the opposite breast will be assumed to be a new primary malignancy unless obviously contiguous with recurrent chestwall disease or proven on cytology/biopsy to be of metastatic origin.

8.6 New Primary Malignancies

Patients developing any new primary malignancies, except for adequately treated, superficial squamous or basal cell carcinoma of the skin, or carcinoma in situ of the cervix will continue with routine study follow-up.

9.0 SERIOUS ADVERSE EVENT REPORTING

This protocol does not contain investigational agent(s), and adverse events occurring as a result of this commercially available treatment should be reported to CCTG in the manner described below. In addition, your local Research Ethics Board (REB) should be notified.

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix III). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events (SAEs) are subject to expedited reporting using the CTEP-AERs reporting system (which may be accessed via the EDC system). The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

9.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 9.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

9.2 Expedited Reporting Instructions – Participating Centres Responsibilities

Expedited AE reporting for this study must use the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). The CTEP-AERS web application and information regarding the use of CTEP-AERS (CTEP, NCI Guidelines: Adverse Event Reporting Requirements) can be accessed at the following address:
https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1394829090464

Within 24 hours:	Complete preliminary Serious Adverse Event Report and submit to CCTG via CTEP-AERS system.

Within 10 days: Update Serious Adverse Event Report as much as possible and submit report to CCTG via CTEP-AERs system.

Copies of reports for this trial submitted via the CTEP-AERS web application will be automatically forwarded by the CTEP-AERS system to the CCTG Central Office for review. You may be contacted by the CCTG Study Coordinator or Senior Investigator for additional information.

Use the NCI protocol number and the protocol specific patient ID provided during trial registration on all reports.

CTEP-AERS web application interruption:
In the rare occurrence when Internet connectivity is lost please contact CCTG at 613-533-6430.

SAE reports must also be provided within 24 hours to:

MA.39 Study Coordinator
Canadian Cancer Trials Group
Phone No.: 613-533-6430

Immediately upon re-establishment of the internet connection, the SAE report that was reported by phone as a 24-hour notification MUST be entered into the CTEP-AERS web application.

Local internet interruption:
Please follow the instructions above for CTEP-AERS web application interruption. In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

9.3 Other Protocol Reportable Events – Pregnancy Reporting

9.3.1 *Pregnancy Prevention*

Women of Childbearing Potential (WOCBP) who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 3.1.20.

9.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG and CTEP any pregnancy occurring in female participants during protocol treatment. Pregnancies occurring up to 90 days after the completion of study treatment must also be reported.

Pregnancy of a trial participant must be reported in an expedited manner via CTEP AERS. In addition to the submission of the CTEP AERS report, the centre is also required to complete the "Pregnancy Information Form" and fax (along with additional medical information) to **301-230-0159**.

Once informed consent has been obtained, the CTEP-AERS report and the associated Pregnancy Information Form should be updated to provide further information and to reflect the outcome of the pregnancy.

Additional information regarding these requirements (including guidance on grades, Standard of Care (SOC), and other reporting instructions) can be found in the "NCI Guidelines for Investigators: Adverse event reporting requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" document.
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

CCTG must also be notified of pregnant participants. To do so, centres are expected to copy CCTG Safety Desk (safety-desk@ctg.queensu.ca) when submitting the CTEP AERS report (and on any updates to the report), as well as fax/email a copy of the completed Pregnancy Information Form (and any updates to the report) to CCTG safety desk (613-533-2812/ safety-desk@ctg.queensu.ca).

Once informed consent has been obtained, the form should be updated to provide further pregnancy information and to reflect the outcome of the pregnancy. All follow-up reports must be submitted to CCTG in a timely manner. For pregnant participants, if required by local policy, a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/ safety-desk@ctg.queensu.ca).

If the pregnancy results in death (e.g. spontaneous abortion, stillbirth); is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting.

9.4 Reporting Serious Adverse Events to Investigators

CCTG will notify Investigators of all serious adverse events from this trial that are reportable to regulatory authorities in Canada as reported to CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. For Canadian sites, the reports will be posted to the CCTG trial MA.39 web-based safety monitoring utility. For US sites, reports will be posted to the CTSU website and will be distributed through the Broadcast.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. For Canadian sites, the date of REB Submission for these SAEs will need to be entered into the CCTG trial MA.39 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity
- Disease recurrence as defined in Section 8.0.
- Request by the patient.
- Completion of therapy as outlined in Section 6.0. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Therapy After Protocol Treatment is Stopped

If patients are removed from therapy because of toxic effects or disease recurrence, further treatment, if any, is at the discretion of the investigator.

10.3 Follow-up Off Protocol Treatment

Patients must be assessed and follow-up forms need to be completed during the last week of RT (if receiving RT), 2 months after randomization (if not receiving RT), at 6 months after randomization, 12 months after randomization then annually.

11.0 CENTRAL REVIEW PROCEDURES

11.1 Central Radiology Review

There will be no central radiology review for this study.

11.2 Central Pathology Review

There will be no central pathology review for this study.

11.3 Central Radiotherapy Review

Please refer to Section 7.0.

12.0 CORRELATIVE STUDIES

A detailed Correlative Studies Manual with details regarding sample preparation, handling and shipping, is provided on the CCTG MA39 website for Canadian sites, while sites in the US should refer to the CTSU website for the CCTG MA.39 trial.

Specimens collected may be used by researchers now or in the future to better understand the nature of breast cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial the surgical/ histology number and/or patient initials. Material issued to researchers will be anonymized and only identified by a coded number. Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient. All patients on whom a diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

12.1 Protocol-Mandated Correlative Studies

Archival FFPE Tumour Tissue Submission (Mandatory)

The submission of a representative block of the diagnostic tumour tissue is an important part of this trial and required for eligibility. One tumour block and one adjacent normal tissue block are requested from any of the biopsies or resections of the tumour. Where local centre regulation prohibit submission of blocks of tumour tissue, the approval of the CCTG must be sought prior to randomization of the first patient to allow cores (two 2 mm cores of tumour from the block) and slides (20 x 5 micron thick unstained slides) of representative tumour tissue to be substituted instead.

Blocks are the preferred material to collect, as it is well known that tissue materials (including protein and nucleic acid integrity) on unstained sections deteriorate rapidly within 3-6 months after preparation. Submission of blocks will optimize the amount of tissue available to investigators and permit the preservation of the block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

Directions:
At the same time that the baseline form is submitted, an original tumour block should be sent to the CCTG Pathology Coordinator. Centres should contact the CCTG Study Coordinator and/or the Pathology Coordinator if they are unable to submit a tumour block, as sufficient tissue is required for the assays described.

Complete the EDC Archival Tumour Tissue Submission Form. Print a copy of the completed form and ship tumour blocks/slides within 4 weeks of randomization to:

Shakeel Virk
Pathology Coordinator Canadian Cancer Trials Group
Richardson Labs Bldg, 4th Floor
88 Stuart St.
Queen's University
Kingston, ON K7L 3N6
Tel: 613-533-2906 / Fax: 613-548-2486
Email: virks@queensu.ca

See Section 2.5 for planned priority assays on archival tumour tissue.

Detailed instructions for FFPE sample acquisition, preparation, and shipping are found in the MA.39 Lab Manual.

Whole Blood Collection (Mandatory)

The CCTG is interested in exploring the use of whole blood for circulating tumour DNA. Collection of whole blood is an important part of this trial and required for eligibility. Blood samples will be collected for planned studies from all patients at baseline (post-consent, prior to RT or within 6 weeks for patients not receiving RT).

See Section 2.5 for planned priority assays on whole blood.

Detailed instructions for blood sample acquisition, preparation, and shipping are found in the MA.39 Lab Manual.

12.2 Optional Banking of Samples

Mandatory submission of tumour tissue and blood for planned studies has been described above. The subsequent banking of collected diagnostic tissue for future research related to the trial is not mandatory for participation in the study, but patients will be asked to consent to this. Any remaining tumour tissue and blood samples of consenting participants will be carefully banked as part of the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario.

Collection of paraffin tumour blocks are preferred, as one of the objectives will be to create tissue micro arrays. These will optimize the amount of tissue available to investigators and permit the preservation of the tumour block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

Proposals to use the banked specimens for the purposes of assessing markers involved in predicting treatment response and outcomes may be submitted to the bank. A scientific review process of any proposals to use the tissue and blood samples will take place and any proposals approved will have undergone ethics approval. Note: Exploratory biomarker testing and correlative studies of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

The primary outcome is BCRFI defined as time from randomization to time of invasive recurrent disease in ipsilateral chestwall, breast, regional nodes, distant sites or death due to breast cancer *[Hudis 2007]*. Demonstrating non-inferiority in BCRFI would assure clinicians that there is not a major impact on important breast cancer outcomes. Eligible subjects will be randomized to one of the following two treatment groups: without regional RT (Arm 1) and with regional RT (Arm 2). Patients will be stratified according to: (1) surgery type (BCS or mastectomy); (2) axillary dissection (yes or no); (3) adjuvant chemotherapy (yes or no); (4) lymphovascular invasion (present or not present); (5) Oncotype score (0-10, 11-17, or 18-25); and (6) centre. A minimization procedure *[White 1978]* will be used to allocate patients with equal probabilities to one of the two treatment groups.

13.2 Primary Endpoints and Analysis

The analysis will include both intention to treat (ITT) and per protocol populations (PPP). The ITT population consists of all randomized patients regardless of actual treatment while the PPP includes only those who were treated according to protocol defined as no regional RT for those randomized to that arm or at least 5 fractions (1 week) of protocol therapy for those randomized to regional RT. The primary analysis will be conducted on the ITT population. The primary endpoint for the study is BCRFI. A subject that has not had a recurrence or died of breast cancer at the time of data cut-off will be censored on the date of last follow-up. The experience of patients in both treatment groups will be described by the Kaplan Meier method, and a stratified log-rank test adjusting for stratification factors (excluding center) will be performed to compare treatment arms. If the upper bound of a one-sided 95% interval for the hazard ratio is <1.4, non-inferiority will be declared. As a sensitivity analysis, we will describe BCRFI experience in both treatment groups using cumulative risk and compare using the Gray's Test for competing risk. Secondary outcomes including invasive DFS, breast cancer mortality, survival, locoregional RFI, and distant RFI, will also be described by either the Kaplan Meier method or the cumulative incidence method and the treatment arms compared using the stratified log-rank test or the Gray's test for competing risk. As part of the secondary analysis of all time to event endpoints, Cox proportional hazards models will be used to control for the effects of potential prognostic variables. Likelihood ratio tests will be used to assess the prognostic importance of each variable and treatment/covariate interactions will be investigated.

All randomized subjects will be evaluated for toxicity according to the treatments they received. Toxicities will be graded using the current CTCAE version 5.0. The rates of selected toxicities by arm will be summarized by type of adverse event. The incidences of lymphedema and arm abduction deficit will also be assessed. A Fisher's Exact Test will be used to compare selected toxicities, lymphedema and arm abduction deficit between two arms and the 95% confidence interval for the toxicity rates difference will be reported.

13.3 Sample Size and Duration of Study

The 5-year BCRFI for patients with 1-3 nodes who were ER+, PR+ and grades 1 and 2 (luminal A-like) and were treated with BCS and systemic therapy with regional RT in MA.20 was 92%. The 5-year BCRFI for ER positive good prognosis patients with 1-3 positive nodes post-mastectomy treated with adjuvant systemic therapy is also similar *[McBride 2014; Moo 2013]*. Based on the MA.20 subgroup analysis, we would expect limited loss of benefit from avoidance of regional RT in these patients. If the observed loss of control is 3% or less (equivalent to a maximum tolerated HR of 1.40), then we would consider avoidance of regional RT in biomarker low risk cancer to be acceptable. This non-inferiority margin is small clinically and it is unlikely to be associated with a major impact on breast cancer mortality. Hence, we would want to detect any difference larger than 3%. Based on these considerations with a one-sided α of 0.05 and a power of 87%, it is anticipated that 278 events are required. To ensure that there are sufficient events to trigger the protocol specified final analysis, the proportion of patients with micrometastases will be limited to 20% of the target sample size. With an expected 5 years of accrual and 4.5 years of follow-up, 2140 patients are needed for the final sample size. The total duration of study will be 9.5 years.

The following tables indicate the gender and minority accrual estimates for the study.

DOMESTIC PLANNED ENROLLMENT REPORT (SCREENING)					
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
Racial Categories	Female	Male	Female	Male	Total
American Indian/ Alaska Native	29	NA	0	NA	29
Asian	45	NA	0	NA	45
Native Hawaiian or Other Pacific Islander	15	NA	0	NA	15
Black or African American	105	NA	15	NA	120
White	1251	NA	29	NA	1280
More Than One Race	0	NA	0	NA	0
Total	1445	NA	44	NA	1489

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT (SCREENING)					
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
Racial Categories	Female	Male	Female	Male	Total
American Indian/ Alaska Native	0	NA	0	NA	0
Asian	309	NA	0	NA	309
Native Hawaiian or Other Pacific Islander	0	NA	0	NA	0
Black or African American	309	NA	0	NA	309
White	3243	NA	0	NA	3243
More Than One Race	0	NA	0	NA	0
Total	3861	NA	0	NA	3861

DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
Racial Categories	Female	Male	Female	Male	Total
American Indian/ Alaska Native	18	NA	0	NA	18
Asian	26	NA	0	NA	26
Native Hawaiian or Other Pacific Islander	9	NA	0	NA	9
Black or African American	61	NA	9	NA	70
White	737	NA	17	NA	754
More Than One Race	0	NA	0	NA	0
Total	851	NA	26	NA	877

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT (TREATMENT)					
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
Racial Categories	Female	Male	Female	Male	Total
American Indian/ Alaska Native	0	NA	0	NA	0
Asian	101	NA	0	NA	101
Native Hawaiian or Other Pacific Islander	0	NA	0	NA	0
Black or African American	101	NA	0	NA	101
White	1061	NA	0	NA	1061
More Than One Race	0	NA	0	NA	0
Total	1263	NA	0	NA	1263

13.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators' meetings. The Data Safety Monitoring Committee (DSMC) will regularly review events on trial.

13.5 Interim Analysis

ER +ve biomarker low risk breast cancer has a long natural history. A formal interim analysis is planned after 139 (50%) events have occurred. We would declare omitting regional RT to be inferior to regional RT for an observed HR>1.69, which is equivalent to rejecting a null hypothesis of equal recurrence rates with a one-sided $p<0.001$. The interim analysis is expected to occur at 7.5 years after trial activation.

13.6 Quality of Life Analysis

Sample Size Considerations:

The primary objective of the study is to determine the effects of regional RT on arm symptoms using the NSABP Questionnaire for patients treated by BCS or mastectomy. The NSABP B32 trial demonstrated that patients treated with SLNB alone compared to an additional axillary dissection had fewer arm symptoms with a difference between treatment arms of 1.9 (SD=5.7, $p<0.001$). It is expected that patients where regional RT is omitted will also have fewer arm symptoms. A sample size of 552 patients will be sufficient to provide 90% statistical power to determine an effect size of 0.25 on the NSABP Questionnaire with a significance level of 5% (one-sided). The overall sample size will be adjusted upwards to allow for a 25% non-compliance rate at 5 years, resulting in a final sample size 736 patients accrued to the PRO and QOL substudy. (Note: enrollment completed 2022AUG02.)

Among the 736 patients, we expect 30% or 220 patients will be treated by mastectomy and 514 will be treated by BCS. This will provide power of 79% to detect a difference between groups of 1.9 points on the NSABP Questionnaire in patients treated by mastectomy and over 90% power to detect a difference between groups of 1.5 points on the NSABP questionnaire for patients treated with BCS.

Analysis:

The primary outcome will be evaluated using NSABP Arm and Breast Symptom Questionnaire. Profile of change scores over time between the treatment arms will be compared using a generalized linear mixed model. The presence of a treatment by time interaction will be tested, if the interaction effect is significant, treatment differences will be tested at each time point. If significant differences are identified, results will also be reported in terms of the percent of patients experiencing different arm symptoms including: arm swelling, pain, and weakness.

For the secondary objectives we will evaluate the effect of regional RT on arm symptoms separately for patients treated by BCS and mastectomy and an interaction term for surgery type will be included in the generalized linear mixed model. Other secondary outcomes including: overall QOL (EORTC QLQ-C30), breast symptoms (NSABP B32 Questionnaire), skin symptoms and fatigue (EORTC QLQ-BR23) will be compared between the two treatment groups using a similar approach. The profile of change scores over time between treatment arms will be compared using a generalized linear mixed model and the presence of a treatment by time interaction and treatment by type of surgery (BCS or mastectomy) interaction will be tested.

13.7 Economic Evaluation

Costs will be expressed in $US and $CAN base currencies based on the final year of the study. We will generate an average cost per study subject by treatment arm for an overall mean cost per study arm.

An incremental cost over benefit analysis will be conducted to generate a value assessment between the two treatment arms. For the benefit portion of the value assessment, if the efficacy results are different, we will conduct a cost effectiveness analysis, evaluating both incremental costs and clinical outcomes (e.g., survival). If there is no significant clinical benefit, we anticipate that there will be differences in quality of life between the two treatment arms and will conduct a cost-utility analysis. As such, we will determine the health preference of study subjects to calculate a quality adjusted life year (QALY) by marrying the health preference value and the time frame in which one experiences that health state. Health preference will be measured with the EQ-5D-5L. The EQ-5D-5L is a well-used and standardized measure of health status for economic analyses (https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf). The EQ-5D-5L will be collected alongside the study QOL instrument.

A 1.5% discount rate will be used for benefits resources utilized beyond one year. To test the robustness of the economic analysis; we will conduct a number of one-way sensitivity analyses (e.g. ranges of costs, resources, health preference) and subgroup analyses (e.g. country, age, currency).

14.0 PUBLICATION POLICY

14.1 Authorship of Papers, Meeting Abstracts, Etc.

14.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the Canadian Cancer Trials Group and Alliance may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.
- In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.

14.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

14.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results

CCTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the CCTG web site (http://www.ctg.queensu.ca).

14.3 Submission of Material for Presentation or Publication

Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts should be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release.

15.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

15.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This study is affiliated with the US National Cancer Institute (NCI US). Therefore, the conduct of this study must comply with the US regulations regarding the Protection of Human Subjects (Title 45, Part 46, US Code of Federal Regulations).

15.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is CCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrollment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

15.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in a CCTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

15.3.1 *Obtaining Consent for Pregnancy Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the main consent form adequately addresses the collection of information regarding the outcome of a pregnancy of a trial participant, a "Pregnancy Follow-up consent form will not be required by CCTG.

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy*/exposure*.

Obtaining Consent for Research on Children

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/guardian.

15.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

15.5 Retention of Patient Records and Study Files

All essential documents must be maintained in accordance with ICH-GCP.

In accordance with GCP 4.9.5, essential documents must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. In most cases, this will be for 10 years following the completion of the trial (10 years post final analysis, last data collected, or closure notification to REB, whichever is later) at the centre, or until notified by CCTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

For international participating regions, local regulatory guidance should be followed with respect to duration of records retention, unless otherwise contractually dictated.

15.6 Centre Performance Monitoring

For Canadian sites, this study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

15.7 On-Site Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at participating Canadian centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

Sites in the US will undergo on site monitoring/auditing by the US Cooperative group (SWOG, Alliance, ECOG-ACRIN or NRG) or NCORP Research Base to which they credited their enrollment. As is the case for other NCTN trials, that will be done in accordance with CTMB guidelines: https://ctep.cancer.gov/branches/ctmb/default.htm

As the trial is NCI US affiliated, the findings will be reported to the NCI US Clinical Trials Monitoring Branch as required.

The above mentioned documentation, in addition to any submitted source documents, may be accessed remotely in the event of a public health emergency either through remote access to Electronic Medical Records or through a secure file sharing portal.

15.8 CDUS Reporting

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

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APPENDIX I - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX II - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all eligible patients.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "CCTG EDC Generic Data Management Guidebook" posted on the MA.39 area of the CCTG web-site (www.ctg.queensu.ca) (for Canadian sites) and on the CTSU website (for US sites).

The ELECTRONIC CRFs to be used in this trial, through the EDC system, are as follows:

Electronic Folder	Required at	To be completed electronically	Supporting Documentation Required for Randomized Patients ONLY *
Eligibility Checklist		At the time of randomization	Consent form** mammogram/breast MRI report and other relevant radiology reports, relevant operative and pathology report(s) Oncotype DX report
Baseline Report		Within 2 weeks of randomization	
Correlative Studies Report (Tumour and blood)	Continuous running log folder See Section 4.0	As required	Consent form**
Radiotherapy Report (for patients receiving RT)	At the time of radiotherapy completion/discontinuation (for patients receiving RT)	Within 2 weeks from end of radiotherapy treatment	
Follow-up Report	2 months from randomization (for patients not receiving RT), 6 months and 12 months from randomization, then annually	Within 2 weeks of follow-up visit	Mammogram report *(if applicable)*
Recurrence Report	Upon breast cancer recurrence	Within 4 weeks of breast cancer recurrence	Relevant radiology, operative and pathology reports
Death Report	At the time of patients death	Within 4 weeks of patient death	Autopsy, if available
SAE Report***	At the time of serious adverse event	Within 1 working day of event	
Minimal Follow-Up Report****	Annual	Within 2 weeks of contact	If available/applicable: • autopsy report • CT/MRI report

footnotes on next page …

* Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. Supporting documents should be uploaded immediately after the report they refer to has been submitted electronically. EDC forms submitted without supporting documentation are not considered submitted and will be reflected in the Centre Performance Index (CPI) as not submitted. All patient identifiers, other than the CCTG patient ID assigned at enrollment, and any other prohibited personal information must be fully and completely redacted (blacked-out) on all source documentation, per national and local privacy protection regulations and requirements. Acceptable methods include:

- fully opaque sticker/tab placed over the identifiers prior to scanning
- fully opaque black marker; prior to upload please ensure that the information is no longer visible on the scanned document
- electronic black box placed over identifiers in PDF document that is subsequently printed and then scanned. (NOTE: do not send the unprotected PDF file with black boxes included as those can be moved / removed easily after opening)
- electronic stripping of identifiers prior to upload (typically only possible for DICOM images)

Note that supporting documents must include the participant's trial code, CCTG patient serial number, and participant initials (or a two/three masking letter code assigned by your centre).

** For Canadian centres, it is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated. US sites are not required to submit consent forms.

*** See Section 9.0 Serious Adverse Event Reporting for details.

**** For ineligible patients who have received no protocol therapy (see Section 4.1 for details).

The collection of the following information will involve the combination of paper and electronic forms, as follows:

Data	Required at	Collection /Submission	Comments
Quality of Life Questionnaires (QLQ-C30 +BR23 and Arm and Breast Questionnaires) Health Utilities Questionnaire (EQ-5D-5L) Lost Productivity Questionnaire	• Within 14 days prior to randomization • During last week of RT (*for patients receiving RT*) *OR* 2 months after randomization (*for patients not receiving RT*) • At 6 months after randomization • At 1, 3 and 5 years after randomization	Patient to complete on paper; site to enter relevant data (as required) in the EDC system within corresponding folders	Retain questionnaires at the site.
Trial Specific Economics Questions	• During the last week of RT (for patients receiving RT)	Patient to complete on paper; site to enter relevant data (as required) in the EDC system within Radiotherapy Report	Retain questionnaire at the site.

APPENDIX III - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

APPENDIX IV - QUALITY OF LIFE ASSESSMENT

Note: enrollment completed on 2022AUG02 (for patients randomized after this date, completion of questionnaires is not applicable).

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire.

The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

   Quality of life data are collected for research purposes, and will usually not be used for the patient’s individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - pre-randomization or pre-registration (baseline)
   - during treatment
   - during follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-Treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment, as required by the schedule in the protocol (up to 3 days prior to treatment is acceptable). If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

We will not require a patient to complete the quality of life questionnaires if s/he cannot comprehend either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then s/he is still eligible and could be put on study.

8. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)

   An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

   If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Quality of Life Questionnaires – ENGLISH

CCTG Trial: **MA.39**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to randomization

☐ During last week of RT *(for patients receiving RT)*

OR

☐ 2 months from randomization *(for patients not receiving RT)*

Follow up (timing from randomization):

☐ 6 months ☐ 1 year ☐ 3 years ☐ 5 years ☐ Other____

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

MA.39 Arm & Breast Symptom Questionnaire

INSTRUCTIONS TO PATIENT

Please complete the following questionnaire by circling the number that corresponds to your response to each question. If you have any questions about how to answer the items in this questionnaire, please ask a staff member for help. Please use a pencil (rather than a pen) so that you will be able to erase a circle if you decide to change your response.

All information collected in this questionnaire will be kept confidential and will be used only for research purposes. If you feel uncomfortable about answering any question(s), you may leave the item blank. Your answers will not affect your continued participation in the MA.39 trial.

NOTE: All questions refer to the affected arm or breast on the side you had your breast surgery. Even if you do not normally perform an activity listed below, or your doctor or nurse has advised you not to perform an activity listed below, please choose the answer that best applies to you. **We are not asking you to attempt these activities.**

In the past 7 days, how difficult has it been for you to do the following activities with your AFFECTED arm (on the treatment side)? *(Circle only one number on each line. If you are not sure, answer as best as you can.)*

	Not difficult at all	A little difficult	Somewhat difficult	Very difficult	Unable do do
1. Push or pull large objects, like a living room chair, with your affected arm?	1	2	3	4	5
2. Lift items over 10 pounds, like a heavy bag or groceries with your affected arm?	1	2	3	4	5
3. Reach or extend your affected arm above shoulder level?	1	2	3	4	5
4. Wash your back with your affected arm?	1	2	3	4	5
5. Bend and straighten your affected arm?	1	2	3	4	5

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

In the past 7 days, how much have you been bothered by the following problems in your AFFECTED underarm, arm or hand (on the treatment side)? *(Circle only one number on each line. If you are not sure, answer as best as you can.)*

	Not bothered at all	Bothered a little	Bothered somewhat	Bothered quite a bit	Bothered very much
6. Tenderness in the underarm, arm or hand?	1	2	3	4	5
7. Swelling in the underarm, arm or hand?	1	2	3	4	5
8. Numbness in the underarm, arm or hand?	1	2	3	4	5
9. Tingling sensation ("pins & needles") in the underarm, arm or hand?	1	2	3	4	5
10. Increased skin sensitivity in the underarm, arm or hand?	1	2	3	4	5
11. Tightness, pulling, or stretching in the underarm, arm or hand?	1	2	3	4	5
12. Discomfort or pain in the underarm, arm or hand?	1	2	3	4	5
13. Arm weakness?	1	2	3	4	5
14. Arm heaviness?	1	2	3	4	5
15. Shoulder stiffness?	1	2	3	4	5

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

In the past 7 days, how much have you been bothered by the following problems in your AFFECTED breast or chest area (on the treatment side)? *(Circle only one number on each line. If you are not sure, answer as best as you can.)*

	Not bothered at all	Bothered a little	Bothered somewhat	Bothered quite a bit	Bothered very much
16. Tenderness in the breast or chest area?	1	2	3	4	5
17. Swelling in the breast or chest area?	1	2	3	4	5
18. Numbness in the breast or chest area?	1	2	3	4	5
19. Tingling sensation ("pins & needles") in the breast or chest area?	1	2	3	4	5
20. Increased skin sensitivity in the breast or chest area?	1	2	3	4	5
21. Tightness, pulling, or stretching in the breast or chest area?	1	2	3	4	5
22. Discomfort or pain in the breast or chest area?	1	2	3	4	5

In the past 7 days, to what extent has the effect of your breast cancer treatment on your arm disrupted the following activities? *(Circle only one number on each line. If you are not sure, answer as best as you can.)*

	Not disrupted at all	Disrupted a little	Disrupted somewhat	Disrupted quite a bit	Disrupted very much
23. Social activities with family and friends?	1	2	3	4	5
24. Work (including housework)?	1	2	3	4	5
25. Recreational activities?	1	2	3	4	5
26. Self-care (bathing, dressing)?	1	2	3	4	5
27. Normal sleep?	1	2	3	4	5

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (MA.39)

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in a bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms during the past week.

During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
31. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
32. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
33. Did you find it difficult to look at yourself naked?	1	2	3	4
34. Have you been dissatisfied with your body?	1	2	3	4
35. Were you worried about your health in the future?	1	2	3	4
36. Did you have any pain in your arm or shoulder?	1	2	3	4
37. Did you have a swollen arm or hand?	1	2	3	4
38. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
39. Have you had any pain in the area of your affected breast?	1	2	3	4
40. Was the area of your affected breast swollen?	1	2	3	4
41. Was the area of your affected breast oversensitive?	1	2	3	4
42. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

APPENDIX V - HEALTH UTILITIES ASSESSMENT

Note: enrollment completed on 2022AUG02 (for patients randomized after this date, completion of questionnaires is not applicable).

Introduction

The assessment of overall health benefits is complicated by the need for a measure that can combine various benefits, such as overall survival, disease free survival, and quality of life into a single measure of benefit. Patients may value particular benefits differently. There is no obvious way to add together independently collected benefits for an individual or for a trial to yield a measure of overall benefit. Health utilities are a measure of how people value particular health outcomes. They provide a common denominator that can be combined with survival to form a measure of overall health benefits.

Such a measure of overall health benefit can then be used as part of a health economic analysis. Health economic analyses assess the benefits and costs of an intervention, for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about health utilities is becoming more common in clinical protocols. In clinical trials, health utilities are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Health utility and quality of life assessments provide different but complementary information.

- Health utility is a measure of preference for a given health state that acknowledges the risk and uncertainty of outcomes in choices patients face and in clinical decision-making.
- They can be used as a weighting factor to adjust survival by quality of life.
- Depending on whether a disease-specific or generic quality of life instrument is used, often only utility assessments may be able to compare patient groups with different diseases.
- Only utilities provide a single meaningful measure that can be incorporated in health policy and health economic analyses.

Health utilities data can be used in a variety of ways:

- to try and achieve the best possible outcome for patients and populations
- to evaluate the extent of change in health benefits of an individual, group, or population across time
- to evaluate new treatments, technologies, and patient management strategies
- to support approval of new drug applications or patient management strategies
- to try to provide the best value for health care dollars within and across diseases and health
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using health utilities as part of a health economic analysis.

Instructions for Administration of a Health Utilities Questionnaire

The instructions below are intended as a guide for the administration of the Health Utilities Questionnaire

1. Preamble

Health utilities data are collected for research purposes, and will not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

The usual scheduled times to obtain the questionnaires are as follows:

- pre-randomization (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g. psychological distress, social disruption, symptoms, side-effects, *et cetera*.

The Clinical Research Associate (CRA) should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The health utilities questionnaire should be given to the patient before being seen by the doctor, and prior to treatment, as required by the schedule in the protocol (not required during treatment for this trial).

4. Assessments During Follow-up

The health utilities questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how overall health is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If…

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Four situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

D. The patient is no longer attending clinic during the scheduled follow-up period.

Should the patient no longer be attending clinic, he/she should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. In order to facilitate this, ensure that after randomization all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was received should be recorded on the questionnaire. The date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic.

6. Inability to Complete Health Utilities Questionnaire (for reason other than illiteracy in English or French)

   An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the EQ-5D assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

   If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Health Utilities Questionnaires – ENGLISH

CCTG Trial: **MA.39**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain health utilities assessment: please check (✓)

☐ Prior to randomization

☐ During last week of RT *(for patients receiving RT)*

OR

☐ 2 months from randomization *(for patients not receiving RT)*

Follow up (timing from randomization):

☐ 6 months ☐ 1 year ☐ 3 years ☐ 5 years ☐ Other____

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

EQ-5D Questionnaire

CCTG: MA.39

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

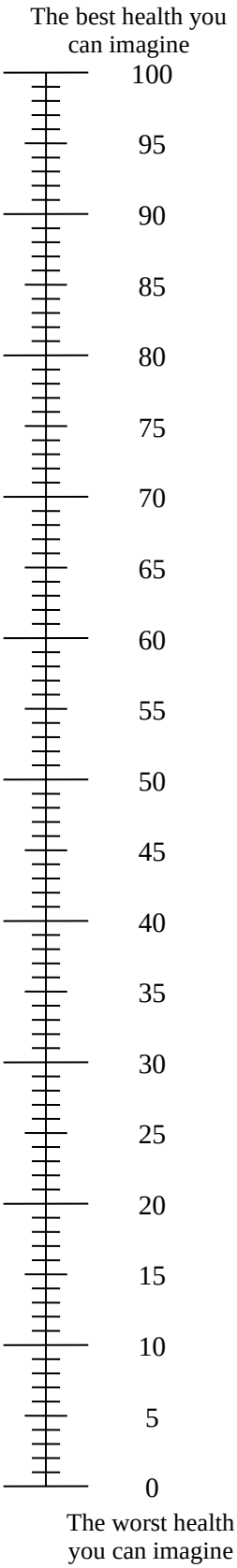
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Please check to make sure you have answered all questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____
Today's date (Year, Month, Day): _____

Thank you.

APPENDIX VI – LOST PRODUCTIVITY QUESTIONNAIRE

Note: enrollment completed on 2022AUG02 (for patients randomized after this date, completion of questionnaires is not applicable).

Introduction

Economic evaluations assess the benefits and costs of an intervention for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about costs is becoming common in clinical trial protocols. Direct costs include the costs of treatment, such as drug therapy and hospital admission. However, there are also indirect costs, such as costs to the patient and society, for example through lost productivity or loss of work. The collection of information about indirect costs is also becoming common in clinical protocols. In clinical trials, lost productivity and patient costs are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Data on costs, both direct and indirect, can be used in various ways, including (a) to support approval of new drug applications or patient management strategies, (b) to provide the best value for health care dollars within and across diseases and health, and (c) to compare costs and benefits of various financial and organizational aspects of health care services.

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using economic analysis techniques.

Instructions for Administration of the Lost Productivity Questionnaire

The instructions below are intended as a guide for the administration of the Lost Productivity Questionnaire

1. Preamble

   Lost productivity data are collected for research purposes, and will not be used for the patient's individual medical care. The assessment is in the form of a self-reported questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The scheduled times to obtain the questionnaires is:

   - Pre-study (prior to randomization)
   - last day of radiotherapy (if receiving RT) OR at 2 months after randomization (if not receiving RT)
   - At 6 months after randomization
   - At 1, 3 and 5 years

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

   If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-Treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, for example productivity, change in work status, caregiver assistance, and so on.

The Clinical Research Associate (CRA) should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The Lost Productivity Questionnaire should be given to the patient on the final day of treatment, as required by the schedule in the protocol.

A patient may, on occasion, be reluctant to complete the questionnaire because he/she may feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how overall health is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if productivity data can still be collected.

4. What If…

4A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one.

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

4B. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

4C. The patient is no longer attending clinic during the scheduled follow-up period.

Should the patient no longer be attending clinic, he/she should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. In order to facilitate this, ensure that after randomization all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was received should be recorded on the questionnaire. The date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic. If the patient has deterioration to ECOG PS 4 or hospitalization for end of life care they need not be contacted for questionnaire completion.

5. Waiving the Lost Productivity Component

We will not require a patient to complete the Lost Productivity questionnaires if s/he is not literate in either English or French. In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

6. Unwillingness to Complete Lost Productivity Questionnaire

If a patient speaks and reads English or French, but does not wish to complete this questionnaire then s/he is still eligible and could be put on study.

7. Inability to Complete Lost Productivity Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the Lost Productivity Questionnaire in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Lost Productivity Questionnaire: BASELINE – ENGLISH

CCTG Trial: **MA.39**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain assessment: Prior to randomization

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

MA.39 Lost Productivity Questionnaire – [Baseline]

To the patient:

We would like to ask you several questions about the work that you do for pay. The answers to these questions will allow us to study the financial impact of breast cancer and its treatment. The information collected will be used for research purposes only.

We would appreciate it if you answered all of the questions; however, you do not need to answer any question you do not wish to answer. The answers provided will not affect your medical care.

Section A: General Questions

1) What type of medical insurance do you currently have?

(Check ✓all that apply.)

☐ Government health insurance (e.g. Medicaid, Medicare, provincial)
☐ Private health insurance (e.g. employer insurance)
☐ Out of Pocket payment
☐ Other (specify): _____

2) If you are working for pay or have done paid work in the past year prior to the start of your breast cancer treatment, what would best describe your field of employment?

(Check ✓one only. Choose your most recent employment; if more than one paid job at once, choose the employment involving the most time commitment.)

☐ Management
☐ Business/ finance/ administrative
☐ Natural and applied sciences
☐ Health services
☐ Education
☐ Government services
☐ Social science
☐ Religion
☐ Art/culture
☐ Recreation and/or sport
☐ Sales and/or service
☐ Trades/ transport/ construction
☐ Primary industry
☐ Processing/manufacturing/utilities
☐ Other (specify): _____

☐ Not applicable; no paid work
COMMENTS: _____
_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

3) Which of the following best describes your work status prior to your treatment for breast cancer?

(Check ✓ one only.)

☐ Working full-time for pay (> 30 hours per week) -- (includes self-employed)
☐ Working part-time for pay (≤ 30 hours per week) -- (includes self-employed)
☐ On sick leave from full- or part-time work: (Date leave started: _____)
(Year – Month – Day)
☐ On disability leave from full- or part-time work: (Date leave started: _____)
(Year – Month – Day)
☐ Unemployed
☐ Retired
☐ Homemaker/ Stay at home parent or caregiver
☐ Other, specify _____

4) Which of the following best describes your work status at the present time?

(Check ✓ one only.)

☐ Working full-time for pay (> 30 hours per week) -- (includes self-employed)
☐ Working part-time for pay (≤ 30 hours per week) -- (includes self-employed)
☐ On sick leave from full- or part-time work: (Date leave started: _____)
(Year – Month – Day)
☐ On disability leave from full- or part-time work: (Date leave started: _____)
(Year – Month – Day)
☐ Unemployed
☐ Retired
☐ Homemaker/ Stay at home parent or caregiver
☐ Other, specify _____

5) *Since the start of your breast cancer treatment*, has there been any change in your work status compared to before that?

(Check ✓ one only.)

☐ No, no change
☐ Yes, started working full time hours (> 30 hours per week)
☐ Yes, started working part time hours (≤ 30 hours per week)
☐ Yes, started sick or disability leave: (Date leave started: _____)
(Year – Month – Day)
☐ Yes, quit work/ became unemployed or retired: (Date leave started: _____)
(Year – Month – Day)
☐ Yes, other: specify _____

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

6a) *Since the start of your breast cancer treatment*, how much paid work time have you missed due to illness, treatment and/ or being in hospital for your breast cancer?

(Check ✓one only.) Estimate to the nearest month.

☐ None

☐ < 1 month (specify # of weeks: _____)

☐ 1 to 3 months (specify # of weeks: _____)

☐ More than 3 months (specify # of months _____)

☐ Not applicable – not currently working

☐ Don't know – can't remember

6b) *Since the start of your breast cancer treatment*, how much unpaid work time (usual activities) have you missed due to illness, treatment and/ or being in hospital for your breast cancer?

(Check ✓one only.) Estimate to the nearest month.

☐ None

☐ < 1 month (specify # of weeks: _____)

☐ 1 to 3 months (specify # of weeks: _____)

☐ More than 3 months (specify # of months _____)

☐ Not applicable – not currently working

☐ Don't know – can't remember

7) What is your usual yearly gross (before taxes) income? (all income data will be anonymized and kept entirely confidential. It will be used only by the research team)

☐ < $10,000

☐ $10,000 to $24,999

☐ $25,000 to $49,999

☐ $50,000 to $74,999

☐ $75,000 to $99,999

☐ $100,000 to $124,999

☐ $125,000 to $149,999

☐ ≥ $150,000

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Thank you

Lost Productivity Questionnaire: FOLLOW UP – ENGLISH

CCTG Trial: **MA.39**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain assessment: please check (✓)

☐ During last week of RT *(for patients receiving RT)*

OR

☐ 2 months from randomization *(for patients not receiving RT)*

Follow up (timing from randomization):

☐ 6 months ☐ 1 year ☐ 3 years ☐ 5 years ☐ Other____

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

MA.39 Lost Productivity Questionnaire – [Follow-up]

To the patient:

We would like to ask you several questions about the work that you do for pay. The answers to these questions will allow us to study the financial impact of breast cancer and its treatment. The information collected will be used for research purposes only.

We would appreciate it if you answered all of the questions; however, you do not need to answer any question you do not wish to answer. The answers provided will not affect your medical care.

Section A: General Questions

1) What type of medical insurance do you currently have?

(Check ✓all that apply.)

☐ Government health insurance (e.g. Medicaid, Medicare, provincial)
☐ Private health insurance (e.g. employer insurance)
☐ Out of Pocket payment
☐ Other (specify): _____

2) If you are working for pay or have done paid work in the past (2 months, 6 months or 2 years), what would best describe your field of employment?
(Check ✓one only. Choose your most recent employment; if more than one paid job at once, choose the employment involving the most time commitment.)

☐ Management
☐ Business/ finance/ administrative
☐ Natural and applied sciences
☐ Health services
☐ Education
☐ Government services
☐ Social science
☐ Religion
☐ Art/culture
☐ Recreation and/or sport
☐ Sales and/or service
☐ Trades/ transport/ construction
☐ Primary industry
☐ Processing/manufacturing/utilities
☐ Other (specify): _____

☐ Not applicable; no paid work
COMMENTS: _____
_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

3) Which of the following best describes your work status at this time?

(Check ✓ one only.)

☐ Working full-time for pay (> 30 hours per week) -- (includes self-employed)
☐ Working part-time for pay (≤ 30 hours per week) -- (includes self-employed)
☐ On sick leave from full- or part-time work: (Date leave started: _____)
(Year – Month – Day)
☐ On disability leave from full- or part-time work: (Date leave started: _____)
(Year – Month – Day)
☐ Unemployed
☐ Retired
☐ Homemaker/ Stay at home parent or caregiver
☐ Other, specify _____

4) *Since your last visit (2 months, 6 months, 2 years ago)*, has there been any change in your work status compared to before that?

(Check ✓ one only.)

☐ No, no change
☐ Yes, started working full time hours (> 30 hours per week)
☐ Yes, started working part time hours (≤ 30 hours per week)
☐ Yes, started sick or disability leave: (Date leave started: _____)
(Year – Month – Day)
☐ Yes, quit work/ became unemployed or retired: (Date leave started: _____)
(Year – Month – Day)
☐ Yes, other: specify _____

5a) *Since your last visit (2 months, 6 months, 2 years ago)*, how much **paid** work time have you missed due to illness, treatment and/ or being in hospital for your breast cancer?

(Check ✓ one only.) Estimate to the nearest month.

☐ None
☐ < 1 month (specify # of weeks: _____)
☐ 1 to 3 months (specify # of weeks: _____)
☐ More than 3 months (specify # of months _____)
☐ Not applicable – not currently working
☐ Don't know – can't remember

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

5b) *Since your last visit (2 months, 6 months, 2 years ago),* how much **unpaid** work (usual activities) time have you missed due to illness, treatment and/ or being in hospital for your breast cancer?

(Check ✓one only.) Estimate to the nearest month.

☐ None
☐ < 1 month (specify # of weeks: _____)
☐ 1 to 3 months (specify # of weeks: _____)
☐ More than 3 months (specify # of months _____)
☐ Not applicable – not currently working
☐ Don't know – can't remember

6) What is your usual yearly gross (before taxes) income? (all income data will be anonymized and kept entirely confidential. It will be used only by the research team)

☐ < $10,000
☐ $10,000 to $24,999
☐ $25,000 to $49,999
☐ $50,000 to $74,999
☐ $75,000 to $99,999
☐ $100,000 to $124,999
☐ $125,000 to $149,999
☐ ≥ $150,000

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Thank you

Trial Specific Economics Questions – ENGLISH

CCTG Trial: **MA.39**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____
(first-middle-last)

Institution: _____ Investigator: _____

To be completed during the last week of RT *(for patients receiving RT)*

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

MA.39 Trial Specific Economics Questions

1. How far did you travel to receive your radiotherapy treatment (estimate for one-way travel)?
   _____km *OR* _____miles

2. Did you have to pay for parking during your radiotherapy treatment? YES NO

   If yes,

   a) How much did you pay daily for parking? _____ $CAD *OR* _____ $US
   b) How many days did you pay for parking? _____

APPENDIX VII - THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 8th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org). These staging criteria should be used for new trials.

APPENDIX VIII - EMERGENCY SITUATIONS AND COMPLIANCE

Management of Protocol Variances in Emergency Situations

Compliance with the trial protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial as well as any associated sub-studies should be ensured to every extent possible, however in emergency situations, specific variances from the protocol that occur as a result of efforts to minimize or eliminate hazards and protect the safety and well-being of patients are permissible.

In these rare circumstances, minor deviations that do not impact patient safety or willingness to participate or trial integrity, which have been justified and documented in the medical record by the QI/SI will not be considered to be REB reportable deficiencies requiring action, but must be reported to CCTG (e.g. in Electronic Data Capture (EDC) or using trial specific deviation logs as directed by CCTG) within 4 weeks of the end of the Emergency Situation, unless otherwise instructed by CCTG, and to your REB at the next amendment or annual approval.

Centres should also discuss these reporting requirements with their local REB, and review the trial website for additional guidance specific to the trial.

Minor Protocol Deviations:

- Missed or delayed protocol mandated visits or investigations on treatment or in follow up.
- Changes in study drug distribution (e.g. drug distributed remotely or IV drug given at satellite site), providing permitted by local SOPs, or written procedure established and is approved by CCTG or acceptable per further instruction from CCTG. *Note there will be no exceptions for injectable/IV investigational agents as must be administered at participating site.*
- Alternative methods for safety assessments (e.g. telephone contact, virtual visit, alternative location for assessment).
- Patient care and evaluations provided by non-research staff, providing overseen by QI/SI who must make all treatment decisions and ensure that all required information and results will be reported to allow central data submission. Includes physical exam, clinical laboratory tests, research blood collections that can be shipped centrally, imaging, non-investigational drug therapy*, standard radiation therapy, surgery, and other interventions that do not require protocol-specified credentialing*.

  **Must be approved by CCTG or acceptable per further instruction from CCTG.*
- Re-treatment following extended treatment delays if protocol specifies that excessive delays require discontinuation, providing other protocol requirements for discontinuation have not been met and either discussed with CCTG or acceptable per further instruction from CCTG.

Note:

- Applicable only to COVID-19 and other CCTG designated emergency situations.
- No waivers will be given for eligibility, including performance of protocol mandated tests/imaging.
- Deficiencies will be issued if patients are enrolled when trial is on accrual hold, for unreported Serious Adverse Events as well as changes in drug distribution/administration and/or re-treatment after extended treatment delays when not discussed and approved by CCTG or acceptable per further instruction from CCTG.
- Deviations or changes that are believed to impact patient safety, compromise the study integrity or affect willingness to participate are still considered Major Protocol Violations and must be reported to CCTG and your REB. These include more than a minimal delay in protocol therapy administration.

LIST OF CONTACTS

	Contact	Tel. #	Fax #
ELIGIBILITY CHECKLIST Must be completed prior to allocation.	Julie Baran Clinical Trials Assistant, CCTG Email: jbaran@ctg.queensu.ca or: Vicki Classen Clinical Trials Assistant, CCTG Email: vclassen@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY SUPPLIES Forms, Protocols	Available on CCTG MA.39 Website for Canadian sites and CTSU website for sites in the US.		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Nadine Magoski Study Coordinator, CCTG Email: nmagoski@ctg.queensu.ca or: Dr. Wendy Parulekar Senior Investigator, CCTG Email: wparulekar@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Timothy Whelan Study Chair Email: twhelan@hhsc.ca	905-387-9711, ext. 64501	905-575-6368
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Dr. Wendy Parulekar Senior Investigator, CCTG or Nadine Magoski Study Coordinator, CCTG	613-533-6430	613-533-2941

Additional US contact information:

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com. Please refer to the patient enrollment section of the protocol for detailed instructions.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related): See Contacts page above this table		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		