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Pragmatic Randomized Clinical Trial of Proton vs. Photon Therapy for Patients with Non-Metastatic Breast Cancer: The Radiotherapy Comparative Effectiveness (RadComp) Consortium Trial

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On behalf of RadComp (Radiotherapy Comparative Effectiveness Consortium)

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Abstract:

Introduction:

A broad range of stakeholders have called for randomized evidence on the potential clinical benefits and harms of proton therapy, a type of radiation therapy, for patients with breast cancer. Radiation therapy is an important component of curative treatment, reducing cancer recurrence and extending survival. Compared to photon therapy, the international treatment standard, proton therapy reduces incidental radiation to the heart. Our overall objective is to evaluate whether differences between proton and photon therapy cardiac radiation dose distributions lead to meaningful reductions in cardiac morbidity and mortality after treatment for breast cancer.

Methods: We are conducting a large scale, multi-center pragmatic randomized clinical trial for patients with breast cancer who will be followed longitudinally for cardiovascular morbidity and mortality, health-related quality of life and cancer control outcomes. A total of 1,716 patients with non-metastatic breast cancer will be randomly allocated to receive either photon or proton therapy. The primary outcomes are major cardiovascular events, defined as myocardial infarction, coronary revascularization, cardiovascular death, or hospitalization for unstable angina, heart failure, valvular disease, arrhythmia, or pericardial disease. Secondary endpoints are urgent or unanticipated outpatient or ER visits for heart failure, arrhythmia, valvular disease, or pericardial disease. The RadComp Clinical Events Center will conduct centralized, blinded adjudication of primary outcome events.

Ethics and dissemination: The RadComp trial has been approved by the institutional review boards of all participating sites. Recruitment began in February 2016. Dissemination plans

include presentations at scientific conferences, scientific publications, stakeholder engagement efforts and presentation to the public via lay media outlets.

Trial registration number: NCT02603341, Pre-results.

Strengths and Limitations of this study

- The RadComp trial will assess the effectiveness of proton versus photon therapy in reducing major cardiovascular events through a multi-center, randomized trial.
- The pragmatic and holistic approach reflects 'real world' clinical practice, identifies subgroups of patients who might benefit more from proton therapy and helps patients and physicians understand and apply findings to their own lived experience.
- Engagement of patients and other essential stakeholders in the design and conduct of large scale pragmatic randomized control trials of a promising, but expensive, medical technology will inform future efforts to conduct holistic, patient-centric, and pragmatic comparative effectiveness research as part of a learning health care system.
- Blinded, centralized adjudication of primary outcomes applies consistent, relevant definitions of fatal and non-fatal events comprising the major cardiovascular endpoint to detect possible events and avoids the influence of investigator or patient ascertainment bias.
- The RadComp Consortium may have the appearance of conflict of interest (COI) as it involves centers with proton therapy capabilities. COI concerns are addressed by randomized study design, blinded adjudication of primary outcome, accountability by the Data Safety Monitoring Board, and declaration, disclosure and management of COI.

INTRODUCTION

The Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients with Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RadComp) Consortium Trial (NCT02603341) is a large scale, multi-center pragmatic randomized clinical trial following patients longitudinally for cardiovascular morbidity and mortality, health-related quality of life (HRQOL) and cancer control outcomes. We focus on radiotherapy for breast cancer requiring internal mammary nodal irradiation because: 1) regional node radiotherapy is an important component of curative treatment for high risk breast cancer; 2) the survival advantages of radiotherapy may be reduced by incidental radiation to the heart; 3) proton therapy, by reducing incidental radiation to the heart and other normal tissues, may lead to meaningful reductions in cardiac morbidity and mortality and improvements in health-related quality of life; and 4) patients with breast cancer seek evidence on disease control, quality of life and cardiovascular outcomes after proton versus photon therapy to help make shared decisions with their physicians about treatment options.

Our primary hypothesis is that proton therapy, as part of multi-modality curative treatment for patients with non-metastatic breast cancer who have indications for regional nodal irradiation, reduces major cardiovascular events (MCE) compared to photon therapy. Major cardiovascular events are defined as myocardial infarction, coronary revascularization, cardiovascular death, or hospitalization for unstable angina, heart failure, valvular disease, arrhythmia, or pericardial disease. Photon therapy, delivered as either intensity-modulated radiotherapy (IMRT) or 3D conformal radiotherapy, uses multiple x-ray beams to irradiate a tumor target but unavoidably deposits radiation in normal tissues beyond the target volume. In contrast, proton therapy directs a beam of *protons* (positively charged subatomic particles) at the

target volume, where they deposit the bulk of their energy in the last few millimeters of their range.[1] Proton radiation dose distributions may appear superior to photon therapy, particularly in the reduction of low and intermediate radiation dose to normal tissues like the heart and lungs.

However, both photon and proton therapy have physical and biologic uncertainties that could impact important clinical outcomes. For example, investigators have noted uncertainties about the exact range of the proton therapy in tissue and its biological effects at the end of the range.[2] In addition, due to their distinct physical properties, there may be differences in the biological effect of proton therapy and photon therapy on normal tissues.

Thus, a broad range of stakeholders (patients, providers, manufacturers, researchers and policy makers) have called for randomized evidence on the clinical benefits and harms of proton therapy for patients with breast cancer.[3-9]

METHODS

Study design

This study is a superiority pragmatic randomized clinical trial in breast cancer to compare two external beam radiation therapies: proton vs. photon therapy. Treatment techniques represent current care standards and are easy to replicate. Study endpoints are assessed via self-report, medical record review, vital records database search and centralized adjudication. The primary outcome is assessed by an adjudication team of cardiologists who are blinded to treatment assignment.

Informed by the work of Sedrakyan, Luce, Ellenberg, and Treweek,[10-14] the conceptual framework for the trial (**Figure 1)** addresses sources of variability that are unique to radiation devices, including facility and device characteristics.

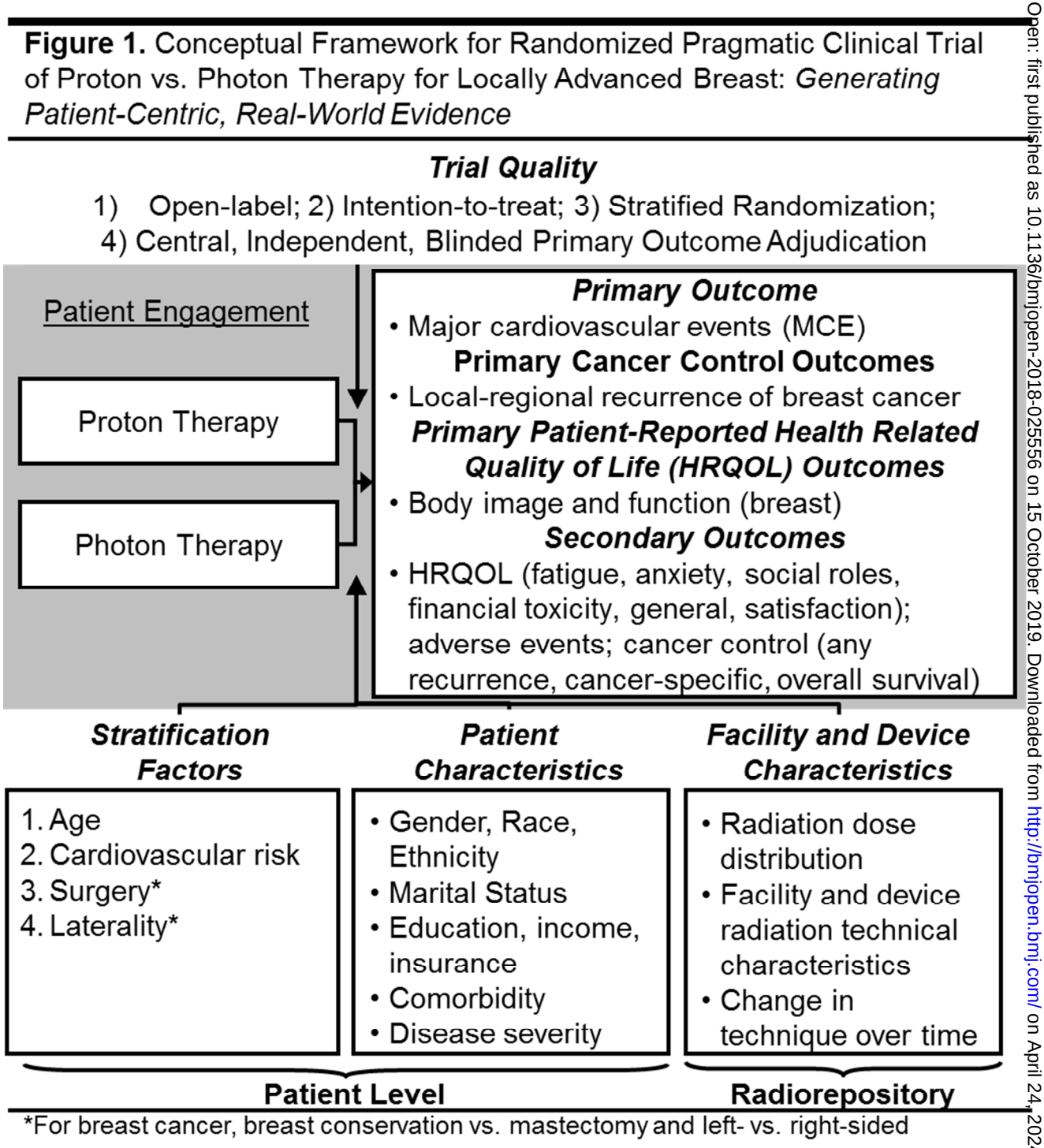


Figure 1. Conceptual Framework for Randomized Pragmatic Clinical Trial of Proton vs. Photon Therapy for Locally Advanced Breast: *Generating Patient-Centric, Real-World Evidence*

The RadComp trial has in common a highly pragmatic approach in most Pragmatic Explanatory Continuum Indicator Summary (PRECIS) domains [15] (**Table 1**). We highlight 3

choices essential to maintaining internal and external validity: First, the trial is open-label (both the researchers and participants know which treatment is administered); however, we conduct independent, centralized primary outcome adjudication of MCEs to protect against differential misclassification between treatment groups. Second, participant eligibility is minimally restricted, without exclusions for pre-existing co-morbidities, and treatment is flexible in dosing and technique; however, we provide best practice guidelines for radiotherapy delivery, consistent with prior pragmatic clinical trials of technologically complex treatments (based on consensus among RadComp centers).[16] Third, treatment decisions are at the discretion of the local treating providers and patients; however, we will store radiotherapy treatment plans within the RadComp Radiorepository for retrospective research review.

Table 1. Key Elements of the RadComp Pragmatic Approach to Study Design

Domain	Typical Explanatory RCT	RadComp Pragmatic Randomized Clinical Trial
Blinding	Open-label	Open-label
Participant Eligibility	Highly selected (avoid diluting effect)	Little selection beyond the clinical indication for RT
Intervention Flexibility	Standardized, inflexible treatment guidelines	Flexible treatment guidelines, promote local care standards
Practitioner Expertise	Expert sub-specialists at elite academic settings	Academic and community settings, real-world care
Follow-up	Frequent research visits, more extensive than routine care	Annual research visits, tied to routine care; engage patients
Primary Outcome	Clinically meaningful, often surrogate	Clinically meaningful, patient-centric MCE and HRQOL
Event Adjudication	Variable	Independent, blinded, centralized primary outcome adjudication
Adherence	Stringent for both patient	Relaxed, usual care, best

	and provider	practice recommendations
Analysis	Intention-to-treat	Intention-to-treat
Relevance to practice	Indirect: trial design ≠ needs of stakeholders	Direct: trial design = needs of patients and stakeholders

Overall Aims

Aim 1 addresses the effectiveness of proton versus photon therapy in reducing major cardiovascular events. Aim 2 assesses the non-inferiority of proton versus photon therapy in reducing risk of breast cancer local-regional recurrence and in reducing risk of any recurrence, defined as the first reported breast cancer recurrence of any type (local-regional or distant recurrence or cancer-specific mortality). Aim 3 considers the effectiveness of proton versus photon therapy in improving physical, mental and social HRQOL; specifically, body image and function in breast cancer, and fatigue, anxiety, social roles, general HRQOL, side effects burden, and satisfaction. Aim 4 focuses on development of predictive models to examine the associations of radiation dose distributions and MCE and HRQOL to identify subgroups of patients most likely to benefit from proton or photon therapy.

Eligibility

Eligibility criteria are defined broadly to maximize generalizability of results, striking a balance between pragmatism and treatment appropriateness (**Table 2**). Rarely, patients will be ineligible if proton or photon therapy cannot be administered safely.

Table 2. Summary of inclusion and exclusion criteria for the RadComp trial

Inclusion Criteria	• Age ≥21 years • Females or males diagnosed with pathologically (histologically) proven invasive mammary carcinoma (ductal, lobular or other) of the breast who have undergone either mastectomy or lumpectomy/local excision with any type of axillary or internal mammary node chain surgery or sampling or who have had a local recurrence • Must be proceeding with breast/chest wall and nodal radiation therapy including internal mammary node treatment • Confirmation that participant's health insurance or an alternative source will pay for the cost of proton or photon therapy treatment on the study
Exclusion Criteria	• Definitive clinical or radiological evidence of metastatic disease • Prior radiotherapy to the ipsilateral chest wall, breast or thorax • Scleroderma

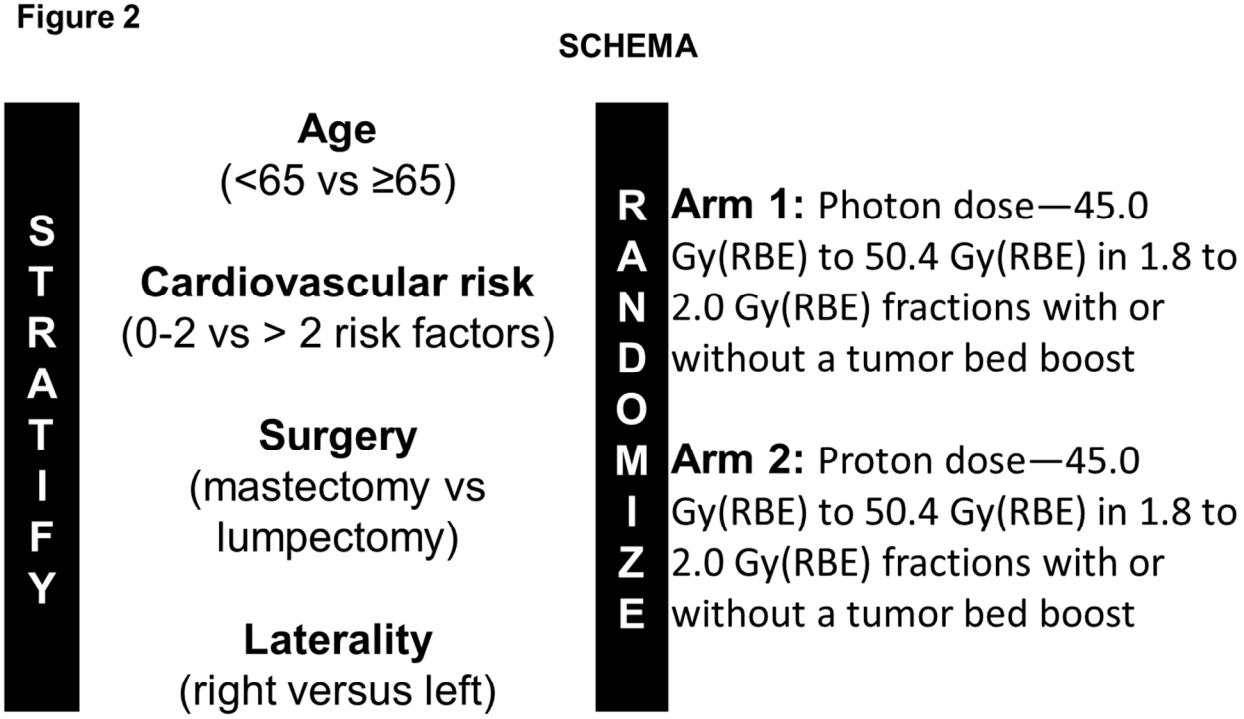
Baseline Assessments

Prior to randomization, enrolled patients complete initial assessments that include a patient interview and medical record review to assess relevant pre-randomization covariates. Additional data regarding patient contact and alternate contacts information and baseline HRQOL are collected.

Interventions

Patients are randomly assigned to receive either photon or proton therapy. Participants are stratified by age (<65 vs. ≥65), cardiovascular risk (0-2 v >2 risk factors), surgery (mastectomy vs lumpectomy) and laterality (left- vs. right-sided) (**Figure 2**). Bilateral patients are classified as left-sided.

Figure 2



*Risk factors include history of coronary artery disease or myocardial infarction, atrial fibrillation/flutter, hypertension, diabetes, hypertension, renal insufficiency or failure, hyperlipidemia, heart failure, cardiomyopathy, smoking (current/former), prior contralateral left breast or chest wall radiation, prior anthracycline therapy, or prior trastuzumab therapy.

Proton therapy techniques may include passively scattered or scanning technology. All patients receive breast/chest wall and comprehensive nodal radiation therapy including internal mammary node treatment. Treatment planning guidelines are described in the protocol, available upon request. A contouring atlas has been developed for guidance and is available at https://www.rtog.org/CoreLab/ContouringAtlases/RADCOMPBreastAtlas.aspx. A novel aspect of this atlas is that it can be viewed in coronal, axial, and sagittal planes by treating physicians.

RadComp Radiorepository

In a technology-based medical discipline like radiation oncology, significant center-to-center variations exist in implementation of technologies.[11] We draw a balance between allowing

for local practice variation while promoting best practice radiotherapy delivery across centers; this effort is crucial to conduct a valid, credible study, as well as to minimize the number of patients required and maximize the protection of participants.[17,18] The RadComp Radiorepository collects and stores three-dimensional radiation treatment plans for all patients through the data collection infrastructure provided by The Cancer Imaging Archive (TCIA)[19,20] to ensure efficiency of these processes for participating centers. Data is stored in TCIA with the approval of the National Cancer Institute, as a private collection and can be made publicly available at an appropriate time following the completion of the trial.

Centralized Adjudication of Primary Outcomes

The RadComp Clinical Events Center (CEC) will conduct centralized adjudication of clinical events related to the primary outcomes of major cardiovascular events. The objectives of the CEC are 1) to apply consistent, simple, relevant definitions of the fatal and non-fatal cardiovascular events comprising the MCE endpoint to detect possible events and to avoid the influence of investigator or patient ascertainment bias; and 2) to conduct adjudication blinded to treatment assignment to protect against differential misclassification events. The goal of centralized adjudication of primary outcomes is to increase confidence in the validity of our findings.[21-23] Leveraging best practice adjudication procedures from the National Lung Screening Trial (NLST)[24] and prior work at the University of Pennsylvania in managing large, complex clinical event adjudication programs[25,26], the CEC employs key processes to define, identify, track, investigate, and determine whether a primary event has occurred. The RadComp adjudication manual is available upon request.

Outcomes, Patient Characteristics, and Facility and Device Characteristics

As shown in the conceptual framework, study measures include primary outcomes (MCE), secondary outcomes, baseline stratification factors, patient characteristics, and facility characteristics.

Major Cardiovascular Events (MCE). The primary outcome is MCE, defined as myocardial infarction, coronary revascularization, cardiovascular death, or hospitalization for unstable angina, heart failure, valvular disease, arrhythmia, or pericardial disease.

Local-regional recurrence and any recurrence. The primary cancer control outcome is local-regional recurrence, defined as the local recurrence as a first event.[27-29] We will also evaluate any recurrence, defined as the first reported breast cancer recurrence of any type (local-regional or distant recurrence or cancer-specific mortality).

Baseline Cardiovascular Disease. Assessed at baseline, elevated risk of cardiovascular disease is defined by a history of coronary artery disease or myocardial infarction, atrial fibrillation/flutter, hypertension, diabetes, renal failure, hyperlipidemia, heart failure, cardiomyopathy, smoking (current/former), prior contralateral left breast or chest wall radiation, prior anthracycline therapy, or prior trastuzumab therapy. We choose this approach as both valid (based on the Framingham risk score) and consistent with our pragmatic framework, acknowledging that some cardiovascular risk stratification schemes include laboratory or echocardiographic assessment.[30] Other cardiovascular risk factors (including family history) will be assessed but will not contribute to the definition of cardiovascular risk factors for the purposes of stratification.

Patient Characteristics. We will collect demographic information including gender, race, ethnicity, marital status, educational attainment, insurance, household income, comorbidity

assessment and disease severity, leveraging the Patient-Reported Outcomes Measurement Information System (PROMIS) sociodemographic and comorbidity questionnaire.[31]

Facility/Device Characteristics and Radiation Dose Distribution. We will investigate the relationship between proton and photon dose distribution metrics and differences in MCE and HRQOL in order to identify subgroups of patients that might benefit from proton or photon therapy. To facilitate this analysis, we will record patient-level radiation dose distributions and treatment delivery parameters, facility and device radiation technical characteristics, and any evolution of radiation techniques over time through the RadComp Radiorepository. We also will conduct centralized contouring of organs at risk, including the heart and its substructures (left anterior descending artery, left and right atria, left and right ventricles, left main, left circumflex and the right coronary artery, lungs, esophagus, and thyroid). Centralized contouring is important in any radiotherapy trial but is particularly pertinent to a pragmatic trial in which the local norms of anatomic delineation for radiation treatment planning vary widely.[32,33] While patients will be treated according to anatomic delineation of local providers, centralized contouring will be conducted by trained staff at the RadComp Coordinating Center and the results stored in the Radiorepository.

HRQOL Instruments

The HRQOL instruments and outcomes chosen for the proposed trials are hypothesis-driven, validated, reliable and have been shown to be meaningful to patients.[34-37] Each instrument is described below. The estimated patient response burden to complete these instruments is approximately 30 minutes.

FACT-B. The Functional Assessment of Cancer Therapy-Breast (FACT-B) measures general

and breast cancer specific health-related quality of life.[38] It has multiple subscales, three of which are combined to form a Trial Outcome Index that is useful for clinical trials. It also has a four-item arm mobility subscale[39,40] and two items to measure pain and swelling.

BREAST-Q. The BREAST-Q was designed to evaluate outcomes among women undergoing different types of breast surgery.[41] A 5-item subscale to assess adverse effects of radiotherapy will be used in this trial.

Satisfaction with Breast Cosmetic Outcomes. This 6-item scale was developed to provide a brief assessment of patient-reported cosmetic outcomes after breast cancer treatment.[42]

PROMIS Fatigue. The 4-item Fatigue short form combines items on fatigue experience and interference derived from the Functional Assessment of Chronic Illness Therapy (FACIT) system and PROMIS.[31,43-45] It has been used extensively in oncology trials and is responsive to change after radiation therapy.

PROMIS Anxiety. Anxiety is a common concern among cancer patients[34] and is especially relevant for the RadComp trials. The PROMIS 4-item short form for Anxiety was developed based on content and psychometric measurement precision.[46]

PROMIS Social Roles. Social function has historically been a relatively neglected domain due to the lack of measures for clinical populations. A 4-item PROMIS short form will be used in this trial, derived from the validated a 35-item measure of ability to participate in social roles and activities.[47].

PRO-CTCAE Shortness of Breath & Chest Pain Case Report Form. This side effects short form will solicit experience, shortness of breath and chest pain. Items were selected from the NCI's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) system, which was developed to collect patient reports of symptoms they

are experiencing while undergoing treatment, for the purpose of enhancing adverse event (AE) reporting (http://healthcaredelivery.cancer.gov/pro-ctcae/) or were written for this trial using the PRO-CTCAE format. A single item from the FACT-B will also be used to measure the overall burden of side effects ("I am bothered by side effects of treatment: not at all, a little bit, somewhat, quite a bit, very much"), as used in prior cancer studies.[48-50]

FACIT-TS-G. The FACIT system includes an 8-item measure of general satisfaction with treatment, developed and validated with patients with cancer and HIV/AIDS.[51] Six of the 8 items will be used in this trial.

Financial Burden. In discussion with the Stakeholder Advisory Committee, we included an item to assess overall financial burden. This item is part of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 instrument: "Has your physical condition or medical treatment caused you financial difficulties?" (not at all, a little bit, quite a bit, very much)[52].

Productivity. This single item has been developed to assess the extent that a patient was able to resume normal activities. It is rated on a 0% to 100% scale[53].

EuroQOL 5D (EQ-5D). The EQ-5D is a standardized two-part, self-administered instrument for direct and indirect assessment of health state utilities; it is cognitively simple, takes only a few minutes to complete, and yields a utilities index value for health status[54].

Recruitment

All patients will be recruited in clinic settings between the time of presentation with breast cancer and prior to start of radiation therapy. Radiation oncologists at each recruiting site will assess willingness for their patients to be enrolled.

RadComp recruiting sites have been selected to represent a broad range of geographic locations and practice settings in the US, including large teaching and non-teaching treatment centers and smaller community facilities. The site selection process for RadComp included consideration of volume of breast cancer patients, treatment practices and presence of buy-in from clinical leaders. Over 95% of existing proton therapy treatment centers in the United States are participating in the trial.

AE monitoring

At each contact with the subject, including the pre-treatment assessment, the investigator seeks information on adverse events by specific questioning and, as appropriate, by examination. Adverse events will be recorded by clinicians using the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0, a comprehensive, multimodality grading system for reporting the acute and late effects of cancer treatment.[55]

Data Analysis and Management

Analyses for all endpoints will follow the intention-to-treat principle. As-treated analyses will be conducted for major cardiovascular events and other safety endpoints secondarily. The primary analysis will be a comparison of time to MCE between treatment arms. Log rank tests will be used to compare the time to MCE between treatment arms; Kaplan-Meier plots will be used to graphically depict time to MCE by treatment arm. The main subgroups assessed for heterogeneity of treatment effects (HTE) within Cox models will be the stratification factors as defined in the schema. In secondary analyses, we will assess the influence of patient characteristics (gender, race, ethnicity, marital status, education, health literacy, income,

insurance status, comorbidities, and disease severity) and device and facility characteristics (radiation dose distribution, facility and device radiation technical characteristics, change in technique over time). To account for the presence of competing risks, we also will conduct secondary analyses of the cumulative incidence of MCE using nonparametric cumulative incidence functions. We will use the Fine-Gray semiparametric model for subdistribution hazards to estimate the effects of stratification factors and other covariates.

Initial evaluation of HTE will be made by analysis of interactions between treatment and patient-level and facility/device covariates using a Cox regression model with the primary outcome (MCE) as the dependent variable. Treatment effects within subgroups, such as ethnicity and race, will be conducted if any treatment-covariate interactions are at least suggestive ($p<0.20$) and sample sizes and numbers of events within these subgroups are sufficient for analysis. Due to the exploratory nature of these analyses and the expected limited sample size in each subgroup, no adjustments for multiple comparisons will be made. These analyses will follow the primary comparisons as specified for MCE.

Power and Sample Size

Our primary hypothesis is that treatment with proton therapy as compared to photon therapy will reduce the rate of major cardiovascular events. Two-sided significance tests are employed for all analyses.

The study will randomize 1,716 patients to photon therapy vs proton therapy for treatment of breast cancer. The 10-year estimate of the proportion of breast cancer patients with major cardiovascular events in the photon arm is estimated to be 6.3% based on study team analyses of data from the Surveillance Epidemiological End Results database (available upon

request from the authors). Assuming a 45% relative reduction of major cardiovascular events using proton therapy, resulting in a major cardiovascular event rate of 3.5% for the proton arm, this sample will provide 80% power to detect this difference between the two arms. A sample size of 1,716 will allow sufficient power with a loss to follow-up rate of 13%.

The planned sample size will also provide sufficient power for testing hypotheses related to our secondary outcomes. An underlying assumption is that proton therapy will not negatively impact cancer control outcomes. This assumption is biologically plausible given similar radiation doses and biological effects of protons and photons on tumor bed targets; yet, clinical evidence is scarce. We plan to evaluate local-regional relapse, the primary cancer control outcome of interest for radiation, using a non-inferiority approach. Non-inferiority margins were evaluated based on prior studies showing improvements in local-regional relapse rates with photon therapy, relative to no radiation.[28,29] With a sample size of 1,716 patients, there is 80% power for a 5-year non-inferiority margin not higher than 3.5% for local-regional recurrence assuming local-regional recurrence in the photon arm of 5% at 5 years. All calculations assume use of a log-rank test with a 1-sided alpha of 0.025. We will examine cancer-specific and overall survival according to methods described above for time-to-event analyses.

For HRQOL outcomes, effect sizes were estimated as the expected difference between groups at the 6-month assessment. A correlation of 0.40 to 0.60 between repeated measures was assumed, based on data from previous longitudinal studies of HRQOL and satisfaction in cancer patients.[56-58] An effect size of 0.33 corresponds to a clinically important difference in HRQOL outcomes.[59,60] The proposed sample sizes in each treatment arm (n=858 for breast cancer) will be sufficient to detect an effect size of 0.33 under various scenarios. For example, even with a correlation as low as 0.40, 174 patients per treatment arm will provide power of 80% at a two-

sided significance level of 0.05. Adjusting for multiple primary endpoints in the breast cancer trial, 330 patients per treatment arm will provide power of 90% at a two-sided significance level of 0.01. There will be adequate statistical power even with assuming 15% drop out.

Study monitoring

The RTOG Foundation Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity, and at any other times on an "as needed" basis. The review of the study will include, but not be limited to, the following items: accrual, baseline demographic characteristics, withdrawal rates, toxicity data, protocol compliance, treatment arm-specific data including radiation dose, toxicity and compliance, HRQOL questionnaire compliance, interim analyses of adverse events and safety results and outcome analyses results. Data by treatment arm will be seen only by the DMC, which will assess the integrity of the accruing data and compare selected measures between treatment arms that may affect study validity or raise potential ethical concerns regarding safety.

Stakeholder Engagement

Since 2009, leaders of the RadComp Consortium have convened or participated in workgroups of patients, clinicians, methodologists, cancer researchers, payers, product developers, vendors, and government representatives to explore the feasibility of alternative efficacy and effectiveness study designs and to build momentum for comparative studies of proton and photon therapy (These efforts resulted in the currently accruing NCI-sponsored efficacy PARTIQoL trial).[61-63] In 2014, RadComp investigators called for randomized trial

evidence generation for proton therapy in breast and lung cancer[64] and the current multi-institutional RadComp Consortium of 22 proton/photon centers agreed to seek PCORI funding for a pragmatic randomized clinical trial. In June 2014, in partnership with the NCI's Radiation Research Branch, the Consortium hosted a stakeholder engagement meeting on the NCI campus, in which we gained important insights on the formulation of the research questions, study designs, study implementation plans, and other key characteristics of comparative effectiveness research.[3]

We learned from stakeholders that one essential challenge in conducting randomized trials of proton therapy is restrictive insurance coverage for proton therapy, particularly for breast cancer.[65] While Medicare typically covers proton therapy for breast cancer indications, commercial insurers are more restrictive; however, reasonable clinical rationale supports coverage of radiation modalities such as intensity-modulated photon therapy or proton therapy for patients with breast cancer who require internal mammary node treatment (that is, patients with breast cancer clinically eligible for RadComp). Restrictive commercial coverage policies for proton therapy may impact the pace of enrollment to RadComp and the generalizability of the results. Therefore, RadComp engages with stakeholders to develop potential solutions to support for trial participation for eligible and interested patients.

The Stakeholder Advisory Committee and the larger stakeholder group have and will continue to participate in stakeholder deliberations. The Stakeholder Advisory Committee provides their insight on: (1) the creation of strategies to recruit and retain all patient populations, (2) developing study talking points in plain language to overcome patient confusion or fear of the concept of equipoise / uncertainty among treatment options, (3) translating study findings, and (4) mechanisms for the broad dissemination and implementation of best practices.

CONCLUSION

The RadComp trial will evaluate outcomes after proton or photon therapy for patients with breast cancer through a real-world, patient-centered pragmatic randomized clinical trial. RadComp's goal is to generate new knowledge about the relative effects of these approaches while ensuring that treatment reflects high-quality routine clinical practice, identifies subgroups of patients that might benefit more from either treatment, and helps patients and physicians understand and apply our findings to their own experience. Patients with breast cancer considering photon or proton therapy make treatment decisions in the context of extremely sparse comparative effectiveness evidence, and then may live for years with clinically burdensome treatment-related morbidity that affects their quality of life and engagement in activities of living. The RadComp trial results will be directly relevant to many thousands of patients who confront these difficult treatment decisions every day.

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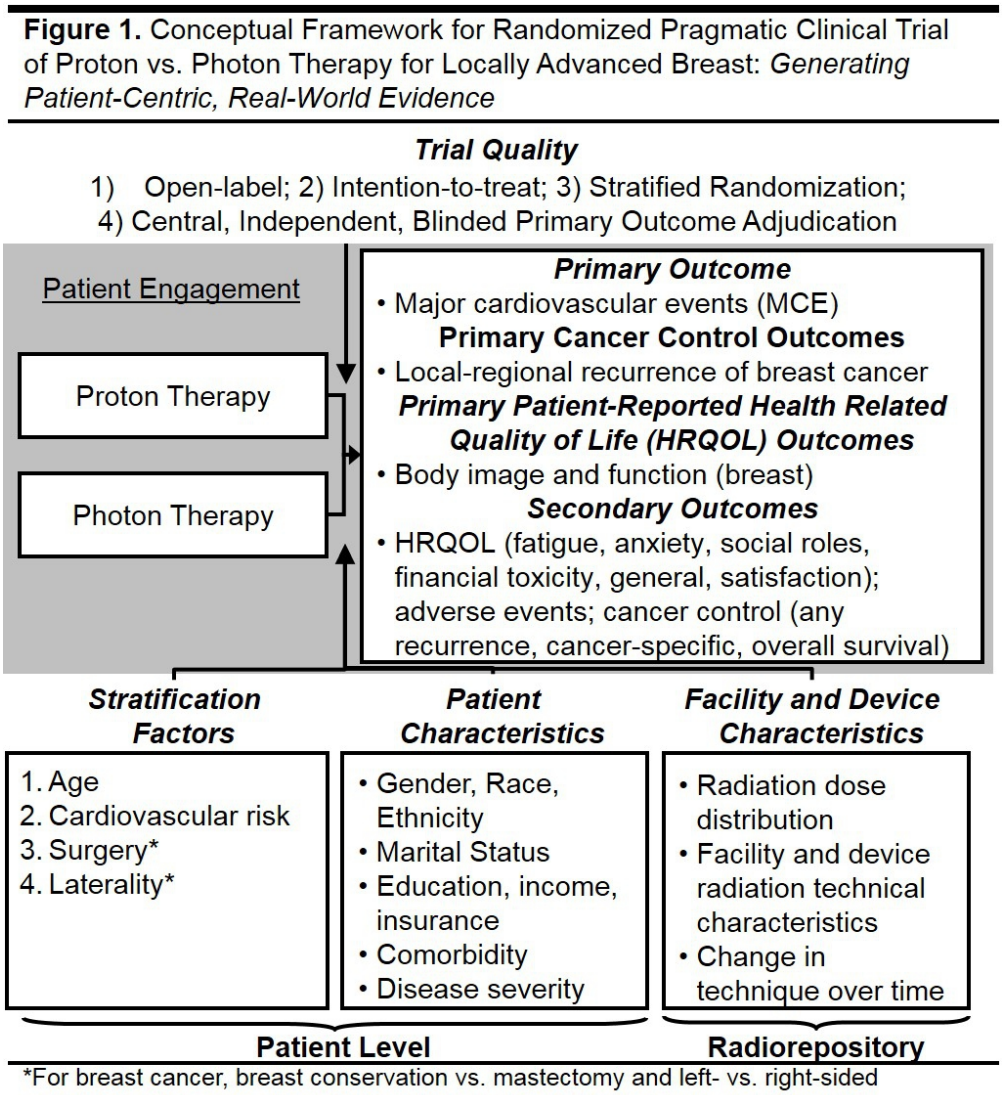

Figure 1. Conceptual Framework

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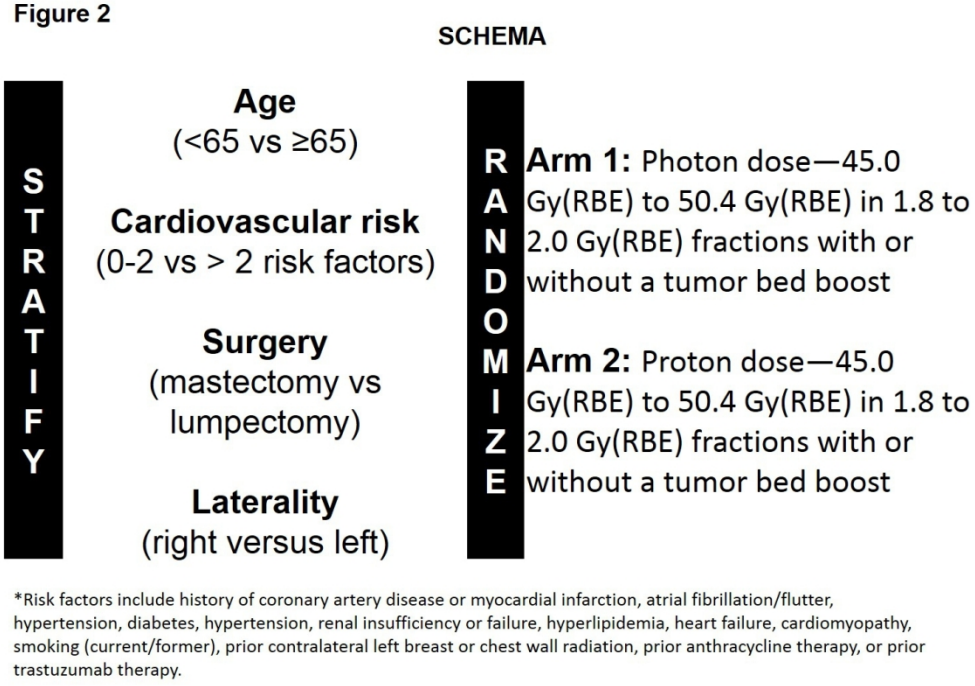
Figure 2



*Risk factors include history of coronary artery disease or myocardial infarction, atrial fibrillation/flutter, hypertension, diabetes, hypertension, renal insufficiency or failure, hyperlipidemia, heart failure, cardiomyopathy, smoking (current/former), prior contralateral left breast or chest wall radiation, prior anthracycline therapy, or prior trastuzumab therapy.

Figure 2. Schema

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Pragmatic Randomized Clinical Trial of Proton vs. Photon Therapy for Patients with Non-Metastatic Breast Cancer: The Radiotherapy Comparative Effectiveness (RadComp) Consortium Trial Protocol

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Pragmatic Randomized Clinical Trial of Proton vs. Photon Therapy for Patients with Non-Metastatic Breast Cancer: The Radiotherapy Comparative Effectiveness (RadComp) Consortium Trial Protocol

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Ethics Approval: University of Pennsylvania Perelman School of Medicine Institutional Review Board (IRB) and the IRBs or Research Ethics Boards (REBs) of 23 participating US institutions.

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Abstract:

Introduction:

A broad range of stakeholders have called for randomized evidence on the potential clinical benefits and harms of proton therapy, a type of radiation therapy, for patients with breast cancer. Radiation therapy is an important component of curative treatment, reducing cancer recurrence and extending survival. Compared to photon therapy, the international treatment standard, proton therapy reduces incidental radiation to the heart. Our overall objective is to evaluate whether differences between proton and photon therapy cardiac radiation dose distributions lead to meaningful reductions in cardiac morbidity and mortality after treatment for breast cancer.

Methods: We are conducting a large scale, multi-center pragmatic randomized clinical trial for patients with breast cancer who will be followed longitudinally for cardiovascular morbidity and mortality, health-related quality of life and cancer control outcomes. A total of 1,278 patients with non-metastatic breast cancer will be randomly allocated to receive either photon or proton therapy. The primary outcomes are major cardiovascular events, defined as myocardial infarction, coronary revascularization, cardiovascular death, or hospitalization for unstable angina, heart failure, valvular disease, arrhythmia, or pericardial disease. Secondary endpoints are urgent or unanticipated outpatient or ER visits for heart failure, arrhythmia, valvular disease, or pericardial disease. The RadComp Clinical Events Center will conduct centralized, blinded adjudication of primary outcome events.

Ethics and dissemination: The RadComp trial has been approved by the institutional review boards of all participating sites. Recruitment began in February 2016. Current version of the

protocol is A3, dated 11/08/2018. Dissemination plans include presentations at scientific conferences, scientific publications, stakeholder engagement efforts and presentation to the public via lay media outlets.

Trial registration number: NCT02603341, Pre-results.

Strengths and Limitations of this study

- The pragmatic and holistic approach reflects 'real world' clinical practice, identifies subgroups of patients who might benefit more from proton therapy and helps patients and physicians understand and apply findings to their own lived experience.
- Engagement of patients and other essential stakeholders in the design and conduct of large scale pragmatic randomized control trials of a promising, but expensive, medical technology will inform future efforts to conduct holistic, patient-centric, and pragmatic comparative effectiveness research as part of a learning health care system.
- Blinded, centralized adjudication of primary outcomes applies consistent, relevant definitions of fatal and non-fatal events comprising the major cardiovascular endpoint to detect possible events and avoids the influence of investigator or patient ascertainment bias.
- The RadComp Consortium may have the appearance of conflict of interest (COI) as it involves centers with proton therapy capabilities. COI concerns are addressed by randomized study design, blinded adjudication of primary outcome, accountability by the Data Safety Monitoring Board, and declaration, disclosure and management of COI.

INTRODUCTION

The Pragmatic Randomized Trial of Proton vs. Photon Therapy for Patients with Non-Metastatic Breast Cancer: A Radiotherapy Comparative Effectiveness (RadComp) Consortium Trial (NCT02603341) is a large scale, multi-center pragmatic randomized clinical trial following patients longitudinally for cardiovascular morbidity and mortality, health-related quality of life (HRQOL) and cancer control outcomes. We focus on radiotherapy for breast cancer requiring internal mammary nodal irradiation because: 1) regional node radiotherapy is an important component of curative treatment for high risk breast cancer; 2) the survival advantages of radiotherapy may be reduced by incidental radiation to the heart; 3) proton therapy, by reducing incidental radiation to the heart and other normal tissues, may lead to meaningful reductions in cardiac morbidity and mortality and improvements in health-related quality of life; and 4) patients with breast cancer seek evidence on disease control, quality of life and cardiovascular outcomes after proton versus photon therapy to help make shared decisions with their physicians about treatment options.

Our primary hypothesis is that proton therapy, as part of multi-modality curative treatment for patients with non-metastatic breast cancer who have indications for regional nodal irradiation, reduces major cardiovascular events (MCE) compared to photon therapy. Major cardiovascular events are defined as myocardial infarction, coronary revascularization, cardiovascular death, or hospitalization for unstable angina, heart failure, valvular disease, arrhythmia, or pericardial disease. Photon therapy, delivered as either intensity-modulated radiotherapy (IMRT) or 3D conformal radiotherapy, uses multiple x-ray beams to irradiate a tumor target but unavoidably deposits radiation in normal tissues beyond the target volume. In contrast, proton therapy directs a beam of *protons* (positively charged subatomic particles) at the

target volume, where they deposit the bulk of their energy in the last few millimeters of their range.[1] Proton radiation dose distributions may appear superior to photon therapy, particularly in the reduction of low and intermediate radiation dose to normal tissues like the heart and lungs.

However, both photon and proton therapy have physical and biologic uncertainties that could impact important clinical outcomes. For example, investigators have noted uncertainties about the exact range of the proton therapy in tissue and its biological effects at the end of the range.[2] In addition, due to their distinct physical properties, there may be differences in the biological effect of proton therapy and photon therapy on normal tissues.

Thus, a broad range of stakeholders (patients, providers, manufacturers, researchers and policy makers) have called for randomized evidence on the clinical benefits and harms of proton therapy for patients with breast cancer.[3-9]

METHODS

Study design

This study is a superiority pragmatic randomized clinical trial in breast cancer to compare two external beam radiation therapies: proton vs. photon therapy. Treatment techniques represent current care standards and are easy to replicate. Study endpoints are assessed via self-report, medical record review, vital records database search and centralized adjudication. The primary outcome is assessed by an adjudication team of cardiologists who are blinded to treatment assignment.

Informed by the work of Sedrakyan, Luce, Ellenberg, and Treweek,[10-14] the conceptual framework for the trial (**Figure 1)** addresses sources of variability that are unique to radiation devices, including facility and device characteristics.

The RadComp trial has in common a highly pragmatic approach in most Pragmatic Explanatory Continuum Indicator Summary (PRECIS) domains [15] (**Table 1**). We highlight 3 choices essential to maintaining internal and external validity: First, the trial is open-label (both the researchers and participants know which treatment is administered); however, we conduct independent, centralized primary outcome adjudication of MCEs to protect against differential misclassification between treatment groups. Second, participant eligibility is minimally restricted, without exclusions for pre-existing co-morbidities, and treatment is flexible in dosing and technique; however, we provide best practice guidelines for radiotherapy delivery, consistent with prior pragmatic clinical trials of technologically complex treatments (based on consensus among RadComp centers).[16] Third, treatment decisions are at the discretion of the local treating providers and patients; however, we will store radiotherapy treatment plans within the RadComp Radiorepository for retrospective research review.

Table 1. Key Elements of the RadComp Pragmatic Approach to Study Design

Domain	Typical Explanatory RCT	RadComp Pragmatic Randomized Clinical Trial
Blinding	Open-label	Open-label
Participant Eligibility	Highly selected (avoid diluting effect)	Little selection beyond the clinical indication for RT
Intervention Flexibility	Standardized, inflexible treatment guidelines	Flexible treatment guidelines, promote local care standards
Practitioner Expertise	Expert sub-specialists at elite academic settings	Academic and community settings, real-world care
Follow-up	Frequent research visits, more extensive than routine care	Annual research visits, tied to routine care; engage patients

Primary Outcome	Clinically meaningful, often surrogate	Clinically meaningful, patient-centric MCE and HRQOL
Event Adjudication	Variable	Independent, blinded, centralized primary outcome adjudication
Adherence	Stringent for both patient and provider	Relaxed, usual care, best practice recommendations
Analysis	Intention-to-treat	Intention-to-treat
Relevance to practice	Indirect: trial design ≠ needs of stakeholders	Direct: trial design = needs of patients and stakeholders

Overall Aims

Aim 1 addresses the effectiveness of proton versus photon therapy in reducing major cardiovascular events. Aim 2 assesses the non-inferiority of proton versus photon therapy in reducing risk of breast cancer local-regional recurrence and in reducing risk of any recurrence, defined as the first reported breast cancer recurrence of any type (local-regional or distant recurrence or cancer-specific mortality). Aim 3 considers the effectiveness of proton versus photon therapy in improving physical, mental and social HRQOL; specifically, body image and function in breast cancer, and fatigue, anxiety, social roles, general HRQOL, side effects burden, and satisfaction. Aim 4 focuses on development of predictive models to examine the associations of radiation dose distributions and MCE and HRQOL to identify subgroups of patients most likely to benefit from proton or photon therapy.

Eligibility

Eligibility criteria are defined broadly to maximize generalizability of results, striking a balance between pragmatism and treatment appropriateness (**Table 2**). Rarely, patients will be ineligible if proton or photon therapy cannot be administered safely.

Table 2. Summary of inclusion and exclusion criteria for the RadComp trial

Inclusion Criteria	• Age ≥21 years • Females or males diagnosed with pathologically (histologically) proven invasive mammary carcinoma (ductal, lobular or other) of the breast who have undergone either mastectomy or lumpectomy/local excision with any type of axillary or internal mammary node chain surgery or sampling or who have had a local recurrence • Must be proceeding with breast/chest wall and nodal radiation therapy including internal mammary node treatment • Confirmation that participant's health insurance or an alternative source will pay for the cost of proton or photon therapy treatment on the study
Exclusion Criteria	• Definitive clinical or radiological evidence of metastatic disease • Prior radiotherapy to the ipsilateral chest wall, breast or thorax • Scleroderma

Baseline Assessments

Prior to randomization, enrolled patients complete initial assessments that include a patient interview and medical record review to assess relevant pre-randomization covariates. Additional data regarding patient contact and alternate contacts information and baseline HRQOL are collected.

Interventions

Patients are randomly assigned to receive either photon or proton therapy. Participants are stratified by age (<65 vs. ≥65), cardiovascular risk (0-2 v >2 risk factors), surgery (mastectomy vs lumpectomy) and laterality (left- vs. right-sided) (**Figure 2**). Bilateral patients are classified as left-sided.

Proton therapy techniques may include passively scattered or scanning technology. All patients receive breast/chest wall and comprehensive nodal radiation therapy including internal mammary node treatment. Treatment planning guidelines are described in the protocol, available upon request. A contouring atlas has been developed for guidance and is available at https://www.rtog.org/CoreLab/ContouringAtlases/RADCOMPBreastAtlas.aspx. A novel aspect of this atlas is that it can be viewed in coronal, axial, and sagittal planes by treating physicians.

RadComp Radiorepository

In a technology-based medical discipline like radiation oncology, significant center-to-center variations exist in implementation of technologies.[11] We draw a balance between allowing for local practice variation while promoting best practice radiotherapy delivery across centers; this effort is crucial to conduct a valid, credible study, as well as to minimize the number of patients required and maximize the protection of participants.[17,18] The RadComp Radiorepository collects and stores three-dimensional radiation treatment plans for all patients through the data collection infrastructure provided by The Cancer Imaging Archive (TCIA)[19,20] to ensure efficiency of these processes for participating centers. Data is stored in TCIA with the approval of the National Cancer Institute, as a private collection and can be made publicly available at an appropriate time following the completion of the trial.

Centralized Adjudication of Primary Outcomes

The RadComp Clinical Events Center (CEC) will conduct centralized adjudication of clinical events related to the primary outcomes of major cardiovascular events. The objectives of the CEC are 1) to apply consistent, simple, relevant definitions of the fatal and non-fatal

cardiovascular events comprising the MCE endpoint to detect possible events and to avoid the influence of investigator or patient ascertainment bias; and 2) to conduct adjudication blinded to treatment assignment to protect against differential misclassification events. The goal of centralized adjudication of primary outcomes is to increase confidence in the validity of our findings.[21-23] Leveraging best practice adjudication procedures from the National Lung Screening Trial (NLST)[24] and prior work at the University of Pennsylvania in managing large, complex clinical event adjudication programs[25,26], the CEC employs key processes to define, identify, track, investigate, and determine whether a primary event has occurred. The RadComp adjudication manual is available upon request.

Outcomes, Patient Characteristics, and Facility and Device Characteristics

As shown in the conceptual framework, study measures include primary outcomes (MCE), secondary outcomes, baseline stratification factors, patient characteristics, and facility characteristics.

Major Cardiovascular Events (MCE). The primary outcome is MCE, defined as myocardial infarction, coronary revascularization, cardiovascular death, or hospitalization for unstable angina, heart failure, valvular disease, arrhythmia, or pericardial disease.

Local-regional recurrence and any recurrence. The primary cancer control outcome is local-regional recurrence, defined as the local recurrence as a first event.[27-29] We will also evaluate any recurrence, defined as the first reported breast cancer recurrence of any type (local-regional or distant recurrence or cancer-specific mortality).

Baseline Cardiovascular Disease. Assessed at baseline, elevated risk of cardiovascular disease is defined by a history of coronary artery disease or myocardial infarction, atrial

fibrillation/flutter, hypertension, diabetes, renal failure, hyperlipidemia, heart failure, cardiomyopathy, smoking (current/former), prior contralateral left breast or chest wall radiation, prior anthracycline therapy, or prior trastuzumab therapy. We choose this approach as both valid (based on the Framingham risk score) and consistent with our pragmatic framework, acknowledging that some cardiovascular risk stratification schemes include laboratory or echocardiographic assessment.[30] Other cardiovascular risk factors (including family history) will be assessed but will not contribute to the definition of cardiovascular risk factors for the purposes of stratification.

Patient Characteristics. We will collect demographic information including gender, race, ethnicity, marital status, educational attainment, insurance, household income, comorbidity assessment and disease severity, leveraging the Patient-Reported Outcomes Measurement Information System (PROMIS) sociodemographic and comorbidity questionnaire.[31]

Facility/Device Characteristics and Radiation Dose Distribution. We will investigate the relationship between proton and photon dose distribution metrics and differences in MCE and HRQOL in order to identify subgroups of patients that might benefit from proton or photon therapy. To facilitate this analysis, we will record patient-level radiation dose distributions and treatment delivery parameters, facility and device radiation technical characteristics, and any evolution of radiation techniques over time through the RadComp Radiorepository. We also will conduct centralized contouring of organs at risk, including the heart and its substructures (left anterior descending artery, left and right atria, left and right ventricles, left main, left circumflex and the right coronary artery, lungs, esophagus, and thyroid). Centralized contouring is important in any radiotherapy trial but is particularly pertinent to a pragmatic trial in which the local norms of anatomic delineation for radiation treatment planning vary widely.[32,33] While patients will be

treated according to anatomic delineation of local providers, centralized contouring will be conducted by trained staff at the RadComp Coordinating Center and the results stored in the Radiorepository. Participating sites must submit a facility questionnaire, complete a physics plan review and demonstrate successful digital data submission to the Radiorepository prior to study initiation.

HRQOL Instruments

The HRQOL instruments and outcomes chosen for the proposed trials are hypothesis-driven, validated, reliable and have been shown to be meaningful to patients.[34-37] Each instrument is described below. The estimated patient response burden to complete these instruments is approximately 30 minutes.

FACT-B. The Functional Assessment of Cancer Therapy-Breast (FACT-B) measures general and breast cancer specific health-related quality of life.[38] It has multiple subscales, three of which are combined to form a Trial Outcome Index that is useful for clinical trials. It also has a four-item arm mobility subscale[39,40] and two items to measure pain and swelling.

BREAST-Q. The BREAST-Q was designed to evaluate outcomes among women undergoing different types of breast surgery.[41] A 5-item subscale to assess adverse effects of radiotherapy will be used in this trial.

Satisfaction with Breast Cosmetic Outcomes. This 6-item scale was developed to provide a brief assessment of patient-reported cosmetic outcomes after breast cancer treatment.[42]

PROMIS Fatigue. The 4-item Fatigue short form combines items on fatigue experience and interference derived from the Functional Assessment of Chronic Illness Therapy (FACIT) system and PROMIS.[31,43-45] It has been used extensively in oncology trials and is responsive to

change after radiation therapy.

PROMIS Anxiety. Anxiety is a common concern among cancer patients[34] and is especially relevant for the RadComp trials. The PROMIS 4-item short form for Anxiety was developed based on content and psychometric measurement precision.[46]

PROMIS Social Roles. Social function has historically been a relatively neglected domain due to the lack of measures for clinical populations. A 4-item PROMIS short form will be used in this trial, derived from the validated a 35-item measure of ability to participate in social roles and activities.[47].

PRO-CTCAE Shortness of Breath & Chest Pain Case Report Form. This side effects short form will solicit experience, shortness of breath and chest pain. Items were selected from the NCI's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) system, which was developed to collect patient reports of symptoms they are experiencing while undergoing treatment, for the purpose of enhancing adverse event (AE) reporting (http://healthcaredelivery.cancer.gov/pro-ctcae/) or were written for this trial using the PRO-CTCAE format. A single item from the FACT-B will also be used to measure the overall burden of side effects ("I am bothered by side effects of treatment: not at all, a little bit, somewhat, quite a bit, very much"), as used in prior cancer studies.[48-50]

FACIT-TS-G. The FACIT system includes an 8-item measure of general satisfaction with treatment, developed and validated with patients with cancer and HIV/AIDS.[51] Six of the 8 items will be used in this trial.

Financial Burden. In discussion with the Stakeholder Advisory Committee, we included an item to assess overall financial burden. This item is part of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 instrument: "Has your physical condition or

medical treatment caused you financial difficulties?" (not at all, a little bit, quite a bit, very much)[52].

Productivity. This single item has been developed to assess the extent that a patient was able to resume normal activities. It is rated on a 0% to 100% scale[53].

EuroQOL 5D (EQ-5D). The EQ-5D is a standardized two-part, self-administered instrument for direct and indirect assessment of health state utilities; it is cognitively simple, takes only a few minutes to complete, and yields a utilities index value for health status[54].

Recruitment

All patients will be recruited in clinic settings between the time of presentation with breast cancer and prior to start of radiation therapy. Radiation oncologists at each recruiting site will assess willingness for their patients to be enrolled.

RadComp recruiting sites have been selected to represent a broad range of geographic locations and practice settings in the US, including large teaching and non-teaching treatment centers and smaller community facilities. The site selection process for RadComp included consideration of volume of breast cancer patients, treatment practices and presence of buy-in from clinical leaders. Over 95% of existing proton therapy treatment centers in the United States are participating in the trial.

AE monitoring

At each contact with the subject, including the pre-treatment assessment, the investigator seeks information on adverse events by specific questioning and, as appropriate, by examination. Adverse events will be recorded by clinicians using the National Cancer Institute Common

Toxicity Criteria for Adverse Events (CTCAE) version 4.0, a comprehensive, multimodality grading system for reporting the acute and late effects of cancer treatment.[55]

Data Analysis and Management

Analyses for all endpoints will follow the intention-to-treat principle. As-treated analyses will be conducted for major cardiovascular events and other safety endpoints secondarily. The primary analysis will be a comparison of time to MCE between treatment arms. Log rank tests will be used to compare the time to MCE between treatment arms; Kaplan-Meier plots will be used to graphically depict time to MCE by treatment arm. The main subgroups assessed for heterogeneity of treatment effects (HTE) within Cox models will be the stratification factors as defined in the schema. In secondary analyses, we will assess the influence of patient characteristics (gender, race, ethnicity, marital status, education, health literacy, income, insurance status, comorbidities, and disease severity) and device and facility characteristics (radiation dose distribution, facility and device radiation technical characteristics, change in technique over time). To account for the presence of competing risks, we also will conduct secondary analyses of the cumulative incidence of MCE using nonparametric cumulative incidence functions. We will use the Fine-Gray semiparametric model for subdistribution hazards to estimate the effects of stratification factors and other covariates.

Initial evaluation of HTE will be made by analysis of interactions between treatment and patient-level and facility/device covariates using a Cox regression model with the primary outcome (MCE) as the dependent variable. Treatment effects within subgroups, such as ethnicity and race, will be conducted if any treatment-covariate interactions are at least suggestive ($p<0.20$) and sample sizes and numbers of events within these subgroups are sufficient for

analysis. Due to the exploratory nature of these analyses and the expected limited sample size in each subgroup, no adjustments for multiple comparisons will be made. These analyses will follow the primary comparisons as specified for MCE.

Power and Sample Size

Our primary hypothesis is that treatment with proton therapy as compared to photon therapy will reduce the rate of major cardiovascular events.

The study will randomize 1,278 patients to photon therapy vs proton therapy for treatment of breast cancer. The 10-year estimate of the proportion of breast cancer patients with major cardiovascular events in the photon arm is estimated to be 6.3% based on study team analyses of data from the Surveillance Epidemiological End Results database (available upon request from the authors). Assuming a 45% relative reduction of major cardiovascular events using proton therapy, resulting in a major cardiovascular event rate of 3.5% for the proton arm, this sample will provide 80% power to detect this difference between the two arms using a log-rank test with a 1-sided alpha of 0.05. A sample size of 1,278 will allow sufficient power with a loss to follow-up rate of 13%.

The planned sample size will also provide sufficient power for testing hypotheses related to our secondary outcomes. An underlying assumption is that proton therapy will not negatively impact cancer control outcomes. This assumption is biologically plausible given similar radiation doses and biological effects of protons and photons on tumor bed targets; yet, clinical evidence is scarce. We plan to evaluate local-regional relapse, the primary cancer control outcome of interest for radiation, using a non-inferiority approach. Non-inferiority margins were evaluated based on prior studies showing improvements in local-regional relapse rates with photon therapy, relative

to no radiation.[28,29] With a sample size of 1,278 patients, there is 80% power for a 5-year non-inferiority margin not higher than 3.8% for local-regional recurrence assuming local-regional recurrence in the photon arm of 5% at 5 years using a log-rank test with a 1-sided alpha of 0.025. We will examine cancer-specific and overall survival according to methods described above for time-to-event analyses.

For HRQOL outcomes, effect sizes were estimated as the expected difference between groups at the 6-month assessment. A correlation of 0.40 to 0.60 between repeated measures was assumed, based on data from previous longitudinal studies of HRQOL and satisfaction in cancer patients.[56-58] An effect size of 0.33 corresponds to a clinically important difference in HRQOL outcomes.[59,60] The proposed sample sizes in each treatment arm (n=650) will be sufficient to detect an effect size of 0.33 under various scenarios. For example, even with a correlation as low as 0.40, 174 patients per treatment arm will provide power of 80% at a two-sided significance level of 0.05. Adjusting for multiple primary endpoints in the breast cancer trial, 330 patients per treatment arm will provide power of 90% at a two-sided significance level of 0.01. There will be adequate statistical power even with assuming 15% drop out.

Study monitoring

The RTOG Foundation Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity, and at any other times on an "as needed" basis. The review of the study will include, but not be limited to, the following items: accrual, baseline demographic characteristics, withdrawal rates, toxicity data, protocol compliance, treatment arm-specific data including radiation dose, toxicity and compliance, HRQOL

questionnaire compliance, interim analyses of adverse events and safety results and outcome analyses results. Data by treatment arm will be seen only by the DMC, which will assess the integrity of the accruing data and compare selected measures between treatment arms that may affect study validity or raise potential ethical concerns regarding safety.

Patient and Public Involvement

Since 2009, leaders of the RadComp Consortium have convened or participated in workgroups of patients, clinicians, methodologists, cancer researchers, payers, product developers, vendors, and government representatives to explore the feasibility of alternative efficacy and effectiveness study designs and to build momentum for comparative studies of proton and photon therapy (These efforts resulted in the currently accruing NCI-sponsored efficacy PARTIQoL trial).[61-63] In 2014, RadComp investigators called for randomized trial evidence generation for proton therapy in breast and lung cancer[64] and the current multi-institutional RadComp Consortium of 22 proton/photon centers agreed to seek PCORI funding for a pragmatic randomized clinical trial. In June 2014, in partnership with the NCI's Radiation Research Branch, the Consortium hosted a stakeholder engagement meeting on the NCI campus, in which we gained important insights on the formulation of the research questions, study designs, study implementation plans, and other key characteristics of comparative effectiveness research.[3]

We learned from stakeholders that one essential challenge in conducting randomized trials of proton therapy is restrictive insurance coverage for proton therapy, particularly for breast cancer.[65] While Medicare typically covers proton therapy for breast cancer indications, commercial insurers are more restrictive; however, reasonable clinical rationale supports

coverage of radiation modalities such as intensity-modulated photon therapy or proton therapy for patients with breast cancer who require internal mammary node treatment (that is, patients with breast cancer clinically eligible for RadComp). Restrictive commercial coverage policies for proton therapy may impact the pace of enrollment to RadComp and the generalizability of the results. Therefore, RadComp engages with stakeholders to develop potential solutions to support for trial participation for eligible and interested patients.

The Stakeholder Advisory Committee and the larger stakeholder group have and will continue to participate in stakeholder deliberations. The Stakeholder Advisory Committee provides their insight on: (1) the creation of strategies to recruit and retain all patient populations, (2) developing study talking points in plain language to overcome patient confusion or fear of the concept of equipoise / uncertainty among treatment options, (3) translating study findings, and (4) mechanisms for the broad dissemination and implementation of best practices.

Ethics and Dissemination

Of currently approved sites, nine have designated the University of Pennsylvania IRB as the IRB of record. Recruitment began in February 2016 and will continue through the end of 2021. Changes to the protocol will be communicated via teleconferences and memos to all sites with an expected date of implementation. Training on the changes will be documented.

Protected health information is only shared with research team members as required for completion of designated study tasks. Patient contact information for follow-up is only transmitted to the Coordinating Center via secure network servers. All team members needing access to identifiable study data will be required to submit appropriate trainings and roster forms

to request access. Logs of dates and times of database accessed will be kept, including an audit trail of data changes.

CONCLUSION

The RadComp trial will evaluate outcomes after proton or photon therapy for patients with breast cancer through a real-world, patient-centered pragmatic randomized clinical trial. RadComp's goal is to generate new knowledge about the relative effects of these approaches while ensuring that treatment reflects high-quality routine clinical practice, identifies subgroups of patients that might benefit more from either treatment, and helps patients and physicians understand and apply our findings to their own experience. Patients with breast cancer considering photon or proton therapy make treatment decisions in the context of extremely sparse comparative effectiveness evidence, and then may live for years with clinically burdensome treatment-related morbidity that affects their quality of life and engagement in activities of living. The RadComp trial results will be directly relevant to many thousands of patients who confront these difficult treatment decisions every day.

Contributorship Statement: JEB, SP, KB, ABG, WB, CC, BY, CL, HML, CDM, MP, FWP, SMM, and OC each made substantial contributions to the conception or design of the study protocol. JEB conceived the overall study and wrote the first draft of the protocol and with HLL, the first draft of this manuscript. KB, CB, ABG, WB, CC, EH, HML, CDM, MP, FWP, SMM and OC provided critical input regarding the design of the study intervention, study outcomes and study procedures; JEB, SP and SSE designed the data analysis and management plan. JEB, HLL, SP, KB, WB, SSE, HML, CDM, MP, SMM and OC revised the protocol critically for important intellectual content and approved the final version to be published. LZB, LMF, GMF, BGH, AJK, RBJ, CMK, MVM, RWM, SN, SNP, KDS, AZT, JBW, SMM and OC and RadComp Consortium all contributed to the data collection. JEB, HLL, SP, SSE, SMM and OC agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Competing Interests: JEB, SSE, CDM, BK report grants from PCORI, during the conduct of the study. SP, WB, LMF, BGH, CMK, MVM, RWM, FWP, SMM, OC report grants from University of Pennsylvania subcontracts as study investigator, during the conduct of the study.

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Data Sharing Statement: There are no data in this work.

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Figure Legend/Captions

Figure 1. Conceptual Framework for Randomized Pragmatic Clinical Trial of Proton vs. Photon Therapy for Locally Advanced Breast: Generating Patient-Centric, Real-Word Evidence

Figure 2. Study Stratification Schema

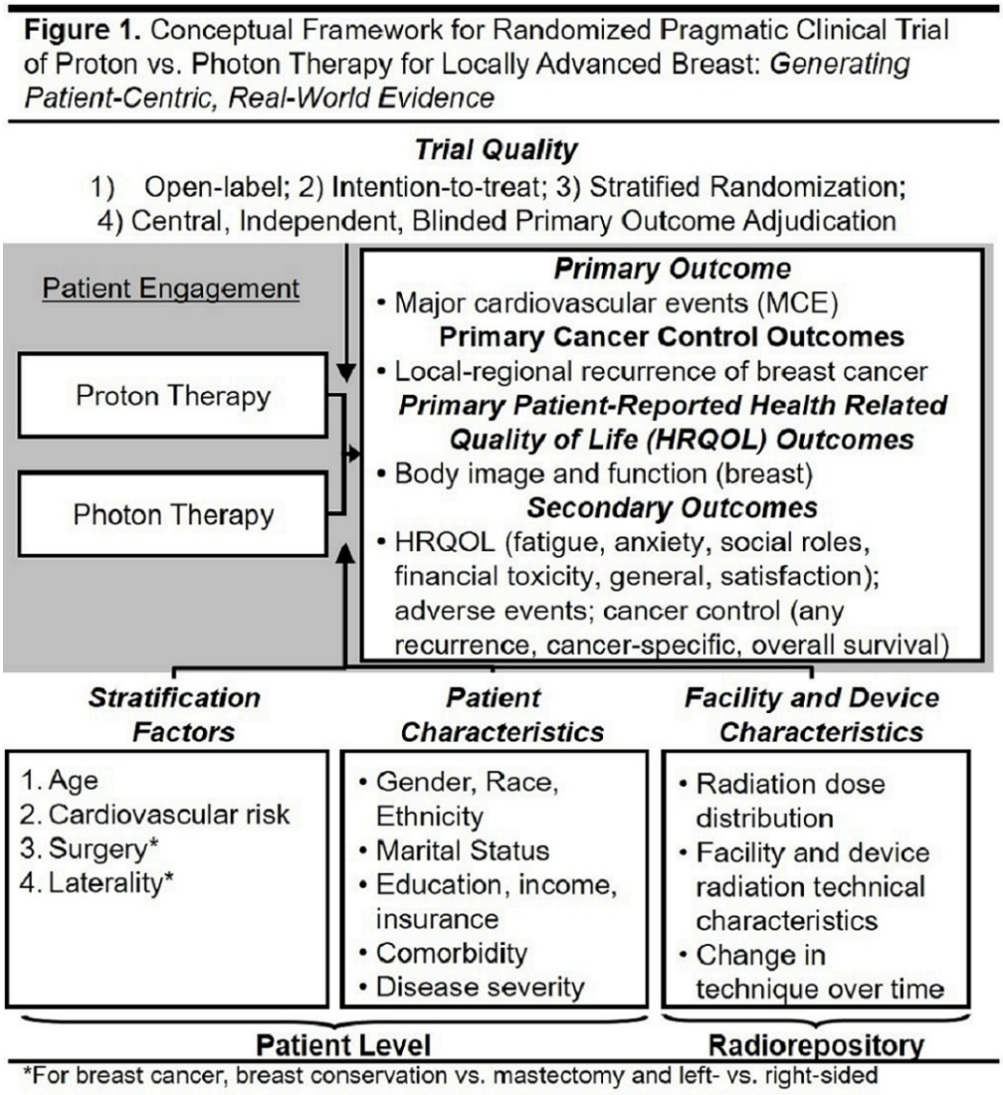

Figure 1. Conceptual Framework for Randomized Pragmatic Clinical Trial of Proton vs. Photon Therapy for Locally Advanced Breast: Generating Patient-Centric, Real-Word Evidence

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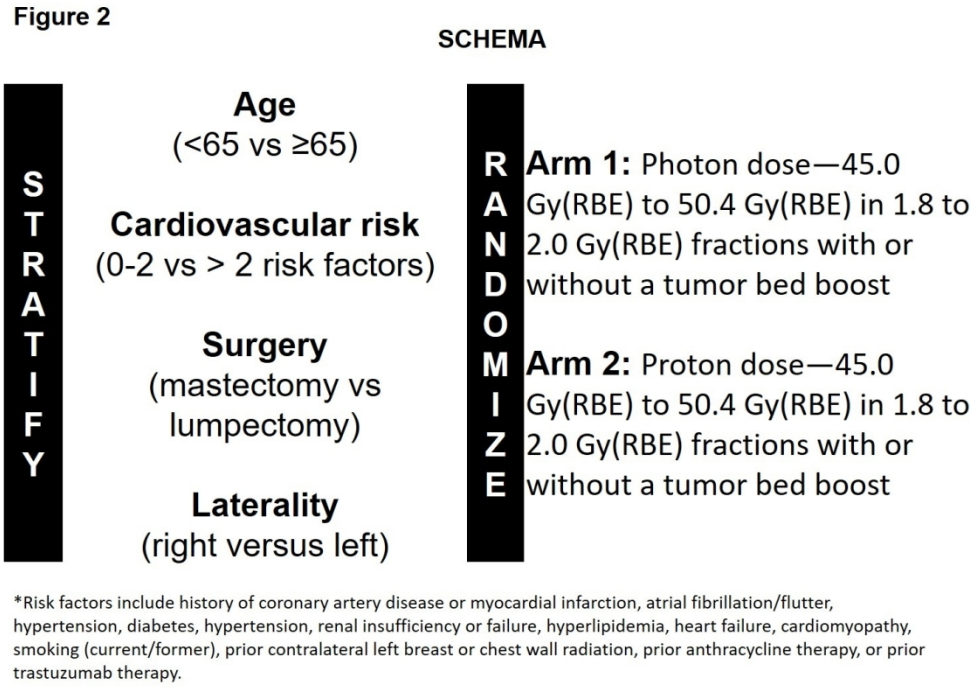

Figure 2. Study Stratification Schema

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