This is a multi-site clinical trial. The lead site, coordinating center, and regulatory sponsor for this study is Dana-Farber/Harvard Cancer Center (DF/HCC). The DF/HCC Protocol Number is #16-304.

TITLE Study of Radiation **F**ractionation on Patient Outcomes **A**fter **B**reast **REC**onstruction (FABREC) for Invasive Breast Carcinoma

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This study does **not** involve any INDs (investigational new drugs or devices).

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The EDC (electronic data capture) application being used for Case Report Forms (CRFs)/data submission is **InForm**.

This study is posted on www.ClinicalTrials.gov (NCT03422003).

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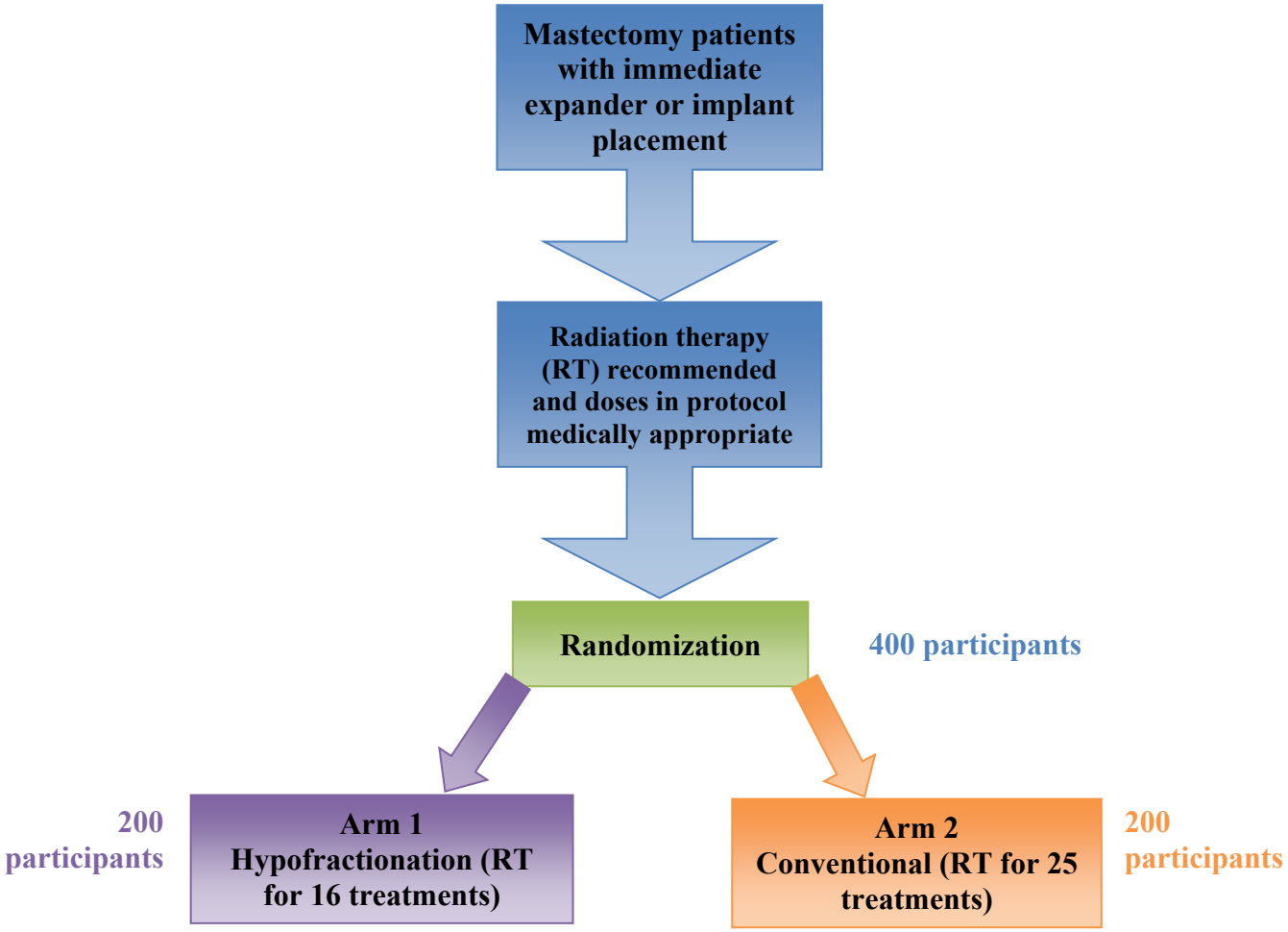

Mastectomy patients with immediate expander or implant placement
Radiation therapy (RT) recommended and doses in protocol medically appropriate
Randomization
400 participants
200 participants
Arm 1 Hypofractionation (RT for 16 treatments)
Arm 2 Conventional (RT for 25 treatments)
200 participants

1. INTRODUCTION

1.1 Study Overview

Almost 100,000 mastectomies are performed in the US to treat breast cancer each year.[1] Breast reconstruction represents a major advance in the care of breast cancer patients undergoing mastectomy and the use of immediate implant-based reconstruction is increasing.[2] However, many women with mastectomy are recommended to undergo radiation therapy to improve cancer outcomes.[3] Radiation therapy currently entails over five weeks of daily treatment and can compromise outcomes of breast reconstruction. An alternative three-week short-course radiation regimen (hypofractionation) may improve reconstruction outcomes and be equally effective. The decision regarding conventional versus short-course radiation therapy after mastectomy and immediate reconstruction is relevant to approximately 20,000 women annually. Currently no information exists to help inform the treatment choice between conventional (long-course) versus hypofractionation (short-course) radiation therapy in women with mastectomy and immediate reconstruction.

Impact of radiation therapy after mastectomy on health of individuals and populations:

Mastectomy, or removal of the entire breast, is a common treatment strategy for breast cancer. In 2015, an estimated 231,840 new cases of invasive breast cancer were expected to be diagnosed in women in the US, including 60,290 new cases of non-invasive (in situ) cancer.[4] Of these cases, almost 40 percent are treated with mastectomy.[5] Patients with multicentric (involving more than one quadrant of the breast) cancers, cancers not easily encompassed by limited surgery such that an unacceptable cosmetic outcome would result, or patients at elevated risk for a new or recurrent breast cancer typically opt for mastectomy. In recent years, there has been an increase in the frequency of mastectomy perhaps due in part to patient preference and the wish to minimize new future breast cancer risk.[1] Radiation therapy is indicated for almost one-third of patients who receive mastectomy.[3] After mastectomy, radiation is used to reduce the risk of breast cancer recurrence in the chest wall or regional lymph nodes. Radiation therapy has been established as standard treatment for patients with four or more positive (involved) axillary nodes, and there is increasing evidence that radiation improves outcomes in patients with one to three positive nodes. An update of the large meta-analysis of randomized trials showed a clear benefit to the use of post-mastectomy radiation therapy in patients with one to three positive axillary nodes, with respect to reducing local regional recurrence (recurrence in the breast area and nearby lymph nodes), overall recurrence, and deaths from breast cancer.[6] After mastectomy, the main areas at risk for local-regional recurrence (and therefore, targeted in the planned radiation) are the nodal basins (axillary, supraclavicular, internal mammary) depending on anatomy, pathology, and extent of axillary surgery. Radiation techniques have continued to evolve to minimize long-term side effects.

Breast reconstruction and radiation therapy after mastectomy:

The option to receive breast reconstruction is a major advance for women undergoing mastectomy. Breast reconstruction has been shown to improve emotional, psychological, and physical well-being of women treated with mastectomy.[7, 8] Patient satisfaction after breast reconstructive surgery has been shown to be improved as well.[9] Awareness of reconstruction as a routine issue to be addressed in the management of patients who require mastectomy [10, 11] and the use of implant-based reconstruction after mastectomy are increasing.[2]

Women who undergo mastectomy can receive immediate or delayed reconstruction. Breast reconstruction can begin at the time of mastectomy ("immediate") as opposed to a separate, later operation ("delayed"). The psychological benefit of immediate reconstruction is established, clearly favoring immediate over delayed.[12] Immediate reconstruction also affords the plastic surgeon the opportunity to utilize more original breast skin, which may improve the ultimate cosmetic outcome. Delayed reconstruction may be preferable in settings where there is high-risk disease that requires an uncomplicated postoperative course in order to plan post-mastectomy radiation therapy, or if the technique and dose aspects of radiation are optimized by the absence of a reconstruction. The two main types of breast reconstruction are implant-based or autologous (patient tissue-based). Implant-based reconstruction typically consists of a tissue expander, which is a temporary, inflatable device placed under the pectoralis major muscle, that has a port or opening that permits the plastic surgeon to sequentially (over weeks to months) instill saline solution to create a breast mound. This process allows the body and skin to gradually adjust to the size of an implant. The tissue expander is eventually replaced with a permanent implant. Alternatively, in selected cases where the anatomy permits, a permanent implant may be placed directly under muscle and skin at the time of mastectomy. Implants are not expected to last a lifetime and may need to be replaced every 10-15 years.

Autologous tissue reconstruction utilizes a muscle-skin combination from another site (e.g., abdomen, back, buttock) or in some settings, can be performed without compromising muscle (using abdominal tissue anterior to the muscle). If post-mastectomy radiation therapy is delivered to an unreconstructed chest wall, delayed implant reconstruction usually is not possible or advisable given the long-term effects of radiation (tightness, scar tissue) on the chest wall and the accompanying inability to place a tissue expander or permanent implant under the irradiated pectoralis muscle and chest wall skin. There has been an increase in immediate implant-based reconstruction in recent years, particularly in patients who may require post-mastectomy radiation therapy. This trend is likely due in part to the ease of planning this type of surgery (shorter operative time, shorter recovery time). Moreover, immediate reconstruction allows for an implant option if radiation therapy will be delivered, as implant-based reconstruction is typically only possible prior to radiation—when the tissues of the chest wall are still pliable.

The combination of post-mastectomy radiation therapy and reconstruction is challenging. Radiation therapy can compromise the cosmetic outcome of the reconstruction and increase complications.[13,14,15] Radiation is associated with an increased likelihood of forming scar tissue around the implant, resulting in long-term problems with increased hardness, suboptimal positioning (the implant can migrate on the chest wall), and the need to remove or replace the implant. There is also an increased risk of complications such as delayed healing and infection (sometimes requiring permanent removal of the implant). Women have reported less satisfaction with reconstruction in the setting of radiation therapy (versus no radiation).[16]

Patient and treatment characteristics have been evaluated in attempts to discern which may contribute to higher risk of complications or poor cosmetic outcomes. Factors described as being associated with poorer outcomes include age, medical conditions (e.g., smoking, high blood pressure, diabetes, body mass index), weight of breast specimen, and scar location.[17-19] There is no agreement upon whether it is preferable to irradiate a tissue expander or a permanent implant.

Cordeiro et al. recently reported that six-year reconstruction failure rates were higher for irradiated tissue expanders compared to permanent implants, but initial tissue expander placement was associated with a higher proportion of good-to-excellent cosmetic results compared to an initial permanent implant.[20]

Modification of the conventional radiation schedule may yield improved outcomes:
Hypofractionation, or short-course radiation therapy, reduces the number of radiation treatments and the overall treatment length, increasing patient convenience. This regimen has been shown in randomized trials (e.g., the START-B trial), largely in the breast-conservation setting, to reduce acute radiation therapy side-effects, decrease fatigue at six months and improve cosmetic results.[21,22] A large randomized study from Canada showed a hypofractionated regimen to be safe and effective in early-stage breast cancer.[23] Despite these results, adoption of hypofractionation was initially sluggish in the breast-conserving therapy setting [24,25] likely due to a preference for the familiarity and experience with conventional long-course radiation therapy. Of note, patients receiving care in community practice are less likely to receive hypofractionation[26] perhaps due to increased financial incentives to treat with longer-course radiation therapy. The majority of patients in the START-B trial, and all of the patients in the Canadian trial, were treated solely to the whole breast, without a separate radiation field to treat lymph nodes. In the post-mastectomy setting, patients routinely have lymph node radiation. Some of the radiation side effects associated with this separate lymph node field include lymphedema (potentially related to the extent of surgery), and, much less likely, radiation pneumonitis (inflammation of the lung due to radiation—typically temporary and treatable), and, extremely rarely, brachial plexopathy (injury to the nerves that supply the arm). Long term data following hypofractionation to the lymph nodes have not revealed an increased risk of brachial plexopathy.[27] While hypofractionation is used commonly in the UK in the post-mastectomy setting, there are no randomized studies specifically studying outcomes following its use in women who undergo breast reconstruction. Therefore, there is an even greater barrier to the use of hypofractionation in this setting in the US. With improved cosmetic results found with hypofractionation in the breast conservation setting, this shorter regimen may have the potential to improve reconstruction success rates (which are modest overall) for patients who require post-mastectomy radiation. In addition, given the financial repercussions of a reduced number of radiation treatments, high-quality, Level I randomized evidence is needed in this population to change practice patterns regarding the radiation regimen.

Gaps in Evidence:
Mastectomy, immediate implant-based reconstruction, and radiation therapy constitute a common treatment paradigm. There are conflicting data on the treatment outcomes with respect to quality of life (QoL), cosmetic results, and complications. Variability in treatment technique (surgery and radiation) contributes to the uncertainty, and in the absence of prospective data with specified treatment protocols and rigorous evaluation of outcomes, this uncertainty is likely to continue. Hypofractionated radiation has been studied well in breast-conserving therapy, with equivalent efficacy in preventing cancer recurrence, and a possible benefit in cosmetic outcome, when compared to conventional, longer- course radiation. There are limited data on its use in the post-mastectomy setting and with nodal irradiation.

1.2 Rationale

Over 180,000 diagnoses of invasive breast cancer are made in the US each year. Over one-third of women with early stage and over half with late-stage breast cancer are treated with mastectomy (removal of the entire breast) due to tumor size, multiple cancers within the breast, genetic cancer predisposition, and/or patient preference. Following treatment with mastectomy, women who receive breast reconstructive surgery may experience better quality of life as they do not have to leave surgery with a bare chest wall. However, large randomized trials of post-mastectomy radiation therapy reveal a survival benefit with the addition of radiation after mastectomy in women who have cancer present in the axillary lymph nodes.[6] The delivery of radiation therapy in the presence of a breast reconstruction is challenging and often leads to undesirable consequences including reconstruction loss, need for major surgical revision, or poor cosmetic outcomes. Therefore, oncologists and patients are forced to decide between the potential for improved oncologic outcomes with radiation therapy versus increased likelihood of complications and suboptimal cosmetic results. Because of this, some patients may be foregoing reconstruction if radiation therapy after mastectomy is needed; or foregoing radiation therapy if they have had breast reconstructive surgery.[28]

Hypofractionation enhances patient convenience and decreases treatment burden. This regimen has been shown in randomized trials largely in the breast-conservation setting to reduce acute radiation therapy side-effects, decrease fatigue at six months and improve cosmetic results.[21, 22] Despite these results, adoption of hypofractionation has been slow among women with breast cancer treated with breast-conserving surgery[24, 25] likely due to familiarity and experience of conventional long-course radiation therapy. While hypofractionation is used commonly in the UK for patients with mastectomy, there are no randomized studies particularly studying outcomes following shorter course radiation therapy in women who undergo mastectomy with breast reconstruction. Therefore, there is an even greater barrier to the use of hypofractionation in this setting in the US. With improved cosmetic results found with hypofractionation, this shorter regimen may have the potential to improve reconstruction success rates which are unfortunately modest overall, for patients who require post-mastectomy radiation. Especially in contrast to financial disincentives to reduce number of radiation treatments, Level I randomized evidence is needed in this population to change practice patterns regarding radiation regimen.

Patient-centeredness:

Our study of radiation fractionation regimens has the potential to increase use of hypofractionation among women treated with mastectomy, thereby decreasing treatment burden. Our team of patient stakeholders ensures that our outcomes measures encompass all domains of survivorship after breast cancer (physical and mental health as well as satisfaction with the decision-making process). Despite the large numbers of breast cancer survivors who undergo mastectomy, reconstruction and radiation therapy, little is known about which domains of quality of life are affected and their importance to these patients. This study uses previously validated tools for measuring patient outcomes, and have added questions for areas which are important to patients that may not have been captured adequately by previous tools. In concert with the increasing awareness of the importance of survivorship care to cancer care, identifying a comprehensive set of outcomes measurement tools following treatment with radiation therapy, mastectomy, and reconstruction is an important asset for future treatment evaluation in these women. In summary, the proposed pragmatic trial is *highly significant* because:

1. A critical knowledge gap exists for a common medical condition in a well-defined population
2. Patients and/or their physicians may be foregoing radiation to preserve the cosmetic results of reconstruction
3. Clinicians are unsure whether to adopt hypofractionation or continue with the familiar but problematic conventional treatment
4. Hypofractionation has the potential to improve outcomes following breast reconstruction
5. Hypofractionation decreases treatment burden for patients with fewer radiation treatments
6. There are no randomized studies specifically evaluating hypofractionation after mastectomy and reconstruction
7. The trial is being conducted in diverse settings including community oncology practices
8. Engaged patient partners will help disseminate findings
9. The trial will examine outcomes that matter to patients including the QoL and cosmetic results
10. The trial will have long-term implications for improving and measuring the QoL of breast cancer survivors and will enhance the increasingly important field of survivorship research.

2. OBJECTIVES

2.1 Study Design

The FABREC study is a pragmatic randomized trial of hypofractionation versus conventional radiation therapy in women who have undergone mastectomy and immediate breast reconstruction.

The trial will be conducted at academic and community practice sites to ensure a diverse and representative patient population. Study participants will be randomized 1:1 to conventional fractionation or hypofractionation after mastectomy and breast reconstruction with a tissue expander or implant.

All participants will be assessed for cosmetic and reconstruction outcomes, lymphedema and cancer status through month 18. During the 10-year follow-up period, participants will be assessed for oncologic outcomes (local recurrence, distant disease, and survival) and side effects. Surveys will be used to ask participants to report pain, appearance, mobility, and self-image.

2.2 Objectives

Objective 1: Compare the effect of short-course versus long-course post-mastectomy radiation therapy on highly-relevant patient-reported outcomes (PROs) and outcomes prioritized by individual trial participants.

Our primary outcome is the Physical Well Being (PWB) domain of the FACT-B instrument. PRO assessment will be further patient-focused, as we will also ask each subject to choose the FACT-B subdomain most relevant to their experience and separately correlate this domain to that patient's radiation schedule. We will thereby create a more

patient-centered outcome by comparing short- versus long-course radiation according to the subscale selected to be most important to the individual patient. In addition, we will assess pain, arm mobility, lymphedema, self-image, satisfaction with decision to undergo reconstruction, sexual well-being, functional well-being, and treatment burden in all patients using standard instruments.

Hypothesis: Short-course radiation therapy will improve patient quality of life in multiple domains.

Objective 2: Compare clinical outcomes for patients receiving short-course versus long-course radiation.

These include complications and clinically-assessed cosmetic results. We will also create an infrastructure to monitor long term oncologic outcomes such as recurrence and breast-cancer specific survival, and rare radiation side effects (secondary malignancy and brachial plexopathy).

Hypothesis: Short-course radiation therapy will decrease complications, improve clinician-quantified cosmetic results, and will have no increased risk of local or regional recurrence or side-effects.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

1. Diagnosed with clinical or pathologic stage 0-III invasive breast cancer with Tis, TX, or T1-T3 tumor
2. Has been treated with mastectomy
3. Has undergone immediate reconstructive surgery with placement of a tissue expander or permanent implant at time of mastectomy
4. Is a candidate for unilateral post-mastectomy radiation therapy as per local, institutional practice (post-mastectomy radiation therapy is indicated for most patients with positive lymph nodes at time of surgery and infrequently for selected node-negative patients)
5. Use of bolus is permitted, but not required
6. Age ≥18

3.2 Exclusion Criteria

1. T4 cancer
2. History of prior ipsilateral breast radiation therapy
3. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, and/or mental health illness that the consenting investigator feels would affect patient's ability to participate in this study
4. Pregnant or nursing
5. History of a different malignancy except for the following circumstances:
   - Either disease-free for at least five years **OR** deemed by the investigator to be at low risk for recurrence of that malignancy.

- Cervical cancer in situ and basal cell or squamous cell carcinoma of the skin

6. Breast cancer requiring bilateral breast/chest wall radiation therapy.

Notes about eligibility:

- If your site can accommodate consenting and orally administering questionnaires via translator to patients in languages other than English, then non-English speaking patients are eligible.
- Participants enrolled to the FABREC Trial may be enrolled to other treatment and/or non-treatment trials if the consenting investigator deems that there are no contraindications.
- Concurrent systemic therapy will be considered on a case-by-case basis. Please ask the study co-chairs about whether any systemic therapy may be administered concurrently with PMRT.
- A pregnancy test is not required per FABREC protocol.
- Microscopically positive surgical margins are permitted.
- Patients should only be enrolled in this study if the treating physician feels it is medically appropriate for the patient to receive the radiation therapy outlined in this protocol.
- Reconstruction will be considered immediate if it occurred:
  - At the time of mastectomy
    OR
  - Up to one month after mastectomy and before radiation treatment planning
- Patients who have stage 0 disease (ductal carcinoma in situ) may undergo radiation therapy after mastectomy to reduce the risk of recurrence, especially in the setting of positive/close margins and/or extensive involvement of the breast. As our purpose is to evaluate patient outcomes after mastectomy and immediate reconstruction, we seek to include patients with stage 0 disease who are receiving radiation in this setting.

3.3 Inclusion of Women and Minorities

Women of any race/ethnicity are eligible for this trial. Women who are pregnant or nursing are excluded from this trial.

4. PRETREATMENT EVALUATIONS/MANAGEMENT

It is necessary to delay enrollment until after mastectomy and reconstruction because a large percentage of patients will not meet the criteria for radiation therapy (and, therefore, for the study) once the pathology results from the mastectomy become available.

5. REGISTRATION AND RANDOMIZATION PROCEDURES

5.1 Registration Process for all sites

This section applies to DF/HCC Institutions (Dana-Farber/Harvard Cancer Center) and all other investigative sites.

To register a participant on the FABREC Trial, please follow these steps:

- Each participating site should identify eligible participants at their site.
- The consenting investigator should approach the patient and hold an informed consent discussion.

- If the potential participant agrees to participate, the consenting investigator and the patient should both sign the Informed Consent document.
- The study staff should then send the following documents to the Central Study Coordinator (CSC) via secure email to FABREC_Study@dfci.harvard.edu or via fax to 617-582-7450 (be sure to write ATTENTION: FABREC Central Study Coordinator on your fax cover sheet).
    1. Signed Informed Consent Form (all pages)
    2. Signed HIPAA authorization form (if applicable: At some sites the HIPAA authorization form and the informed consent document are two separate documents. At other sites, the HIPAA authorization form is contained within the informed consent document, so only the informed consent document need be submitted)
    3. Completed Eligibility Checklist
- The CSC will review the eligibility checklist to ensure that all fields are complete and that all values are within the acceptable range allowed by the protocol. If any information is missing, the CSC will contact the site.
- Next the CSC will work with the Dana-Farber Office of Data Quality (ODQ) to register and randomize the participant.
- Within 24 business hours*, the CSC will email the following information to the site:
    1. Confirmation that the participant has been successfully registered
    2. The participant's unique study ID number
    3. The arm to which the participant was randomized

*Business hours for this study are defined as: Monday through Friday from 8:00 AM to 5:00 PM Eastern Time, not including holidays.

If you need expedited assistance during normal business hours (Eastern Standard Time), please contact the FABREC Central Study Coordinator at 617-582-8484 or FABREC_Study@dfci.harvard.edu.

5.2 Study Enrollment Timing

REGISTRATION: Participant must be registered and randomized before protocol treatment (PMRT) begins.

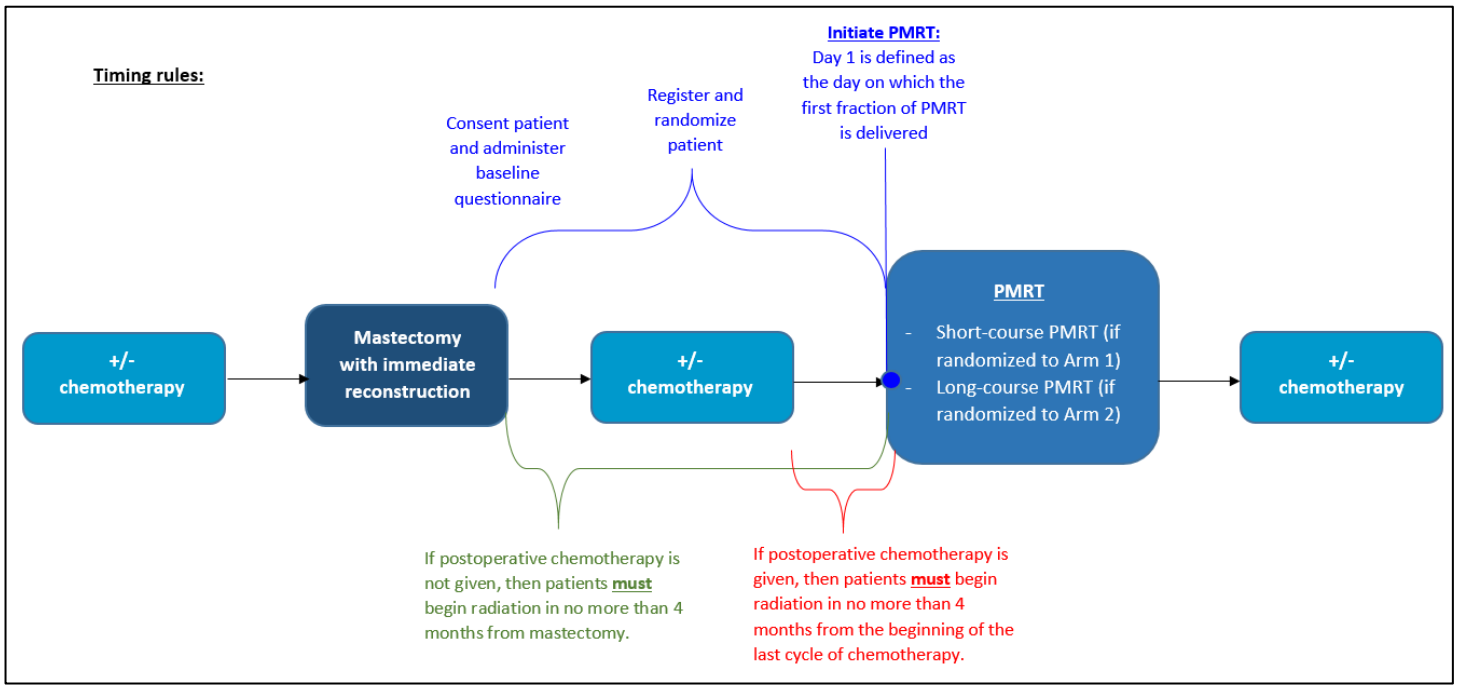
BASELINE PATIENT QUESTIONNAIRE: The baseline questionnaire can be administered to the patient immediately following signed consent (**recommended**). The baseline questionnaire must be completed by the participant after she signs informed consent but before PMRT begins.

TREATMENT: Protocol treatment (PMRT) must begin <=4-months after randomization. Issues that would cause treatment delays should be discussed with the Study Chairs. Permission to deviate from DF/HCC SOP REGIST-101A has been approved and is documented in OnCore.

The rationale for allowing <=4 months between randomization and start of PMRT is that there are a lot of treatment-related activities that must occur between Arm Assignment and PMRT

Initiation including: chemotherapy must be completed (as/if applicable); sequential inflations of the tissue expander need to be completed (as/if applicable); simulation must be performed locally at the treating site; the physics plan must be generated and approved locally at the treating site; and treatment verification films need to be approved locally at the treating site.
Note: the sponsor does not need to pre-approve your PMRT plan.

Information about PMRT treatment planning will be collected via Medical Record Review CRFs. The PMRT Treatment Plan for a patient does **not** need to be submitted prior to initiation of PMRT; this will reduce study burden on sites and clinicians.



Note: Concurrent systemic therapy will be considered on a case-by-case basis. Please ask the study co-chairs about whether any systemic therapy may be administered concurrently with PMRT.

5.3 Stratification Factors and Treatment Assignment

400 patients will be randomized 1:1 into either Arm 1 (short-course PMRT) or Arm 2 (long-course PMRT).

Randomization will be stratified by treatment center and age of the patient (<45 vs. ≥45).

6. RADIATION THERAPY

6.1 Radiation therapy schedule

Radiation therapy will be delivered to all intended fields, once daily, excluding holidays, weekends, and unavoidable factors limiting machine or patient availability.

Conventional fractionation: 25 fractions of radiation therapy (daily, Monday through Friday) to the chest wall with or without internal mammary nodes, and 23-25 fractions to the supraclavicular (with or without axillary) lymph nodes. Each fraction will consist of 200 cGy per day. Total dose = 5000 cGy to the chest wall and 4600-5000 cGy to the lymph nodes.

Hypofractionation: 16 fractions of radiation therapy (daily, Monday through Friday) to the chest wall with or without internal mammary nodes, and 15 fractions to the supraclavicular (with or without axillary) lymph nodes. Each fraction consists of 266 cGy per day. Total dose = 4256 cGy to the chest wall and 3990 cGy to the lymph nodes.

6.2 Radiation technical factors

- Radiation will be delivered with megavoltage (MV) equipment at energies of 6MV or higher.
- Protons are not permitted.
- Bolus to the mastectomy scar or chest wall will be prescribed at the discretion of the treating physician.
- No boost dose to the scar or other areas of the reconstructed chest wall is permitted.
- No deflation or expansion of tissue expander(s) should occur between simulation and radiation treatment completion.

6.3 Radiation simulation

Simulation will be CT-based. Patients will be positioned supine on the planning table in a customized immobilization device as per institutional protocol. Techniques to limit radiation dose to the heart, such as deep inspiration breath hold (DIBH) or gating are encouraged.

6.4 Treatment planning

The target volume will be the chest wall, tissue expander (or implant), and any associated nodal stations as per physician discretion. Delineation of these volumes will be as per institutional protocol. Per FABREC Trial protocol, microscopically positive margins are permitted. Per FABREC Trial protocol, giving PMRT solely for margins and not to treat nodes is permitted.

Lung and heart volumes will be limited as per institutional protocol. Maximum separation will be recorded. Location of mastectomy incision will be recorded.

Inhomogeneity will be limited to 110% in the chest wall, recording volume above 107%. Efforts will be made to strive for a maximum of 107% in hypofractionated cases (110% permitted). Inhomogeneity in the supraclavicular (+/-axillary) field will be limited to 110%. 3D-conformal RT or IMRT are permitted. There is no specified maximum dose on the composite plan. The composite plan may exceed 110%. Individual plans for the chest wall or lymph nodes must not exceed 110% inhomogeneity.

6.5 Treatment verification

For 3D-CRT and IMRT, quality assurance filming should be done per local, institutional protocol and does not need to be submitted to the sponsor. Dose distribution images and treatment planning fields should be kept by the treating institution for review by the sponsor, if

needed.

6.6 Compliance criteria

If inhomogeneity constraints are not attainable in the hypofractionated setting, the patient will be treated with standard fractionation as per protocol. Switching arms in this case is permitted, and these participants who switch arms will still be asked to complete all patient questionnaires and will be followed for 10 years. If the site plans to have a participant switch arms, the site must submit the Change in Study Status CRF via InForm 2 business days **prior** to the switch which will give the Study Chairs time to pre-approve the switch. Sites will be notified via email if approved.

6.7 Radiation quality assurance review

The Study Chairs will oversee quality assurance reviews for all participants treated on protocol. RT quality assurance review will be ongoing and performed remotely. RT quality assurance reviews will be facilitated by the study chairs and the study staff. The CSC will obtain the radiation therapy data from the Inform database for the Study Chairs to review and assess.

6.8 Radiation adverse events and reporting

All participants will be seen weekly, according to their treatment plan, by an attending radiation oncologist while undergoing treatment. Side effects will be recorded and managed using clinical discretion. For information about adverse events, see Adverse Event Reporting section of protocol. Details on the adverse event reporting can be found in the AE section of the protocol.

6.9 RT Modifications

Treatment breaks should be kept to a minimum but do not constitute protocol violations.

Changes in RT dose will constitute major protocol violations.

6.10 Supportive Care

Supportive care is permitted and is at the discretion of the treating investigator.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial.

Summary of how to collect and report adverse events (AEs) for the FABREC trial:

1. **Standard Care** All patients will be seen per their treatment plan by an attending radiation oncologist while undergoing treatment. ***All adverse events*** should be recorded in the patient's medical record per standard practice at your site and managed using clinical discretion. On the Medical Record Review CRFs for the FABREC Study, Clinical Research Professionals (CRPs) will be asked to report AEs as documented in the patients' charts; these medical record reviews will be done at pre-specified timepoints.

2. **Routine Solicited Adverse Events** will not be collected for the FABREC Trial.

3. **Reportable Serious Adverse Events** should be reported using the FABREC Serious Adverse Event CRF each time a reportable SAE occurs. These CRFs should be submitted using InForm. For a list of reportable SAEs, see below.

7.1 Routine Adverse Events

Routine Adverse Events will not be collected for the FABREC Trial. **Only events outlined in Section 7.2 should be reported via InForm.**

7.2 Reportable Serious Adverse Events

Reportable Serious Adverse Events that occur at any time between initiation of PMRT and 3-years after the initiation of PMRT must be reported using the FABREC Serious Adverse Event CRF. In general, the CRF should be submitted via InForm within 5 calendar days of the AE date. When an adverse event occurs at an institution outside the enrolling site, there may be a delay between when an adverse event occurs and when the study team is alerted to the event. In these instances, it is acceptable for the study team to submit those adverse events in InForm within 5 calendar days of being notified about the event and will not incur a violation.

Only "reportable SAEs" require reporting. For the FABREC trial, a reportable SAE is defined as:

- Grade 1, 2, or 3 **brachial plexopathy** (per NCI CTCAE v 4.03, this AE does not have grade 4 or 5)
- Grade 3 **chest wall pain** (per NCI CTCAE v 4.03, this AE does not have grade 4 or 5)
- Grade 3 **lymphedema** (per NCI CTCAE v 4.03, this AE does not have grade 4 or 5)
- Grade 3, 4, or 5 **myocardial infarction**
- Grade 1, 2, 3, 4, or 5 **pneumonitis**

- Grade 3, 4, or 5 **treatment related secondary malignancy**
- Grade 3, 4, or 5 **wound infection**
- Unexpected grade 3 or 4 with a possible, probable or definite attribution to PMRT
- Grade 5 (death); all deaths on study require expedited reporting regardless of attribution or causality.
- Local/regional recurrence (not in NCI CTCAE v4)
    - **Note:** We are only interested in following participants who experience local/regional recurrences. When participants experience distant recurrences, they should be withdrawn from the study and all follow-up should be discontinued as these patients may not be monitored for local/regional recurrences due to distant disease.

NCI CTCAE v4 can be downloaded from
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Only the events listed above need to be reported in InForm. Events that fall outside the list above do not need to be reported in InForm.

7.3 Submission of SAEs to IRB(s)

The Study chairs will submit all applicable SAEs from both Dana-Farber/Harvard Cancer Center sites and outside institutions to the Dana-Farber Cancer Institute IRB per the DFCI IRB Adverse Event Reporting Policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

7.4 AE Data Collection and Definitions

AE, date of event, grade, attribution, and relation to an underlying disease or condition will be collected for each AE and SAE.

Grade:

- Grade 1 - Mild AE
- Grade 2 - Moderate AE
- Grade 3 - Severe AE
- Grade 4 - Life-threatening or disabling AE
- Grade 5 - Death related to AE

Attribution:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Study treatment = PMRT

7.5 Expected Adverse Reactions

Radiation is associated with an increased likelihood of:

- Forming scar tissue around the implant, resulting in long-term problems with increased hardness
- Suboptimal positioning (the implant can migrate on the chest wall) with a need to remove or replace the implant
- Increased risk delayed healing and infection (sometimes requiring removal of the implant)
- Reddening or tanning of the skin
- Desquamation in the treatment field
- Mild pain
- Thickening of the skin

Some radiation side effects associated with lymph node radiation include:

- Lymphedema (potentially related to the extent of surgery)

8. SCHEDULE OF ASSESSMENTS

	Prior to Enrollment (Screening)	**Baseline** (After participant signs informed consent)	**During Radiation Therapy** (both arms)	**30 Days after RT completion**	**6 mos.** +/- 4 weeks after RT initiation	**12 mos.** +/- 4 weeks after RT initiation	**18 mos.** +/- 4 weeks after RT initiation	**Every year for 10 years** after RT initiation
Medical chart review	X	X		X		X		X
SAE Reporting			Reportable SAEs that occur at any time between initiation of PMRT and 3-years after the initiation of PMRT must be submitted via InForm (see AE section).					
Radiation Treatment Information				X				
Photo Evaluation		X			X	X	X	
Participant Questionnaires		X			X	X	X	
Annual Follow-Up								X

Medical Chart Review. Medical Record Review CRFs will collect data on sociodemographic information, social history, cancer diagnoses, co-morbidities, treatment details, radiation treatment, surgical history and follow up, toxicities, medical history and follow up, disease recurrence, significant clinical events, and mortality.

Study Visits. Because this is a pragmatic trial, there are no protocol mandated study visits. All clinic visits are per standard of care.

Solicited AEs and Expedited SAE Reporting. See Adverse Event Reporting section of protocol for full details.

Radiation Treatment Information. Sites will enter specific information related to the radiation treatment received. This information will be collected by reviewing participants' medical charts at the end of treatment.

Photo evaluation. In order to assess reconstruction, de-identified photos of participant reconstruction will be submitted for evaluation by the Study Chairs or delegate. The participant may take and submit the reconstruction photographs herself (see appendix for patient-facing instructions on how to take and submit reconstruction photographs), or any clinician (nurse, doctor, etc.) who has been trained on the FABREC protocol may take reconstruction photographs.

In extremely rare cases where submission of photographs is not possible, the study chairs will work with the site investigator to complete the Cosmetic Outcome CRFs.

Participant Questionnaires. The following contain items from the following instruments:

- **FACT-B version 4 - Quality of Life** - includes modules for assessing physical well-being, emotional well-being, social well-being, functional well-being and a 2-item question characterizing a breast cancer patient's relationship with her physician. Descriptive statistics for FACT-B have been well characterized.[33,34]
- **BREAST-Q post-operative, reconstruction module** - Satisfaction with Breast Surgery Outcome - tool was developed at Memorial Sloan Kettering Cancer Center and includes questions regarding changes on the appearance and feel of the reconstruction after radiation therapy.[35, 36] Domains covered by the reconstruction module include satisfaction with breast, satisfaction with outcome, psychosocial well-being, sexual well-being, and chest and upper body physical well-being.
- **Lymph-ICF** - Questions regarding lymphedema, selected from the Lymphedema Functioning, Disability and Health Questionnaire.[42, 43]
- **Measures of treatment burden** - These questions have been adapted from Kent et al. and the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) caregiver survey.[44, 45, 46] The measures of treatment burden will only be administered at the 6-month time-point.
- **Sociodemographics** and **social/medical history**.

Change in Study Status. Whenever there is a change in a participant's status on the study including the development of a distant recurrence or metastatic disease, the Change in Study Status CRF should be completed and submitted via InForm within 5 business days of the change.

Reasons a participant might have a change in study status include:

- **ACTIVE PARTICIPANT WITHDRAWAL:** Study participant actively withdrew consent for one or more components of the study, including:

a. protocol treatment (PMRT), and/or
b. participant contact for questionnaires and follow up, and/or
c. access to his/her medical record for Medical Record Abstraction.

HOW TO PROCEED: Unless the participant explicitly (in writing) withdraws consent to access his/her medical record, site study staff SHOULD complete all Medical Record Abstraction CRFs and all Follow-up CRFs through the end of the 10-year follow up period.

- **CLINICIAN WITHDRAWAL:** Clinician took participant off protocol treatment (PMRT). Please note that after taking a subject off protocol treatment, study questionnaires and follow-up CONTINUE through the 10-year follow up period. Site study staff should complete all Medical Record Abstraction CRFs and Follow-up CRFs.

- **DEATH:** If a study participant dies, the site staff should complete all Medical Record Abstraction CRFs through death. After all data has been collected through death, sites may take participant off study by submitting the Off-Study CRF via InForm.

- **FOUND TO BE INELIGIBLE:** Participant was enrolled on the trial but was later found to be ineligible. Select one:
  a. Yes, protocol treatment (PMRT) will continue [treating physician and study chairs agree there are no safety concerns if the patient continues protocol treatment].
  b. No, protocol treatment will not continue [in this case, study questionnaires and follow up should continue through the 10 year follow up period. Site study staff should complete all Medical Record Abstraction CRFs no matter how long the subject actually received protocol treatment].

- **SWITCHED ARMS:** If inhomogeneity constraints are not attainable in the hypofractionated setting, the patient will be treated with standard fractionation as per protocol. Switching arms in this case is permitted, and these participants who switch arms will still be asked to complete all patient questionnaires and will be followed for 10 years

- **OTHER:** Please specify.
  - **Note:** If a participant experiences a distant recurrence, they should be withdrawn from the study by selecting this option in InForm. Once participants are withdrawn from the study due to distant recurrence, all follow-up should be discontinued.

Annual Follow-Up Form/Event Monitoring. Participants will be followed for 10-years for long-term outcomes including recurrence, new malignancy, and survival. "Annual follow up 1 of 10" is defined as 1-year after the date on which the participant initiated PMRT. "Annual follow up 2 of 10" is defined as 2-years after the date on which the participant initiated PMRT, and so on through "Annual follow up 10 of 10". For each annual follow up, if the site has lost track of the participant, then the CSC may send participants the Annual Follow-up Questions sheet (see **Appendix D**) about recent infections, surgeries, and cancer-related issues. Once the CSC receives the completed question sheet, s/he may call participants to follow up on recurrence

and new malignancies. A script for these calls can also be found in **Appendix D.**

8.1 Administration of Patient Questionnaires

Each participant can choose to complete each questionnaire in writing or orally. Each participant can choose to return his/her questionnaire responses in-person, via postal mail, by phone, scanning and emailing, faxing, or texting (participants may text photographs of the completed questionnaire pages).

The enrolling site staff will be responsible for administering the Baseline Questionnaire to the participant. The Baseline Questionnaire must be administered after the participant has signed informed consent but before protocol treatment begins. It is operationally easiest to administer the Baseline Questionnaire immediately after the participant signs informed consent.

The Central Study Coordinator will administer the Follow-up Questionnaires to participants. In the consent form that patients sign, it is clearly stated that the patient's contact information will be shared with the Central Study Coordinator who sits at Dana-Farber Cancer Institute in Boston, MA for the purposes of questionnaire administration and gift card distribution. A participant will be contacted by the Central Study Coordinator up to five times per timepoint in an attempt to complete each patient study questionnaire. The CSC may contact the participant via email, text message (texts will only be used if participant explicitly responds on their baseline questionnaire that we may contact them via text message), in-person, phone, or postal mail, as appropriate. The participant may return their survey via email, in-person, phone, orally, written, fax, or text message, based on patient preference. If a participant does not respond after five attempts, then the Central Study Coordinator will ask the enrolling site's staff to attempt contact before the survey deadline. If the enrolling site's staff is unable to make contact after three attempts, then the questionnaire will be marked as missing and the participant will not be contacted regarding that questionnaire again.

9. DATA COLLECTION AND SUBMISSION

No research biospecimens will be collected as part of this study.

Data will be collected via medical record reviews, CRFs, patient surveys, and photographs of reconstruction taken by the clinician or by the participants themselves.

The EDC (electronic data capture) application being used for this study is **InForm**. To get access to InForm, please contact the Central Study Coordinator at FABREC_Study@dfci.harvard.edu. The CSC will assist you in getting an InForm weblink, a username & password, and will provide training on how to enter data for this study.

9.1 Summary of data collection and submission

Acronyms used in following table:
CRP = Clinical Research Professional (at enrolling site)
CSC = Central Study Coordinator (sits at lead site, Dana-Farber)

Timepoint	Data to be collected	Who's responsible? How to Collect & Submit data?
Enrollment (after participant signs informed consent but before protocol treatment begins)	➢ Eligibility checklist	**Site CRP** should: ➢ Fax or securely email the eligibility checklist, all pages of the signed informed consent form, and the HIPAA authorization form (if it is a separate document from the ICF) to the **CSC**. **CSC** will: ➢ Email site with participant's unique study ID and treatment arm randomization within 24 business hours. ➢ Enter Eligibility Checklist data into InForm
	➢ Baseline Patient Questionnaire	**Site CRP** should: ➢ Administer questionnaire to patient ➢ Submit patient responses via InForm ➢ Keep paper original at your site **CSC** will: ➢ Send participant $50 gift card upon receipt
Baseline (after enrollment but before protocol treatment begins)	➢ Baseline Medical Record Review CRF	**Site CRP** should: ➢ Submit electronically via InForm
	➢ Reconstruction photographs	**Patient or Clinician** should: ➢ Take reconstruction photographs **Patient or Clinician or Site CRP** should: ➢ Send photographs to CSC electronically via secure file transfer protocol (FTP). Contact the CSC for detailed FTP instructions.
	➢ Cosmetic Outcomes CRF	**Study Chair (or delegate)** will: ➢ Evaluate photos ➢ Submit the Cosmetic Outcomes CRF via InForm
<= 30-days after PMRT ends	➢ Off Treatment CRF	**Site CRP** should: ➢ Submit electronically via InForm
Ongoing from initiation of PMRT through 3-years after date of PMRT initiation	➢ Serious Adverse Event (SAE) Reporting CRF	**Site CRP** should: ➢ Enter SAE into InForm ONLY when a reportable event occurs ➢ Submit within 5 calendar days of start of SAE ➢ For a list of "reportable SAEs," see the AE section of protocol.
6-months (defined as 6-months after initiation of PMRT)	➢ 6-month Patient Questionnaire	**CSC** should: ➢ Administer patient questionnaire ➢ Enter patient responses into InForm ➢ Send participant $50 gift card
	➢ Reconstruction photographs	**Patient or Clinician** should: ➢ Take reconstruction photographs **Patient or Clinician or Site CRP** should: ➢ Send photographs to CSC electronically via secure file transfer protocol (FTP). Contact the CSC for detailed FTP instructions.
	➢ Cosmetic Outcomes CRF	**Study Chair (or delegate)** will: ➢ Evaluate photos ➢ Submit the Cosmetic Outcomes CRF via InForm

Table continued on next page.

Acronyms used in following table:
CRP = Clinical Research Professional (at enrolling site)
CSC = Central Study Coordinator (sits at lead site, Dana-Farber)

Timepoint	Data to be collected	Who's responsible? How to Collect & Submit data?
12-months^ (defined as 12-months after initiation of PMRT)	➢ 12-month Patient Questionnaire	**CSC** should: ➢ Administer patient questionnaire ➢ Enter patient responses into InForm ➢ Send participant $50 gift card
	➢ Reconstruction photographs	**Patient or Clinician** should: ➢ Take reconstruction photographs **Patient or Clinician or Site CRP** should: ➢ Send photographs to CSC electronically via secure file transfer protocol (FTP). Contact the CSC for detailed FTP instructions.
	➢ Cosmetic Outcomes CRF	**Study Chair (or delegate)** will: ➢ Evaluate photos ➢ Submit the Cosmetic Outcomes CRF via InForm
18-months (defined as 18-months after initiation of PMRT)	➢ 18-month Patient Questionnaire	**CSC** should: ➢ Administer patient questionnaire ➢ Enter patient responses into InForm ➢ Send participant $50 gift card
	➢ Reconstruction photographs	**Patient or Clinician** should: ➢ Take reconstruction photographs **Patient or Clinician or Site CRP** should: ➢ Send photographs to CSC electronically via secure file transfer protocol (FTP). Contact the CSC for detailed FTP instructions.
	➢ Cosmetic Outcomes CRF	**Study Chair (or delegate)** will: ➢ Evaluate photos ➢ Submit the Cosmetic Outcomes CRF via InForm
Annual Follow up 1 of 10^ (defined as 1-year after initiation of PMRT)	➢ Follow-up Medical Record Review CRF	**Site CRP** should: ➢ Submit electronically via InForm If no follow up data available in medical record, CSC may mail patient brief set of questions and/or call patient for follow up.
Annual Follow up 2 of 10 (defined as 2-years after initiation of PMRT)	➢ Follow-up Medical Record Review CRF	**Site CRP** should: ➢ Submit electronically via InForm If no follow up data available in medical record, CSC may mail patient brief set of questions and/or call patient for follow up.
At EACH: **Annual Follow up 3, 4, 5, 6, 7, 8, 9, and 10 of 10**	➢ Follow-up Medical Record Review CRF	**Site CRP** should: ➢ Submit electronically via InForm If no follow up data available in medical record, CSC may mail patient brief set of questions and/or call patient for follow up.
After "Annual Follow up 10 of 10"	➢ Off-study CRF	**Site CRP or CSC** should: ➢ Submit electronically via InForm
As needed, at any time from baseline through end of 10-year follow up period	➢ Change in Status CRF	**Site CRP or CSC** should: ➢ Submit electronically via InForm

^ The "12-months" timepoint (defined as 12-months after initiation of PMRT) and the "Annual Follow up 1 of 10" timepoint (defined as 1-year after initiation of PMRT) overlap, meaning that they both occur on the same date.

Note about missing forms:

- If any of the following forms are missing for a participant, then this would constitute a major protocol violation:
    - Eligibility checklist
    - Baseline Medical Record Review CRF
    - Solicited Adverse Event CRF
    - Cosmetic Outcomes CRF
    - Off Treatment CRF
    - Expedited Serious Adverse Event (SAE) Reporting CRF
    - Follow-up Medical Record Review CRF
    - Change in Status CRF

- The following questionnaires **are required**; however, if any of the following are missing for a participant despite best efforts by Central Study Coordinator and Site Staff to collect from participant, then this does not constitute a major or minor protocol violation:
    - Baseline Patient Questionnaire
    - 6-month Patient Questionnaire
    - 12-month Patient Questionnaire
    - 18-month Patient Questionnaire
    - Reconstruction photographs (at baseline, 6, 12, and 18 months)

10. STATISTICAL CONSIDERATIONS

10a. Accrual: Based on previous years' treatment records, we anticipate that there will be about 40-50 eligible patients per month across the multiple participating academic and community centers. The accrual rate of this study is expected to be about 22 patients per month. We expect conservatively (based on survey data) that 75% of the eligible patients (after confirmation of the need for radiation therapy) are willing to be randomized to either the long-course or short-course treatment. The accrual will be open until 400 patients are enrolled. Randomization will be stratified by treatment center and age of the patient (<45 vs. ≥ 45). We expect the proportion of patients in the younger cohort of the study sample to be 40%. The anticipated length of the accrual period is 21-27 months.

10b. Statistical analysis plan for patient-reported quality of life outcomes and power considerations

Quality of life (QoL) measurement and the primary endpoint: We will use an array of instruments to rigorously assess quality of life among study participants, such as the FACT-B scores, satisfaction with breast surgery outcomes (BREAST-Q), Lymph-ICF, and financial burden. We will record and report all reasons for dropout and which outcomes were not reported, and include this data in our final reports. FACT-B (version 4) specifically measures quality of life in breast cancer patients and includes modules for assessing physical well-being, emotional well-being, social well-being, functional well-being and a 2-item question characterizing a breast cancer patient's relationship with her physician. QoL will be assessed at baseline, 6 months, 12

months and 18 months. This data will allow peer reviewers and readers of our publications to assess the validity of our study.

To determine the primary endpoint among those measurement scales, we surveyed patients who had undergone radiation therapy after mastectomy and immediate reconstruction and found that the majority of chose **the Physical Well-Being (PWB) subscale of the FACT-B (version 4) to be the most important element of their quality of life, regardless of age** (data not shown, manuscript in preparation). Based on this result, we selected the FACT-B PWB score as the primary endpoint of this study. To adjust for QoL at baseline, we will compare change in PWB score (relative to each patient's pre-radiation score) between the short and long-course treatment groups, instead of comparing PWB scores between the two groups.

Statistical analysis of the primary endpoint and power: As per the intention-to treat principle, the primary analysis population will be all women who are randomly assigned to receive either short-course or long-course (conventional) radiation therapy. The secondary analysis population will be the per-protocol cohort. We hypothesize that the short-course radiation therapy will lead to improved PWB scores compared to the conventional long-course treatment. To confirm this hypothesis, we will use Analysis of Covariance (ANCOVA) models. **Change in the FACT-B PWB subscale (7 items) score at 6 months relative to baseline** will be the response variable, and the intervention group indicator (long-course versus short-course radiation therapy) and age group (below 45 vs. 45 or above) will be included in the ANCOVA model as independent variables. Using change in the PWB score relative to baseline will give us a more normal distribution of outcomes, versus using the score itself. **The age threshold of 45 years was selected by our patient advocates.**

Based on our patient survey data, we anticipate that the mean post-conventional (long-course) PWB score to be 19.0 for the younger patient group and 24.0 for the older group, and that the standard deviation (SD) is 6.0 for each. We also expect the correlation coefficient between the baseline and 6-month value to be 0.65-0.7, thus the SD of change from baseline to 6 months will be 3.6 to 4.2. **"Table: Expected PWB subscale scores at 6 months by treatment arm"** shows the expected treatment effect in each age group, based on our preliminary data and studies of short-course therapy in other breast cancer settings. The effect of short-course radiation on quality of life outcomes in these other breast cancer settings (breast-conserving surgery or mastectomy without reconstruction) are likely underestimates for our study given the relatively poor outcomes of long-course radiation after mastectomy with reconstruction, rendering our treatment effect expectation to be conservative. The PWB subscale of FACT-B has been documented to have sensitivity to change in quality of life measurement,[37] and change in PWB has been used to study other breast cancer interventions.[47,48] A change in PWB score of greater than or equal to 2 has been defined as clinically meaningful in a multicenter radiation technique study in lung cancer patients.[49] In a study of 41 patients with gynecologic cancer, radiation therapy led to a mean decline of 3.1 points in PWB score, and was associated with radiation treatment technique.[50] With expected data from a total of 400 patients (200 for each arm), the study will have sufficient power, at a two-sided 0.05 alpha level, to detect a marginal treatment difference of 2.8 in PWB scores. If the SD of change from baseline to 6 months is 4.0, the study's power will be 93%. We will also perform the test for interaction between age group and intervention group on the outcome to **investigate the heterogeneity of treatment effect (section**

10e).

Table: Expected PWB subscale scores at 6 months by treatment arm			
	Younger patients (under 45)	Older patients (45 and above)	Marginal score
Short-course (hypofractionation) treatment	23.0	26.0	24.8
Long-course (conventional) treatment	19.0	24.0	22.0
Difference in differences from baseline score	4.0	2.0	2.8

Under the same setting as shown described above, "**Table: N=400 randomized patients, α=0.05"** reveals the power to detect an age interaction will be 59%-89%. These are conservative estimates for the 6-month change in PWB, given that patients in our survey were interviewed between 6 and 24 months (data not shown, manuscript in preparation), and there may be some recovery in physical symptoms with time.

Table: N=400 randomized patients, α=0.05.				
PWB score Δ		SD of Δ	Power	
Younger patients	Older patients		Main analysis	Interaction
4.0	2.0	3.5	>0.99	0.80
4.0	2.0	4.0	>0.99	0.69
4.0	2.0	4.5	>0.99	0.59

Strategy for handling missing data: Given the patient incentives, short time required to complete surveys, and enthusiasm voiced by the patients we surveyed, we expect that the dropout fraction from the study at 6 months will be at most 5% and that the dropout mechanism would be mostly random. In a primary analysis, we will exclude those who dropout from the study or who do not have data at 6 months. However, because a random missing mechanism assumption is not verifiable empirically, we will use several methods to handle missing observations to confirm the stability of the findings from the primary analysis. Specifically, we will perform the following: (1) last observation carried forward (LOCF), (2) mean value imputation, (3) worst-case and (4) best-case imputation. We will also conduct (5) multiple imputation[51]. For multiple imputation, we will create 10 complete datasets, imputing the missing values using chained equations. We will perform the analysis with the 10 complete datasets and integrate the results with Rubin's method of imputation.[51] For another approach, we will analyze this data according to (6) the methods described in Schluchter and in Schluchter, Greene and Beck.[52,53] These methods take into account the possibility of informative "missingness" by jointly modeling the longitudinal responses (here, QoL scores) and the time to dropout.

Other QoL analysis: In secondary analyses, we will use generalized estimating equation (i.e., marginal modeling) and random-effects models to analyze longitudinal data[54] (i.e., baseline, 6 months, 12 months and 18 months) for the FACT-B total score (37 items) and each subscale as well as the primary endpoint (FACT-B PWB subscale).

We hypothesize that patients randomized to short-course radiation will have increased satisfaction with their reconstruction as measured by the BREAST-Q reconstruction survey. We

will use a two-sample t-test for the BREAST-Q satisfaction score, and a chi-square test for 2x2 tables for post-decision regret. We consider a difference of 10 points in the BREAST-Q satisfaction score to be clinically meaningful. With the given total sample size of 400 (200 per arm), we will be able to detect this difference with 80% or higher power at a two-sided 0.05 significance level, if the standard deviation of the score is equal to or smaller than 35.6.

Strategy for handling missing data in other QoL analysis: To assess the robustness of our results, we will perform several sensitivity analyses as well as complete case analysis. For example, we will perform worst-case or best-case imputation or generalized linear modeling in combination with multiple imputation[51] methodology.

Patient-centered outcomes analysis: Furthermore, we will also consider a new outcome that integrates tailored patient-prioritized quality of life measurement. As seen in our patient survey, the relative importance of QoL domains vary from patient to patient. At the baseline visit, we will ask each patient to give a weight to each FACT-B subscale based on its importance for her. We will then calculate a "weighted" total score of FACT-B (37 items) for each individual, using these weights. The weights will be standardized for each patient, so that the range of the weighted score can match with that of the FACT-B total score. We will perform the same analyses described above to assess the impact of the intervention on this exploratory new outcome that may enhance the measurement of patient-centered outcomes.

10c. Statistical analysis plan for clinical and oncologic outcomes and power consideration

The primary analysis and power: We hypothesize that hypofractionated (short-course) radiation therapy has a higher reconstruction success rate, compared to the conventional fractionation (long-course) radiation at 18-months. We will use Chi-square test for 2x2 table to test this superiority hypothesis. We will also construct a two-sided 95% confidence interval for the difference in the composite outcome of reconstruction success likelihood (defined as no major complications, presence of reconstruction, and good or excellent cosmetic outcome). Recent estimates of reconstruction success after implant reconstruction and conventional radiation reveal a 71% likelihood at the 2-year time period.[46] **"Table: Effect size and power for superiority tests"** shows the available power with various reconstruction success probabilities for hypofractionation (short-course treatment), given the sample size of 400 patients. Variables that may affect outcomes such as chemotherapy regimen, endocrine therapy and patient age will be assessed for impact to ensure balance between both treatment arms.

Table: Effect size and power for superiority tests

Reconstruction Success Likelihood (%)		Power (%)
Long-course radiation	Short-course radiation	
71.0	82.8	80
71.0	84.4	90

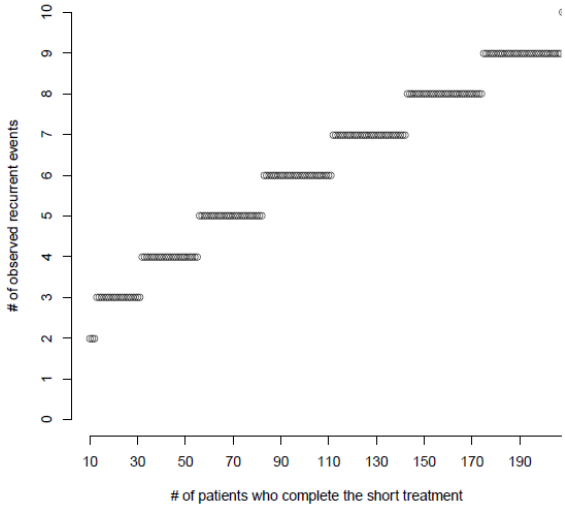
N=400 randomized patients and α(two-sided)=0.05

Data monitoring of local/regional recurrence event:
We will also follow oncologic outcomes to exclude any unexpected increase in the risk of recurrence with hypofractionation (short-course) radiation therapy, although a detectable increase in recurrence rates is unlikely given data from prior experiences of hypofractionation. The cumulative incidence of local or regional recurrence in a recent series of post-mastectomy

radiation therapy is about 2% at 18 months.[3] Therefore, in the case where the recurrence rate is suggested to be statistically significantly greater than 2%, the study will be suspended to allow for investigation.

Local/regional recurrence event rate monitoring will occur at the first meeting of the DF/HCC Data and Safety Monitoring Board (DSMB) and continue until the last patient has completed radiation. Data analysis will be performed every 6 months (see Section 11). Specifically, the event rate and corresponding 0.95 exact binomial confidence interval will be calculated, where the numerator is the number of the local/regional recurrence events and the denominator is the number of patients who have completed short-course treatment at time of analysis. The results will be reviewed by the DSMB. If the lower boundary of the 0.95 confidence interval is greater than 2%, accrual of the study will be suspended and a decision will be made as to whether accrual can be resumed or if the study should be closed by the study team in consultation with the DSMB, IRB and study advisory board. The boundary for this criterion is shown in **"Figure: Stopping boundary for local/regional recurrence-event monitoring"**. With the sample size of 200 in the short-course radiation arm, the probability that the interim data meet the stopping criteria (**see figure**) in the course of the trial is 72% if the true local or regional recurrence rate were 5%. It would be 98% if the true recurrence rate is 8% at 18-months.

Figure: Stopping boundary for local/regional recurrence-event monitoring



There has been no suggestion of increased rare radiation side-effects or mortality with hypofractionation (short-course) radiation therapy with long term follow up in the studies using hypofractionation.[23,24,31] Therefore, we do not expect any increased risk of side-effects in our short-course arm. Nevertheless, to be extra cautious, we will follow these outcomes in our patients. We recognize that our study is too short to detect differences in long-term distant recurrence, cardiac mortality and overall mortality. Therefore, we will create an infrastructure with which monitor these outcomes and apply for additional funding for longer follow up.

10e. Heterogeneity in treatment (HTE) outcomes

In addition to age stratification (see 10a and 10b), heterogeneity or variation in outcomes will be examined based on pre-specified patient, cancer and treatment-related attributes ("**Table: Pre-specified attributes to examine heterogeneity/patient subgroups"**). These factors are included because they may have an independent association with the outcomes examined. As shown in the power considerations for Objective 1, with our sample size we will have a sufficient power to detect heterogeneity of treatment effect. We will not adjust for the multiplicity of the statistical testing, because the goal of the HTE analyses is not to confirm a specific treatment heterogeneity hypothesis, but to generate hypotheses of potential treatment

heterogeneity. Towards this end, we will focus more on describing the estimated treatment differences in each of pre-specified subgroups than testing.
We have also planned analyses to identify subgroups of patients in which the treatment effect (benefit of short-course therapy) is potentially more pronounced than the average treatment effect, using a multivariable scoring approach.[55] Specifically, we will derive a multivariable model that predicts the treatment difference for each patient. Based on the predicted treatment difference scores, we will be able to define subgroups or clusters of patients who benefit more from short-course radiation therapy than the average patient on the study. For example, we will make two subgroups: one which consists of patients only with positive predicted treatment differences, and the other which consists of the remaining patients with negative predicted treatment difference. We will estimate the average treatment difference in each of the two subgroups and also perform a test for interaction.

Table: Pre-specified attributes to examine heterogeneity/patient subgroups	
Patient attributes:	Age (younger than 45, 45 and above) Smoking status Body mass index Comorbidity (hypertension, diabetes) Mastectomy specimen weight
Cancer attributes:	Tumor type (ductal, lobular, mixed histology) Tumor size Receptor status Tumor grade
Treatment attributes:	Number of nodes removed Expander versus permanent implant Volume of implant/expander fill Chemotherapy (yes/no) and regimen and timing of chemo Hormonal therapy Radiation therapy fields Bolus regimen Use of acelluar dermal matrix Mastectomy scar location Use of biologic therapy

10f. AE Monitoring
We will analyze adverse events toxicities experienced by all patients on the study. Adverse event rates will be summarized by types of adverse event (serious/non-serious, grade, and attribution) for each treatment arm, and they will be compared between the arms by using Fisher's exact test. Toxicity data will be monitored by the DSMB every 6 months to assure safety of the participants (see Section 11).

11. REGULATORY CONSIDERATIONS

11.1 Data Safety Monitoring
The DF/HCC Data and Safety Monitoring Board (DSMB) reviews and monitors study progress,

toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance is addressed by the Study Chairs, statistician and study team. Should any major concerns arise; the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet every 6 months to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; local/regional recurrence event rate, adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g., scans, laboratory values) can be provided upon request.

11.2 Multicenter Guidelines

This protocol adheres to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Study Chairs, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix A, Data and Safety Monitoring Plan.

12. PUBLICATION PLAN

Final project results are expected to be reported in a publicly accessible manner within 1 year of the end of the final year of funding, or, after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. Photos could be used in a publication but will be presented in a way that the participant cannot be identified. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors.

To the utmost level permitted, we will comply with all policies on data sharing in a timely, transparent and thorough manner.

The primary methods of data sharing we plan to utilize for this study are:

- Publishing trial results in a peer-reviewed scientific journal
- Submitting study reports to publicly accessible registries dedicated to the dissemination of clinical trial information (including clinicaltrials.gov)
- Releasing de-identified data to interested investigators per Dana-Farber/Harvard Cancer Center Office of Data Quality (DF/HCC ODQ) data sharing policy: DF/HCC ODQ may provide individual-level de-identified datasets that would be sufficient to reproduce results provided in a publication (i.e., published manuscript) containing the main study analysis. Participant contact information cannot be shared under any circumstance. Participant survey data stripped of identifiers may be shared. Source documentation will not be released.
- Providing access to study measurement materials and coding instructions upon request
- Allowing participants to choose if they would like to receive any published study information once it becomes available. A link to clinicaltrials.gov results will be sent to

participants who opt-in (clinicaltrials.gov requires that results be publicly posted on the website within 1 year of completing data collection for the pre-specified primary outcomes of the study). Participants who opt-in will be contacted by lead study coordination site (Dana-Farber) using the contact information they have on file for the purposes of conducting the study questionnaires; the same location/storage/privacy protections will be in place for return of research results.

Site PIs of sites that reach their accrual goal will be included as co-authors on the final manuscript.

13. BUDGET

13.1 Funding

This trial is supported through a Patient-Centered Outcomes Research Institute (PCORI) Award.

13.2 Start-up Payment

A one-time start-up payment will be made to external sites for their unique IRB approval memos at the end of year 1 if the site meets their year 1 accrual goal.

13.3 Per Case Payment

$1,500 per case payment will be made to sites for each participant enrolled to FABREC. In order to receive payment, each site must have a fully executed subcontract in place with the lead site, Dana-Farber Cancer Institute.

13.4 Other costs

This study will not provide any additional payment/funding for any additional costs. All care, including PMRT (either arm) should be billed to the patient's insurance company or the patient as your site does for any other standard clinical care/treatment.

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15. APPENDICES

A. Data Safety Monitoring Plan
B. Radiation Therapy Treatment Guidelines
C. How to Take Reconstruction Photographs
D. List of Patient-Facing Study Materials
E. Script for Annual Follow-up Calls

APPENDIX A: DATA SAFETY MONITORING PLAN

FABREC Trial
DFCI IRB Protocol #: 16-304

APPENDIX A

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

Lead Institution:
- Dana-Farber Cancer Institute

Sponsor:
- Dana-Farber/Harvard Cancer Center (DF/HCC) Overall Investigator

Study Co-Chairs:
- Rinaa Punglia MD MPH
- Julia Wong MD

Coordinating Center:
- Dana-Farber Cancer Institute, Boston, MA

Central Study Coordinator:
- FABREC_Study@dfci.harvard.edu

INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines. The Lead Institution is the home of the DF/HCC Sponsor. The Lead Institution also serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the DF/HCC Overall Principal Investigator, who takes responsibility for initiation, management and conduct of the protocol at all research locations. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. The DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (Lead Institution, Dana-Farber Cancer Institute) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines. The Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible for registering human subjects for trials, ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

DF/HCC Sponsor

The Sponsor, DF/HCC Overall Principal Investigator, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Review registration materials for eligibility and register participants from Participating Institutions with DF/HCC ODQ.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.

- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc.) and maintain documentation all relevant communications.

Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC and protocol requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

Non-life-threatening revisions: Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

Revisions for life-threatening causes: Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

Protocol closures and temporary holds: Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the sub-investigator members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent to interventional trials (i.e. drug and/or device trials).

IRB Documentation

The following must be on file with the Coordinating Center:
Initial approval letter of the Participating Institution's IRB.
Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.
Participating Institution’s IRB approval for all amendments.
Annual approval letters by the Participating Institution's IRB.

IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from

the Participating Institution on or before the anniversary of the previous approval date.

Participant Confidentiality and Authorization Statement

In 1996, Congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC ODQ case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

DF/HCC Multi-Center Protocol Registration Policy

Participant Registration and Randomization

Protocol treatment may not begin without confirmation from the Coordinating Center that the participant has been registered and randomized.

Sites may fax or securely email registration paperwork (eligibility checklist, all pages of signed ICF, and HIPAA authorization form, if separate from ICF) to the lead site at any time, 24 hours a day/7 days a week.

The lead site will process the registration paperwork and send a registration/randomization confirmation email to the site within 24 business hours. Business hours for this study are defined as: Monday through Friday from 8:00 AM to 5:00 PM Eastern Time, not including holidays.

Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

Eligibility Exceptions
The DF/HCC ODQ will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC ODQ requires each institution to fully comply with this requirement.

DF/HCC Unique Study ID Number
At the time of registration, ODQ requires identifiers for all subjects (including, name, date of birth, address, etc.; see eligibility checklist). Once eligibility has been established and the participant successfully registered, the participant is assigned a unique study ID number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this study ID number to identify the subject.

Protocol Deviations, Exceptions and Violations
Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation," "deviation," and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

Definitions
Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is prospectively approved prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

Reporting Procedures
DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating

Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in the Adverse Event Reporting section of the protocol.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy (see AE Reporting section of protocol).

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

Data Management

The DF/HCC ODQ develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC ODQ provides a web based training for eCRF users.

Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data

If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC ODQ Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC ODQ and distributed on a monthly basis.

MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the ODQ provides quality control oversight for the protocol.

Ongoing Monitoring of Protocol Compliance

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study treatment administration, regulatory files, protocol departures, response assessments, and data management.

Participating institutions will receive monthly email updates highlighting overall protocol progress and important announcements.

Remote Monitoring/Auditing

The Participating Institutions will be required to submit participant source documents to the Coordinating Center for the 5th participant they enroll at their site for monitoring.
If the monitoring results in the need for significant retraining, then the Participating Institution will be required to submit participant source documents to the Coordinating Center for the 10th participant they enroll. If the monitoring results in no retraining or minimal retraining, then the Participating Institution will not be required to submit participant source documents to the Coordinating Center for the 10th participant they enroll.
All Participating Institutions will be required to submit participant source documents to the Coordinating Center for the 20th participant they enroll for monitoring.

Source documents can be de-identified, but should be labeled with the participant's unique study ID number.

The Participating Institutions may be required to submit additional participant source documents to the Coordinating Center for monitoring.

Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

Accrual expectations for Participating Institutions: The Study Chairs will visit sites (either in-person or via virtual site visit) who have enrolled fewer than 75% of anticipated participants within the previous 6 months during the enrollment period. These assessments will be made every 6 months after enrollment has started until the end of the enrollment period. During these visits, the Study Chairs will give presentations about the study to the breast oncology, and/or radiation oncology physician teams and meet with the site PI and research coordinators to determine the root-cause for low enrollment and discuss mechanisms to overcome these barriers. The Department of Radiation Therapy at Dana-Farber Cancer Institution has committed to providing the time and covering the expense for these site visits, should they be necessary.

AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

Audit Plan: DF/HCC Sponsored Trials

For this study, remote monitoring and auditing will be performed simultaneously. For the monitoring/auditing schedule, please see section 4.1 of the DSMP above. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

Participating Institution Performance

The DF/HCC Sponsor and DFCI IRB are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

APPENDIX B: RADIATION THERAPY TREATMENT GUIDELINES

General.
Radiation therapy will be delivered to all intended fields, as 5 daily treatments per calendar week, excluding holidays or unavoidable factors pertaining to machine or patient availability. Most patients will receive nodal radiation, but on occasion, a patient may receive solely chest wall radiation, without a separate nodal field. If postoperative chemotherapy is not given, then patients must begin radiation in no more than 4 months from mastectomy. If postoperative chemotherapy is given, patients must begin radiation in no more than 4 months from the beginning of the last cycle of chemotherapy. **Note:** Concurrent systemic therapy will be considered on a case-by-case basis. Please ask the study co-chairs about whether any systemic therapy may be administered concurrently with PMRT.

Dose/fractionation.
1) Conventional fractionation cohort:
   a. Tangential fields: 5000 cGy in 25 fractions (200 cGy each)
   b. Supraclavicular (+/- axillary) field: 4600 – 5000 cGy in 23 – 25 fractions (200 cGy each)
2) Hypofractionation cohort:
   a. Tangential fields: 4256 cGy in 16 fractions (266 cGy each)
   b. Supraclavicular (+/- axillary) field: 3990 cGy in 15 fractions (266 cGy each)

Patient position and simulation. The patient will be positioned supine, in an immobilization device as per institutional protocol. Treatment planning must utilize CT simulation. Techniques to minimize radiation dose to the heart, such as deep inspiration breath hold (DIBH) or gating are encouraged.

Target volumes and field arrangement.
1) Chest wall/tissue expander or implant: tangential fields typically will include the planning target volume (mastectomy scar, skin, subcutaneous tissue, muscles of the chest wall, and ribs underlying the mastectomy site). Ipsilateral internal mammary lymph nodes (IMNs; 1st 2nd or 3rd intercostal spaces) may be included at the discretion of the treating physician. A separate, anterior IMN field is not permitted. There will be no mastectomy scar boost.

2) Supraclavicular (+/- axillary) nodes: Anterior-posterior fields as required to achieve dose homogeneity (see "Treatment planning requirements" below). Typical medial and superior borders are the pedicle and top of first rib, respectively. The inferior border will be matched to the superior border of the tangential fields as per institutional protocol. The lateral border will be set by the treating physician. Blocks (e.g., spinal cord, humeral head) may be utilized.

Treatment planning requirements.
1) Megavoltage (6 MV or above) is required. CT simulation will permit generation of a 3D conformal or IMRT plan.
2) Coverage of the planning target volumes by isodose curves will be as per the treating physician discretion. The only coverage stipulation is 95% coverage at the rib-lung interface.

Other coverage decisions are at the discretion of the treating physician, to allow for clinical judgment to address different clinical scenarios, and to optimize the generalizability of the results of this pragmatic trial.
3) The maximum dose inhomogeneity permitted is 110% for the lymph nodes and 110% (with less than 1 cc > 110%) for the chest wall. Lightly-weighted oblique subfields are permitted.

> **Note:** There is no specified maximum dose on the composite plan. The composite plan may exceed 110%. Individual plans for the chest wall and lymph nodes must not exceed 110% inhomogeneity.

4) Mean cardiac dose and V20 (volume of ipsilateral lung receiving 20 Gy) will be recorded.
5) Inclusion of IMNs will be recorded.
6) The metal port in the tissue expander should be accounted for in the planning process, and if possible, the correct density used.
7) Bolus to the mastectomy scar or chest wall may be prescribed at the discretion of the treating physician (specifics will be recorded at the time of patient registration).

Treatment verification and quality assurance.
1) Machine verification films are required on or prior to the first treatment day, and at least once a week during treatment or as per institutional protocol.
2) The radiation therapy "chart" will be reviewed by the physics staff as per institutional protocol, to evaluate for discrepancies in documentation, dose prescription and dose recording.

APPENDIX C: PHOTOGRAPHIC GUIDELINES

APPENDIX C BEGINS ON THE NEXT PAGE

PHOTOGRAPHIC GUIDELINES
For Clinicians and/or Patients

Thank you for your participation in this study. We greatly appreciate you taking the time to complete study activities and be part of our study.

Instructions:

- Although we encourage you to have your photos taken by a clinician, if you are unable to have your photos taken during your visit to the clinic, or if you will not be in clinic for future photographs, then we kindly request that you take your photographs yourself following the guidelines below. If it is difficult to take your own photographs, then you may have someone (caregiver, family member, friend, etc.) help you.

- You may use a digital camera or cell phone camera to take your photographs. Make sure to remove all articles of clothing to show your surgical site in the photos. You should not have on a bra or shirt for any of these photos.

- We will kindly ask you to retake any photos that do not meet the guidelines set below. This is to ensure the scientific quality of the photographs.

When to take photos:

- Before you receive any radiation treatment, please take and submit 5 photos.
- 6 months after receiving radiation treatment, please take and submit 5 photos.
- 12 months after receiving radiation treatment, please take and submit 5 photos.
- 18 months after receiving radiation treatment, please take and submit 5 photos.

How to submit your photos:

- If your clinician takes your photos for you, the s/he will submit your photos on your behalf.
- If you take your photos yourself, then please call or email the FABREC Central Study Coordinator at 617-582-8484 and/or FABREC_Study@dfci.harvard.edu. She will provide you with a link to a secure webpage where you will be able to upload your photos from your computer or mobile phone.

Why are these photos being collected for the FABREC Study?

In this research study, we are comparing the effects of short-course radiation therapy (hypofractionation) with the effects of long course (conventional) radiation therapy on:

- Quality of life (how much radiation therapy impacts well-being)
- **Cosmetic outcome (how reconstruction looks after receiving radiation therapy)***
- Risks of radiation therapy

This study will help us learn about **which radiation schedule is better for women** who have had breast reconstruction after mastectomy.

***The way we will learn about the cosmetic outcomes is from these photos.**

Photo guidelines continued on the next page →

How to take the photos:

Guidelines

- Please photograph your reconstructive surgery site (the chest area between your neck and just below your belly button; please include your shoulders in the photos).
- Please do not include your face in the photographs.
- Please minimize any extra materials in the background of your photos. You can minimize background issues by taking your photos while standing in front of a solid colored wall (preferably a white wall).
- Please try to minimize shadows on your chest area by taking the photos in a well-lit location.

Note: The model in these photos is wearing a sweater. You should not wear a bra or clothing in your photos in order to view the skin and other areas around your surgery site.

Photo 1 of 5, Frontal View:
For this photo, please capture the reconstruction site in a frame which includes the top of your neck to the bottom of your bellybutton and both arms and shoulders. A little bit of a shadow can be seen in this photo, this is okay.

Photo guidelines continued on the next page →

Reminder:
Photos should be unclothed.

Photo 2 of 5, Left Oblique Angle View:
Facing a left diagonal (at a 45-degree angle), please make sure that your neck, shoulders, both arms, and the bottom of your bellybutton can be seen.

Reminder:
Photos should be unclothed.

Photo 3 of 5, Right Oblique Angle View:
Facing a right diagonal (at a 45-degree angle), please make sure your neck, shoulders, both arms and bottom of your bellybutton can be seen.

Photo guidelines continued on the next page →

Reminder:
Photos should be unclothed.

Photo 4 of 5, Left Lateral View:
Facing left, please make sure your neck, shoulder, right arm, and the bottom of your bellybutton can be seen.

Reminder:
Photos should be unclothed.

Photo 5 of 5, Right Lateral View:
Facing right, make sure your neck, shoulder, left arm, and the bottom of your bellybutton can be seen.

End of photo guidelines.

APPENDIX D: PATIENT-FACING MATERIALS

The patient-facing materials are not enclosed with this protocol. They are included in a separate packet of documents entitled "FABREC Patient-Facing Materials."

To obtain copies of the following materials, email FABREC_Study@dfci.harvard.edu.

- Baseline Study Questionnaire
- 6-month Study Questionnaire
- 12-month Study Questionnaire
- 18-month Study Questionnaire
- Annual Follow-up Question Sheet
- Phone Script for Annual Follow-up Questions
- How to take Reconstruction Photographs (also found in Appendix C)

In addition, sites should obtain a copy of the Model Informed Consent Form from the Lead Site by emailing FABREC_Study@dfci.harvard.edu.