PROTOCOL AND STATISTICAL ANALAYSIS PLAN

Protocol Title:

Patient Experiences with the COVID-19 Vaccination after Breast Cancer Treatment

Principal Investigator:

Alphonse Taghian, MD PhD FASTRO

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March 17, 2023

PARTNERS HUMAN RESEARCH COMMITTEE PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR

Alphonse Taghian, MD PhD FASTRO

PROTOCOL TITLE

Patient Experiences with the COVID-19 Vaccination after Breast Cancer Treatment

FUNDING

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VERSION DATE

04.08.2022

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

- To elicit patient experiences and side effects associated with the COVID-19 vaccine after breast cancer surgery
- Hypothesis 1: Patients will choose to receive the vaccine on the arm contralateral to axillary lymph node removal, or in the lower extremity if they have had bilateral axillary lymph node removal
- Hypothesis 2: Patients with a history of breast cancer will experience axillary lymph node swelling after receiving the COVID-19 vaccine at the same rate as the general population
- Hypothesis 3: Patients with axillary surgery who develop lymph nodes swelling in the ipsilateral side might be at increased risk of developing lymphedema

- Hypothesis 4: Patients who had a COVID infection prior to receiving the vaccine will experience more vaccine side effects than those who were not infected

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Breast Cancer-Related Lymphedema: Overview, Incidence, and Risk Factors

Breast cancer-related lymphedema (BCRL) remains a burdensome and much feared complication of breast cancer treatment. BCRL may occur after lymph node surgery or radiation to the axillary regions, interrupting the proper circulation of lymph fluid. This protein-rich fluid then accumulates in the interstitial tissues of the arm, shoulder, or hand, and/or the breast or trunk, causing swelling that characterizes this condition.[1] Patients may experience a range of symptoms, including heaviness, pain, tightness, changes in skin quality, decreased range of motion, as well as a higher risk for infection in the affected area(s). The morbidity resulting from BCRL is significant and negatively impacts almost all aspects of patients' lives, contributing to anxiety and even depression.[2–7]

Risk factors that have been well established in the literature include axillary lymph node dissection (ALND), regional lymph node radiation (RLNR), number of pathologically involved lymph nodes, and high Body Mass Index (BMI).[8–13] Sentinel lymph node biopsy (SLNB) is favorable to ALND for the axillary staging of early disease because it significantly decreases the risk for BCRL, although the risk is not entirely eliminated.[8,12,14,15] In recent analyses by our team looking at data from over 2,171 women, stratified by BC treatment received, the 5-year point estimate of BCRL was 31.2% after ALND and RLNR, 24.6% after ALND without RLNR, 12.2% after SLNB and RLNR and 8.3% after SLNB without RLNR.[16]

Role of Injections in Lymphedema Risk

As the prevention of lymphedema is preferable to an impairmentbased approach, patients treated for BC historically received advice regarding precautionary behaviors and lifestyle modifications (e.g. avoiding injections) they can adopt, in theory, to reduce their life-long risk of developing this condition, many of which remain unsubstantiated by highlevel, scientific support.[17,18]

Given the paucity of evidential support and controversy surrounding these measures, our team conducted a literature review[18] and two

prospective analyses[19,20] to assess whether lifestyle risk exposures, including injections on the ipsilateral arm, conferred a risk for the development of lymphedema. By multivariate analysis in both prospective

studies (n=632 and n=327), injections were not associated with an increase in arm volume.

In our literature review in The Lancet Oncology,[18] we looked at 85 manuscripts to determine whether historical literature has found a tangible association between presumed risk-increasing behavioral exposures (including ipsilateral skin puncture, cellulitis infections) and BCRL. We found that over the past several decades, the majority of published studies have demonstrated that the clinical benefit of current precautionary guidelines has not been established. Among 31 original studies examining the association between these exposures and BCRL, only eight are prospective cohort studies.[10,19,21–24] Among these, four studies demonstrate a significant correlation between lymphedema and commonly reported lifestyle-based risk factors, in one case, skin puncture.[24] The study that found a correlation between skin puncture and lymphedema was composed only of patients with ALND (n=188), and based on 8 patients who developed lymphedema after skin puncture.

In summary, skin puncture is not associated with increased arm volume based on available evidence.

COVID-19 Vaccine and Lymphedema Risk

Lymph node swelling is a known and common side effect of both the Moderna and Pfizer COVID-19 vaccines. This is the body's normal reaction to the vaccine. According to the Centers for Disease Control and Prevention, axillary swelling or tenderness (i.e., lymphadenopathy) was a solicited adverse event reported in 11.6% of patients (vs 5.0% for placebo) following dose 1 and 16.0% of patients (vs 4.3% for placebo) following dose 2 after the Moderna vaccine.[25] This occurred in the arm and neck 2-4 days following vaccination with a median duration of 1-2 days. After the PfizerBioNTech COVID-19 vaccine, lymphadenopathy was reported as an unsolicited adverse event with 58 more cases in the vaccine group than the placebo group (64 vs 6 respectively). This occurred in the arm and neck within 2-4 days of vaccination and lasted for a mean of 10 days.[26] Rates and duration of adenopathy in both trials were based on clinical assessment (i.e., physical examination). Anecdotally, mammographically detectable axillary adenopathy following COVID-19 vaccinations has been unilateral.[27]

It is worrisome that lymph node swelling after the vaccine mimics that found in breast cancer which has spread to the lymph nodes. This side effect will cause worry and anxiety amongst patients as a result. For patients who have had lymph node removal (ALND or SLNB) and are at risk of lymphedema, we are concerned that the lymph node swelling may tax the lymphatic system and incite lymphedema in those at risk or worsen it in those with BCRL. Fear of lymphedema is high in this population and we need to better understand what risk, if any, lymphadenopathy after the COVID-19 vaccine imparts to BCRL risk.

Although our previous research has found that injections were not associated with increased arm volume[18,19,28], the COVID-19 vaccine is new. We do not know how lymph node swelling associated with the vaccine will affect patients at risk for or suffering from lymphedema. We cannot therefore apply the results from our previous studies to our recommendations for patients around the COVID-19 vaccine.

It is imperative to educate patients about vaccine options, such as receiving the vaccine in an alternative location such as the anterolateral thigh. It is imperative that we study patient experiences, choices, side effects and lymphedema incidence after the COVID-19 vaccine.

Study Summary and Clinical Implications

This study will be a prospective, longitudinal cohort study incorporating patient-reported surveys after vaccine receipt. Given that the COVID-19 vaccine will likely be required in the long term, this data will inform patient recommendations for those receiving the COVID-19 vaccine who are at risk for and with lymphedema.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

This is a prospective, longitudinal observational cohort study incorporating patient-reported surveys before and/or after vaccine receipt. Female patients who are ≥18 years of age and have a history of breast cancer will be eligible. For the MGH site, patients must have received some breast cancer treatment at MGH or its affiliates and received perometry measurements to measure arm volume to be eligible for this study. Per our MGH lymphedema screening records, there are a minimum of 4,947 patients who will qualify for this study. Based on an anticipated survey response of 20%, we anticipate minimal accrual at MGH to be approximately 989 patients.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

REDCap was used to develop surveys to be sent electronically to patients. We will use the surveys to elicit patient choices around receiving/not receiving the vaccine, injection site of choice and side effects. Complete versions of all survey involved in this study have been attached to this application, but not all questions will be relevant to each patient. Therefore, branching logic is built into our REDCap database to ensure patients only

have to answer the questions that are relevant to them. For example, a patient who receives a COVID-19 vaccine that only has one dose will not need to fill out symptoms information for their second dose as it is not applicable to them.
For all eligible patients from MGH who use MGB Patient Gateway, they will be sent a recruitment letter via MGB Patient Gateway with a REDCap survey link embedded. We have been working with the Partners eCare team to build this recruitment report.
The invitation to participate was previously resent a second time after 72 hours with no response, and then a third time at seven days after initial contact (prior to new IRB regulations regarding reminders). An updated version of the recruitment letter was sent with the booster survey once this dose becomes available. The letter includes a new second survey link to questions about the booster vaccine. It is stated in the recruitment letter that this is an updated version of the study which makes the survey more user friendly and includes the booster dose. For this reason, all participants will receive the invitation to participate unless they have specifically asked not to be contacted about our study again. A follow up phone call may be made if we do not hear back in 2 weeks. For patients who do not complete the surveys after consenting to participate (either due to forgetting to finish the surveys or having technical difficulties finding the surveys), the Clinical Research Coordinator will call the participant at the phone number in the EPIC chart to assist in completing all surveys. A telephone script is attached.

Since booster doses of all vaccines are recommended by health officials at differing times, we will contact participants securely through Patient Gateway who have already completed survey(s) about their 1st/2nd doses asking them to complete the booster survey as well. This updated booster letter will include information regarding optional arm measurements as well. This states that we would like participants to make appointments for arm measurements 1-2 weeks before the booster, 7-14 days after the booster, 4-6 weeks after the booster, and 3 months after the booster, +/- 2 weeks. This is an optional component of participation in this study. The letter will be sent through patient gateway. The letter will be sent again to participants who have completed surveys about their 1st/2nd doses in March of 2022 as we anticipate many more responses now as the booster had become more widespread. Depending on response rates, we may reach out by phone, using the attached letter as a script, to help participants complete the booster survey.

98 participants are eligible for our study as well as the CANVAX: Cancer, COVID and Vaccination study (2021P000746). We have been collaborating with the CANVAX team and would like for as many participants as possible of these 98 to complete both studies. In the future, both teams will collaborate

on how best to share our data (perhaps by applying for a data use agreement). Therefore, we will send an additional letter through Patient Gateway to these participants explaining why we would specifically appreciate their participation in the study, signed by the CANVAX PI. These participants have not opted out of being contacted for future research. The Lymphedema Research Program Clinical Research Coordinators are listed as Research Assistants on the CANVAX protocol. If a CANVAX patient is seen in the Breast Cancer Center for routine follow ups or arm measurements, CRCs will offer to have the patient fill out the survey during the visit. Depending on response rate from the Patient Gateway letter, CRCs may also call these patients (a script is attached) unless they decline to participate.

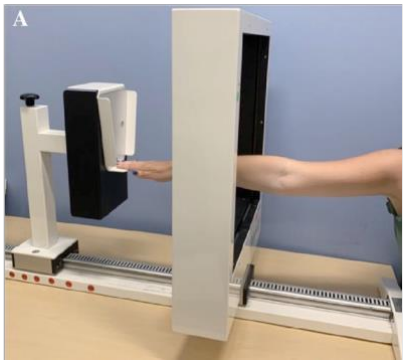
If the participant consents, they will immediately begin a survey asking for information about their first dose and symptoms and second dose and symptoms, if applicable. For participants who have had all doses of their respective vaccines, their participation is complete after responding to a survey about all applicable doses. For participants who have had one dose of their vaccine and plan to have a second, they will fill out the expected date of their second dose and told that the invitation will be resent on that date via Patient Gateway for them to fill out a second survey on that dose. A second link will be available in the recruitment letter directing participants to fill out experiences with the booster dose of the vaccine if they receive it. Copies of both surveys (first/second dose experience and booster dose experience) are attached.

Additionally, we will reach out to participants through Patient Gateway who have consented to the study and experienced some form of swelling and provide them with contact information if they would like to schedule arm measurements before and/or after receiving the booster vaccination. All participants are aware that arm measurements remain available to them as they have in the past. Language for this letter is attached. We will resend an updated letter to participants who reported lymph node swelling after any of the three doses. The updated language is attached. As has been conducted with the booster arm measurements, parking will be compensated for those coming in for additional appointments outside of regular oncology visits. Depending on response rates, we may also reach out to participants by phone using the attached letter as a script.

An additional survey asking questions about prior SARS-CoV-2 infection will be sent to all participants who have consented to participate through answering questions on any doses of the vaccine. The CANVAX study recently published results that prior infection was associated with higher systemic, but not local, symptoms[43]. We would like to test this in our population and therefore must collect data on any prior infections to

compare with the data we have on vaccine experiences. The invitation to complete this survey, attached, will be sent securely through patient gateway, and we may reach out by phone depending on response rates at the discretion of the PI. A consent addendum is included in the survey language, attached. No new subjects will be enrolled through this survey.

Participants will be aware (explained in consent fact sheet) that we may review their medical records for the purposes of this study and that we will analyze their survey data in conjunction with their breast cancer treatment information and lymphedema screening data.
Upon completion of the survey study, we may apply for secondary use of data from our Screening Program to analyze perometry and clinicopathological data for participants who have responded to surveys regarding their COVID-19 vaccinations and who are established participants in our MGH Breast Cancer-Related Lymphedema Screening Program (2008P000540 and 1999P009256). We have applied for and been granted secondary use under Insight number 2021P003414. This program routinely screens patients starting at pre-operative baseline, throughout and beyond treatment at their oncology follow-up visits. Screening consists of perometry measurements, a valid and reliable measure of arm volume used for lymphedema screening[29], as well as a patient-reported outcome measure, the Symptoms Experience Index (SEI), a validated measure of symptoms after breast cancer surgery. Analysis of this data will inform BCRL risk after COVID-19 vaccination versus that from our historical control data.



For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Not applicable: this study does not involve treatment or diagnosis.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

The surveys sent, the main research components of this study, do not present risk to patients. We will protect patients by inviting the majority of the study participants through secure Patient Gateway contact. All surveys will be completed in REDCap and all survey responses will be stored in our secure REDCap database. All patients who are offered to participate in this study are already familiar with the MGH Lymphedema Research Program.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Given minimal risk to patients and the fact that it is an observational study, the main criteria for removing a subject from the study would be patient withdrawal from the study.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Psychosocial risks may include frustration associated with receiving survey prompts as to whether the patient has received the first dose of the COVID19 vaccine, given this is an emotional topic currently. There could also be distress associated with the potential for the known side effect of lymph node swelling after receiving the COVID-19 vaccine in patients at risk for lymphedema.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

Benefits to society would include wide distribution of important patient education regarding the side effects and recommendations for safe receipt of the COVID-19 vaccine. This will minimize distress in our patients who experience a potentially alarming symptom such as lymph node swelling, which may concern patients who underwent lymph node removal. Since we

will be monitoring for symptoms, we will be able to direct patients to seek medical care in the event lymph node swelling symptoms persists to six weeks after the second dose. If there is clinical concern that persists ≥ 6 weeks after the final vaccine dose, axillary ultrasound is recommended per current MGH Breast Imaging standard of care. There are no direct benefits to patients who do not experience lymph node swelling.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

The proposed study will be limited to the enrollment of female subjects who are ≥ 18 years of age. Breast cancer is exceedingly rare in the population under 18 years of age, with only a 0.02% malignancy rate for pediatric breast masses.[30–33] Additionally, less than 1% of all breast cancer patients are male.[33,34] Therefore, accrual of children and males would be limited and would not allow for statistical analysis or comparison. All patients who meet eligibility requirements will be offered the study. This includes all newly diagnosed patients who will be accrued to the pre-existing screening program during the duration of the study. No exclusions will be made on the basis of race, ethnicity, sexual orientation. The clinical staff will make all efforts to enroll eligible patients, including minority subjects.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

The survey will be given to participants who are able to read and consent to the study in English. Given technological REDCap limitations, we will be unable to retroactively add surveys in different languages after the initial survey invitations have been sent out on Patient Gateway. Given that the vast majority of patients in our database speaks English, we believe the imperative nature of beginning this study supports this approach.

It is imperative to translate the COVID-19 vaccine information sheet into several languages as it is crucial that patients receive this education regardless of language spoken. Prior to this, we can have an interpreter present as needed for the screening visits so CRCs can explain the guidelines to patients as they come in for measurements. This will be done per our

clinical service and will be distributed to any patients in the Breast Cancer Center, regardless of their participation in research.

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
https://www.partners.org/Assets/Documents/Medical-Research/ClinicalResearch/Non-English-Speaking-Subjects.pdf

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

There are multiple recruitment methods for this study:

- The majority of patients will be accrued via recruitment letter sent through MGB Patient Gateway. We will send this letter to all MGH patients who are eligible (≥18, female, treated for breast cancer at MGH, have been measured with perometry for BCRL) and are in our database (1999P009256/2008P000540). For patients who are okay with receiving research opportunities, the original letter directly from our study team will be sent to them. For all patients who are not enrolled at the time of the initial survey invitations, but become eligible, they may be accrued either by provider referral or when they are in clinic seeing our Clinical Research Coordinators for a perometry measurement. This group of patients includes those diagnosed with breast cancer after the surveys have been sent out or those who have received perometry measurements for clinical purposes. CRCs will mention the study during a regular screening visit and send the email to the patient if they are interested or give them a flyer (attached) so a patient can decide if they would like to join after the visit is over and they have time to think about it. The same could happen if a provider mentions the study to a patient who then approaches our team about the study.
- For participants who are eligible for our study (MGH patients ≥18, female, treated for breast cancer at MGH, have been measured with perometry for BCRL) who also participated in the CANVAX: Cancer, COVID and Vaccination study (2021P000746), the CRC will send an additional letter through Patient Gateway to describe the crossover between the two studies. If a CANVAX patient is seen in the Breast Cancer Center for routine follow ups or arm measurements, CRCs will offer to have the patient fill out the survey during the visit.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Parking fees will be reimbursed for the optional visit for arm measurements before/after receiving the booster vaccination. Participants will be given a parking pass for a 0-4 hour visit.

For guidance, refer to the following Partners policies:

Recruitment of Research Subjects
https://www.partners.org/Assets/Documents/Medical-Research/ClinicalResearch/Recruitment-Of-Research-Subjects.pdf

Guidelines for Advertisements for Recruiting Subjects
https://www.partners.org/Assets/Documents/Medical-Research/ClinicalResearch/Guidelines-for-Advertisements.pdf

Remuneration for Research Subjects **https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/Remuneration-for-Research-Subjects.pdf**

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

Although this is a minimal risk study, we will ask patients to consent (yes/no) via the initial REDCap survey. There are multiple ways a participant can be recruited to the study, all study patients will first fill out a consent survey that includes the language below.

Are you interested in taking part in this study?

By responding yes, you are confirming your willingness to receive unencrypted emails, complete surveys, that you are over the age of 18, have been diagnosed with breast cancer and received some treatment at MGH or its affiliates, and you have been measured with perometry for lymphedema at MGH. A copy of all the information listed above will be provided to you for your records.

By responding no, you will not be contacted again about this study. Thank you for your time. As a reminder, choosing not to participate in this study will not affect your care at MGH.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decisionmaking capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
https://partnershealthcare.sharepoint.com/sites/phrmApply/aieipa/irb

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects:
https://www.partners.org/Assets/Documents/Medical-Research/ClinicalResearch/Informed-Consent-of-Research-Subjects.pdf

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

Data monitoring will be completed by the Senior Lymphedema Clinical Research Coordinator. Furthermore, the Senior Lymphedema Clinical Research Coordinator and the PI will assure compliance with all MGH IRB requirements as set forth by the institution to protect the rights, safety, and welfare of subjects.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

The Senior Lymphedema Clinical Research Coordinator will review all adverse events as they occur and will work with the Principal Investigator regarding the grade and attribution of events. Adverse events are not anticipated in this study given it is low risk. In the event they do happen, they will be reported to the MGH IRB in accordance with the institution's Adverse Event Reporting Guidelines.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The Senior Lymphedema Clinical Research Coordinator will monitor and assure the validity and integrity of the data and adherence to the IRBapproved protocol. This will include reviewing REDCap survey data every 8 weeks for accurateness and completeness. The Principal Investigator will oversee this monitoring at regular monthly protocol meetings.

For guidance, refer to the following Partners policies: Data and Safety Monitoring Plans and Quality Assurance **https://www.partners.org/Assets/Documents/Medical-Research/Clinical-Research/DSMP-inHuman-Subjects-Research.pdf**

Reporting Unanticipated Problems (including Adverse Events) **https://www.partners.org/Assets/Documents/Medical-Research/ClinicalResearch/Reporting-Unanticipated-Problems-including-Adverse-Events.pdf**

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

In order to protect the privacy of subjects and maintain confidentiality of data collected, we will be using a secure MGB Patient Gateway communication to recruit the majority of patients. Access to study data will be limited to the Lymphedema Research staff. It is possible de-identified data may be shared with statisticians in the future without the additional informed consent of participants.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

Not applicable

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

Not applicable

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

Not applicable

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[4] Khan F, Amatya B, Pallant JF, Rajapaksa I. 2012 Factors associated with long-term functional outcomes and psychological sequelae in women after breast cancer. *Breast* **21**, 314–320.

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Statistical Methods

Side effect frequencies and median duration for each mRNA dose were analyzed. To investigate predictors of side effects, multivariable logistic regression models across all doses were fit separately for each side effect, with random effects for participants to account for clustered responses. We investigated age, BMI (<25, 25–30, ≥ 30 kg/m^2), surgery type (lumpectomy, mastectomy, mastectomy with reconstruction), axillary surgery (none, sentinel lymph node biopsy, axillary lymph node dissection), radiation (yes/no), and chemotherapy (none, neoadjuvant, adjuvant only). Analysis was conducted across all three doses to determine any differences in side effect profiles. Coefficients with $p < 0.05$ were considered significant predictors of that side effect. Because lymph node swelling is not a listed side effect of the J&J vaccine, and because far fewer patients received that vaccine, we analyzed side effects among those receiving the J&J vaccine separately.

The Statistical Analysis Plan (SAP) is included above in the Statistical Methods section and is part of our published paper which is cited below.

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