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TITLE: Prospectively Randomized, Placebo-Controlled Phase 3 Study to Determine the Effect of Denosumab on Breast Cancer Prevention in BRCA1 Mutation Carriers

PRINCIPAL INVESTIGATOR: Judy E. Garber, MD MPH

CONTRACTING ORGANIZATION:
Dana-Farber Cancer Institute, Inc.
450 Brookline Avenue
Boston, MA 02215-5450

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6. AUTHOR(S)
Judy E. Garber, MD MPH

E-Mail: Judy_Garber@dfci.harvard.edu

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14. ABSTRACT

In Europe and the USA, more than 1.3 million women are estimated to carry a germline mutation in the *BRCA1* or *BRCA2* genes. These women have up to 87% lifetime risk of developing breast cancer, with tumors usually developing at an early age. Currently, prophylactic surgery is the only proven procedure that significantly reduces breast cancer risk, and this is can be associated with postoperative complications and a suboptimal cosmetic outcome. Medical prevention, if effective, could present a non-invasive alternative to mastectomy, but would need to be started relatively in early adulthood and has potentially to be offered beyond menopause. This strategy could also 'buy time' for women considering prophylactic mastectomy. There is accumulating evidence that the RANK/RANKL signaling pathway plays a pivotal role in breast tumorigenesis, particularly in the development of *BRCA1*-mutated tumors. Targeting the RANK pathway has been shown to attenuate breast epithelial proliferation in vitro and in vivo, and to profoundly reduce mammary tumor formation in mouse models.

In addition, since *BRCA* germline (g*BRCA*) mutations confer an increased risk for ovarian cancer, the vast majority of g*BRCA* women undergo prophylactic bilateral salpingo-oophorectomy (PBSO) at a young age. This has been shown to reduce ovarian cancer risk, but can significantly compromise bone, sexual and potentially cardiovascular and cognitive health. Many women who undergo PBSO therefore receive some kind of osteoprotective therapy. Current medical breast cancer prevention strategies for g*BRCA* mutation carriers involve the use of tamoxifen or aromatase inhibitors, which - at least in the case of aromatase inhibitors - may further compromise bone health.

The RANKL inhibitor Denosumab is potentially an ideal chemopreventive agent for women with a *BRCA1* germline mutation because it: (a) could potentially reduce breast cancer risk, and (b) concomitantly protect bone health in those women who have already undergone PBSO or in naturally postmenopausal women. It has already been shown to have a positive benefit-risk profile in the treatment and prevention of bone loss in post-menopausal patients undergoing endocrine therapy for breast cancer.

15. SUBJECT TERMS

BRCA1; Breast Cancer; Bone Health; Breast Density; Clinical Trial; Collaboration; Correlative Science; Denosumab; DNA; Imaging; Mammogram; International; Multicenter; Mutation; Prevention; Phase III; Translational Science; Quality of Life; Xtreme CT HR-pQCT

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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

   The BRCA-P/ ABCSG 50 Study is a randomized, double-blinded, placebo-controlled, multi-center, international phase-3-trial, which examines the preventive effect of Denosumab on breast cancer, as well as ovarian cancer and other cancer types in women, who have a *gBRCA1* mutation. One in 400 women in the industrialized world carries the *BRCA1* mutation, which entails a 60-87% risk to develop breast cancer and a 50% risk to develop ovarian cancer throughout the lifetime. Denosumab is already approved for the treatment of various medical indications, such as e.g., prevention of skeletal complications (pathological fracture, radiation of the bone, spinal cord compression or bone surgery) in adults with bone metastases due to solid tumors.
   Denosumab is not yet approved as a breast cancer prevention drug for people carrying the *BRCA1* mutation. The main objective of this prevention study is to determine whether the study medication, Denosumab can reduce the risk to develop breast cancer in women with a *BRCA1* mutation or possibly even prevent it.

   Participants will be randomized 1:1 into one of 2 treatment arms (Arm A or Arm B).

   - TREATMENT ARM A

   Study medication Denosumab 120 mg as a subcutaneous injection every 6 months for 5 years.

   - TREATMENT ARM B

   Placebo as a subcutaneous injection every 6 months for 5 years.

   The study will be conducted in seven countries and 2918 women in total will participate.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

   BRCA1; Breast Cancer; Bone Health; Breast Density; Clinical Trial; Collaboration; Correlative Science; Denosumab; DNA; Imaging; Mammogram; International; Multicenter; Mutation; Prevention; Phase III; Translational Science; Quality of Life; Xtreme CT HR-pQCT

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

   Please refer to the tables below.

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Site 1	Site 2	Site 3
Dana-Farber Cancer Institute 450 Brookline Avenue Boston, MA For the Alliance for Clinical Trials in Oncology, Chicago, IL	Austrian Breast & Colorectal Cancer Study Group* Nussdorfer Platz 8 1190 Vienna, Austria **with national Sponsors in UK, Germany, Israel, Spain (where applicable)*	Australia/ New Zealand Breast Cancer Trials Group Level 4, 175 Scott St Newcastle, NSW 2300
PI: Judy E. Garber MD MPH, CO-PI: Chair, Steering Cmte	PI: Christian Singer, MD Overall PI, BRCA-P	Geoffrey Lindeman, MD PhD Global PI, BRCA-P

Aims and Tasks	Timeline Months	Site 1	Site 2	Site 3	Completion Date / % Complete
Specific Aim 1: To evaluate the reduction in the risk of breast cancer (Invasive and DCIS) in women with germline *BRCA1* mutation treated with Denosumab compared to Placebo					
Major Task 1: Approval of trial protocol and initiation of BRCA-P					
Preparation and submission of core Clinical Trial application forms to IRB's/Ethical committees	1-3	X	X	X	**Site 1:** Following protocol submission to NCI Division of Cancer Prevention (DCP) on 02/28/2020, we received DCP's Consensus Review on the A211801 protocol, on 09/24/2020. The study team responded to these comments and made corresponding edits to the protocol. Revised protocol was re-submitted to DCP on 10/23/2020. DCP Approval on Hold was issued on 11/05/2021. Following this, the CIRB Initial Review application was submitted on 12/01/2020. CIRB Initial Review Pending Modification letter was received on 01/28/2021. We submitted the response to the CIRB Initial Review on 02/19/2021. CIRB Approval was received 02/26/2021. NCI DCP Final Approval is pending the finalization of MoU and Contracts. All approved revisions will be shared with the DoD. **Site 1:** % Complete: 100% preparation; 95% complete (pending full NCI approval) **Site 2 and 3:** This was achieved in several countries (Austria, Australia, Spain, Israel and UK). Completion in

					these countries 100%. Preparation for submission took also place in Germany.
Complete and finalize revisions of the main protocol document to include the scientific projects and additional image and specimen collection. Include modifications necessitated by DOD funding for the correlative science aims.	1-3	X	X	X	**Site 1:** The US group-specific appendix has been updated to include all correlative science aims. The modifications will be shared with the DoD, ABCSG and Australia (site 2 and 3), once full NCI approval is received. **Site 1:** % Complete: 90% preparation. 90% (suggested revisions from the reviewers at the NCI and DoD). **Site 2 and 3:** It was agreed by HRPO, that no changes in language regarding the Research Monitor have to be implemented in the protocol or other trial documents (such as ICF). However, ABCSG has prepared an amendment of the global protocol, that is currently in review with the country sponsors and will be provided to HRPO once finalized. **Site 2 and 3:** % Complete: 90% preparation. 90%
Submit revised protocol document for review at participating IRBs and US CIRB.	1-3	X	X	X	**Site 1:** The NCI CIRB application, including the protocol document was submitted on 12/01/2020. On 02/26/2021, we received the NCI CIRB approval for the protocol. **Site 1:** % Complete: 100% Complete **Site 2 and 3:** Main protocol document complete, amendment see above **Site 2 and 3:** % Complete: 90% preparation. 90%
Submit revised protocol document for review at HRPO/DOD.	1-6	X	X		**Site 1:** On 02/26/2021, we received approval from the NCI CIRB, on the protocol. We currently await final approval from the NCI DCP. Protocol activation and final NCI DCP approval is pending MoU and contract finalization between the ABCSG and Alliance. All approved applications and protocol revisions will be shared with the DoD. **Site 1:** % Complete: 100% preparation; 90% complete (pending suggested revisions from the reviewers at DoD and NCI) **Sites 2 and 3:** It was agreed by HRPO, that no changes in language regarding the

					Research Monitor have to be implemented in the protocol or other trial documents (such as ICF). However, ABCSG has initiated the global protocol to be amended, this amendment is currently in review with the country sponsors and will be provided to HRPO once finalized. **Site 2 and 3:** % Complete: 90% preparation. 90%
Obtain IRB approval from all international IRBs and US-CIRB following submission of required revisions.	3-6	X	X	X	**Site 1:** NCI CIRB: as above **Site 2 and 3:** main protocol submitted in 5 and approved in 4 countries (see above); amendment see above **Site 2 and 3:** % Complete: 80% preparation. 80%
Finalize systems for drug distribution and AE reporting	1-6	X	X		Achieved for **site 1, 2, 3:** Those systems are set-up centrally by ABCSG for all sites. The IxRS system is live and running (used for international drug supply). (S)AE reporting is outlined in the global Study Manual and associated documents. % complete: 100% For **Site 1**, the Alliance continues to work with the ABCSG to harmonize US procedures in line with local / NCI regulations and manufacturer specifications. In addition to the SAE and drug distribution systems set up centrally by ABCSG for all sites, the Alliance, as a grantee of the NCI, will use NCI's electronic reporting system, the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP AERS), for SAE reporting. As the US IND holder Alliance, shall comply with all applicable safety reporting requirements involving the Study Drug, including the requirements set forth in 21 C.F.R. § 312.32.
Post study on ClinicalTrials.gov/EMA registry	4-6	X	X		**Site 1 and 3:** ClinicalTrials.gov (CT.gov) entry for A211801 was approved on 01/14/2021. The NCT ID is NCT04711109. Local and international recruiting sites for the study will be updated on the CT.gov website once the trial is active in the US. **Site 1 and 3**: % Complete: 80% complete

					Site 2: The Study was activated on 25-Jun-2018 (Competent Authority approval date of the first participating EU country, which is Austria) in the EU Clinical Trials Register. **Site 2:** % Complete: 100% preparation. 100% complete.
Initiate enrolment at 64 total sites	4-10	X	X	X	**Site 1:** Received confirmations to participate from 35/35 targeted sites in the US. Enrolment will occur once the trial is active in the US. For activation, we currently await final protocol approval from the NCI and HRPO. **Site 1:** % Complete: 100% preparation **Site 2 and 3:** As of 14-Sep-2021 5 sites in Austria, 15 sites in Australia, 5 sites in Spain and 1 site in Israel are activated. All planned sites are active in Austria, Australia and Spain now. One additional site in Israel is planned to be initiated and activated end of 2021. However due to COVID-19 limitations, other countries might lag behind. **Site 2 and 3:** % Complete: 100% preparation. 80% completion
Coordinate with sites for material transfer agreements	4-10	X	X	X	**Site 1:** An umbrella MTA has been signed to designate MGH as the data coordinating centre for all images collected for the bone density sub-study. MGH will receive only de-identified images for the purpose of the sub-study. These images will be collected and analysed by MGH. Since the trial is being coordinated by the Alliance in the US, no individual site level MTAs will be required for the transfer of biospecimens from recruiting sites to Alliance Biorepository at Mayo Clinic (ABMAYO). **Site 1:** % Complete: 100% complete **Site 2:** Most countries do not have central biobanks in place and store samples locally. **Site 3:** Australia is already shipping material to their central biobank.

					Site 2 and 3: % Complete: 100% preparation. 100% completion
Recruit 2918 women to protocol BRCA-P	6-30	X	X	X	**Site 1:** This will be initiated once the protocol is approved by the NCI and HRPO. **Site 1:** % Complete: 80% preparation, 0% completion **Site 2 and 3:** As of 14-Sep-2021 94 participants have been randomized to the BRCA-P study. Due to COVID-19 pandemic, recruitment is impaired, as was already communicated by ABCSG to DoD on 19-Mar-2020 and more recently during the Milestone Meeting in November 2020 and it cannot be foreseen how long the situation might have an impact on study progress.
Develop and implement systems for paying sites for subject recruitment with NCORP	4-8	X			**Site 1:** Systems are in place to reimburse sites per participant recruitment based on standard NCORP/NCI procedures. **Site 1:** % Complete: 100% completion.
Major Task 2: Implement blood specimen, image, and PRO data collection/storage systems N = 1000 participants					
Formalize procedures for kit assembly and distribution, return to repositories	1-3	X	X	X	**Site 1:** For US sites, a detailed Correlative Science Procedure Manual (CSM) has been prepared including detailed instructions for collection, local and central processing, storage and shipment of all protocol-specified samples, images and questionnaires for all projects. **Site 1:** % Complete: 100% complete **Site 2 and 3:** Achieved in Australia, where a central laboratory is in place. For other countries samples are stored locally at site. Handling of mandatory (and optional samples) is outlined in Australia specific Manual as well as global Study Manual. An update of the global Study Manual, including more detailed instructions for sample handling, has been meanwhile released by ABCSG. **Site 2 and 3:** % Complete: 100% preparation. 100% completion
Finalize plans for image collection and storage in existing data centers	1-4	X	X	X	**Site 1:** Procedures for US sites are finalized in the CSM. **Site 1:** % Complete: 100% complete

					Site 2 and 3: Imaging necessary for enrolment in the BRCA-P trial is stored in the respective Investigator Site Files at the sites (process at Site 2 complete). Additional imaging for exploratory research not applicable at all sites.
Finalize plans for QOL instrument collection in US, UK, and Australia and data transmission to study team in Australia	1-4	X	UK only	X	**Site 1,2 and 3:** QoL questions are finalized on, available in English (so they will be provided to a subset of English-speaking participants) and already implemented in the BRCA-P eCRF and are thus centrally collected using electronic submission systems. % Complete: 100%
Implement specimen, imaging and QOL instrument collection to repositories.	6-48	X	X	X	**Site 1:** The Alliance and Alliance Biorepository at Mayo Clinic (ABMAYO) has finalized plans for specimen collection, management and storage in established repositories in the US using standardized procedures. To avoid material expiration, storage tubes and materials will be acquired closer to the activation date. **Site 1:** % complete: 100% preparation; 80% complete **Site 2 and 3:** Australia has central lab in place for samples; other countries store samples at sites directly. QoL is only applicable in Australia and UK (already finalized eCRF for collection). Images are stored locally and data in general for all sites are stored centrally on eCRF at ABCSG (MACRO).
Implementation of overall site monitoring programs	7-48	X	X	X	**Site 1:** A local site monitoring plan has been drafted by the Alliance based on the basic criteria for monitoring shared by ABCSG. The plan is currently under review by the Alliance leadership. Support to implement the monitoring plan has been secured. The Alliance is working to hire a monitor for this trial. **Site 1:** % complete: 80% preparation; 0% complete. **Site 2 and 3:** Implementing Site monitoring programs is the responsibility of every Country Sponsor. As only Australia, Austria, Spain and Israel have active sites so far, site monitoring is in place in these countries. For Austria a Trial Monitoring Plan is in place and the

					basic criteria for monitoring have been shared by ABCSG with all global partners who need it for their set up. Training for all assigned Site Monitors was provided by ABCSG. **Site 2 and 3:** 100 % complete in active countries
Specific Aim 2: We will investigate whether treatment with denosumab alters serum OPG, RANKL or progesterone levels in pre- and postmenopausal *BRCA1* carriers in **1000** participants					
Collection of blood specimens for measurement of RANKL, OPG, Estradiol, Progesterone levels and repository at baseline and months 12, 24, 36, 48	7-48	X	X	X	**Site 1:** Specimen collection will begin once the trial is activated in the US. **Site 1:** % Complete: 0% Complete **Site 2 and 3:** (Optional) blood samples are collected and stored at sites locally in Austria and Spain, whereas in Australia blood samples are shipped to the central laboratory. Complete: sampling is ongoing; however testing will be performed later on for most countries
Optimize measurement of biomarkers with specified kits	7-9		X		**Site 1:** Specimen collection will begin once the trial is activated in the US. % Complete: 0% Complete **Site 2:** information on which samples to collect and how to proceed with them (including preferable kits) has been shared with active sites. Detailed instructions are also outlined in the Study Manual.
Optimize systems for de-identifying specimens for analysis (protect treatment arm and tumor v none)	4-6	X	X	X	**Site 1,2 and 3:** A detailed Manual has been prepared with instructions to deidentify specimens for analysis. % complete: 100% preparation; 100% complete
Batch analyses of serum specimens for circulating biomarkers as above	13-48	X	X	X	**Site 1,2 and 3:** Analysis will be performed at a later stage of the trial.
Specific Aim 3: To evaluate the change in mammographic breast density (MBD) in premenopausal *BRCA1* mutation carriers (g*BRCA1*m) from baseline to 12 months of denosumab versus placebo. **N= 268 participants (134 per arm)**					
Optimize collection of digital mammogram images and storage all sites	7-12	X	X	X	**Site 1:** Procedures for US sites are finalized in the CSM. % Complete: 100% preparation; 100% Complete **Site 2 and 3:** Imaging is performed as per local standard (MG is performed where feasible, however this is not mandatory). Where image is collected, the respective

					data is documented in the database. Participants where data is available are considered for this Aim % Complete: 100% preparation; 100% Complete
Optimize collection of breast MRI images and storage all sites	7-12	X	X	X	**Site 1:** Procedures for US sites are finalized in the CSM. % Complete: 100% preparation; 100% Complete **Site 2 and 3:** Imaging is performed as per local standard (MRI is performed where feasible, however this is not mandatory). Where image is collected, the respective data is documented in the database. Participants where data is available are considered for this Aim % Complete: 100% preparation; 100% Complete
Analysis of digital mammogram images using Cumulus software*	7-48	X			**Site 1:** Analysis will begin once all images are collected. % Complete; 0% Complete
Analysis of digital mammogram images using semi-automated system*	7-48	X			**Site 1:** Analysis will begin once all images are collected. **Site 1:** % Complete: 0% Complete
Specific Aim 4: To investigate the impact of denosumab use in women with a *BRCA1* germline mutation on health-related quality of life (HRQoL), controlling for potential confounders such as menopausal status and age. **N = 400 participants**					
Optimize systems for collection of QOL instruments from English speaking enrolled participants	4-6	X	UK only	X	**Site 1:** QoL questions are agreed on, available in English (so they will be provided to a subset of English-speaking participants) and already implemented in the BRCA-P eCRF and are thus centrally collected using electronic submission systems. **Site 1:** % complete: 100% preparation; 80 % complete **Site 2 and 3:** QoL is documented for English speaking countries centrally at ABCSG eCRF and as Australia already has participants randomized, they already perform this task. UK is not yet active 100% complete as system is active
Collection of completed instruments at baseline and months 6, 12 and 24 for English-speaking subjects	7-42	X	UK only	X	**Site 2:** Only applicable for UK – since UK has no active sites yet, no collection of QoL questionnaires could be performed **Site 3:** QoL questionnaires are being collected

Specific Aim 5: To characterize changes in bone density, microarchitecture, microstructure, and bone strength in premenopausal and early postmenopausal women receiving denosumab 120 mg and placebo **Enrollment 150 participants: with dropout, analysis 100 participants**, scans at 0, 12 and 24 months.					
Finalize recruitment of sites with ScanCo Xtreme CT HR-pQCT in proximity to active BRCA-P sites	4-12	X	X	X	**Site 1, 2, 3:** The team at MGH has collaborated with ScanCo to identify Xtreme CT HR-pQCT sites in proximity to confirmed BRCA-P sites in US and globally. The team has connected with international sites to finalize site participation. **Site 1:** % Complete: 100% preparation; 50% complete
Optimize systems for image sharing with MGH and site reimbursement for Xtreme HR-pQCT imaging+	4-12	X	X	X	**Site 1:** A contract has been signed to designate MGH as the data coordinating site to optimize image sharing by US participating sites with MGH. MGH is refining operating procedures internally to reimburse sites for Xtreme HR-pQCT imaging in the US and globally. **Site 1:** % complete: 100% preparation; 25% complete **Site 2 and 3:** await system optimization of site 1
Collection of de-identified HR-pQCT images (protection of denosumab vs placebo assignment)	7-48	X	X	X	**Site 1,2,3:** Teams at MGH will work with selected sites to ensure collection of de-identified images. % complete: 0% complete
Specific Aim 6: In exploratory studies, we will examine tumors arising and prophylactic mastectomy specimens from trial participants and conduct phenotypic (including TIL scoring) and molecular characterization, comparing DNSB to controls. The effect on peripheral blood immune cell subsets will also be characterized and cfDNA collected and studied as a potential screening strategy for women with a germline *BRCA1* mutation. **see Peer/Programmatic responses: ~100 participants per subaim**					
Collection of tumor tissue developing in women on the BRCA-P trial	7-48	X	X	X	**Site 1:** Our team has worked out material collection and transfer processes with ABMAYO. Additional guidance on sample processing and shipment is available in the CSM. **Site 1:** % Complete: 100% preparation; **Site 2 and 3:** Guidance is in place in case of tumor occurrence. Sites are advised to collect the respective tumor tissue and document this occurrence accordingly in the eCRF system. **Site 2 and 3:** % Complete: 100% preparation
Collection of prophylactic mastectomy specimens from women who drop out of the BRCA-P trial	7-48	X	X	X	**Site 1:** Our team has worked out material collection and transfer processes with ABMAYO. Additional guidance on sample processing and shipment is

					available in the CSM. **Site 1:** % Complete: 100% preparation; **Site 2 and 3:** Guidance is in place should participants drop out. **Site 2 and 3:** % Complete: 100% preparation
Tissue immune phenotyping	7-48			X	**Site 1:** Materials will be sent to Site 3 for analysis **Site 3:** Analysis will be performed at a later stage of the trial. % Complete: 100% preparation;
Tissue molecular phenotyping and immunohistochemistry	7-48			X	**Site 1:** Materials will be sent to Site 3 for analysis **Site 3:** Analysis will be performed at a later stage of the trial. % Complete: 100% preparation
cfDNA specimens collected from central repositories	7-36	X	X	X	**Site 1:** Use of standardized material transfer practices have been agreed upon to transfer specimens to Site 3. **Site 1:** % Complete: 100% preparation; 0% Complete **Site 2 and 3:** Guidance on collection of cfDNA specimens at sites was developed and distributed to active sites.
cfDNA analyses	7-42			X	**Site 1:** Materials will be sent to Site 3 for analysis **Site 1:** % Complete: 100% preparation; 0% Complete **Site 3:** Analysis will be performed at a later stage of the trial.

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Please see table above.

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."
Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Global/ABCSG
In the next reporting period, we anticipate receiving full regulatory approval for the trial in the remaining countries, UK and Germany. All planned sites are already active in Australia, Austria and Spain. In Israel, a second site will be activated in Q4 2021. In view of two additional countries and one site getting activated in the next reporting period, it can be expected to see a substantial increase in recruitment numbers. However, as the COVID-19 situation remains uncertain in the region, specific predictions cannot be made at this point.
Furthermore, already active sites in Austria, Australia, Spain and Israel will enroll more participants.
Australia, Austria and Spain are also working on promotional campaigns and strategies to raise interest in trial participation. These campaigns are planned to be submitted to the regulatory bodies or be launched in the next reporting period. We are simultaneously working on submitting the trial to the Ethics Committee and Competent Authority in Germany, which should occur in Q3 2021.
It should be noted here that the COVID-19 pandemic remains unpredictable and does slow processes down, starting from EC/CA approvals to be received to enrollment of new participants (as these are healthy women, they often times are advised not to enter a hospital in these times).

However, the local sponsors and ABCSG are following up and supporting local teams as necessary and as possible. ABCSG is working together with local country sponsors regarding strategies on how to increase enrollment by regular Investigator calls and implementation of advertisement campaigns and recruitment materials.
Ongoing regular contact has been established (e.g. via teleconferences and harmonized documents) with all participating countries in order to support their current tasks, as well as with representatives of patient advocacy, and will be further maintained to achieve the set goals. Efforts to harmonize systems for registration and drug distribution between US and ABCSG are expected to be finalized in the next reporting period.

United States

During Q4 of 2021, we anticipate receiving full regulatory approval for the trial in the US. We have received the NCI CIRB approval on the A211801 protocol. We currently await final approval from the NCI Division of Cancer Prevention (DCP). Final NCI DCP approval is pending MoU and contract execution between the ABCSG and the Alliance. Following completion of negotiations between the Alliance and ABCSG, we anticipate that we will receive pending approvals to allow protocol activation in the US.
Our teams have also finalized the data user agreement designating MGH as the Data Coordinating Center (DCC) for the bone health sub-study. This data user agreement will allow transfer of de-identified images to the MGH DCC for analysis by the sub-study team.
In preparation for study activation in the US, the team at DFCI, Alliance and ABCSG have worked together to streamline training modules and processes for confirmed sites. In collaboration with the NCI's Cancer Trials Support Unit (CTSU), our team has made all training materials available online for site level training. Our teams will use the CTSU system to work with participating sites to securely submit regulatory materials to ensure timely study activation.
The US team has drafted a local study monitoring and safety plan. The US team will continue its collaboration with the ABCSG to harmonize participant registration systems and drug distribution processes. We have made significant progress on developing our participant recruitment material with plans in place to encourage diversity in recruitment and ensuring inclusion of minorities in our trial. All trial relevant participant-facing promotional materials will be approved by the NCI DCP, the NCI CIRB and local site level IRBs. To promote the trial, our team has developed recruitment materials focused on the providers, participants and partners. Our draft promotional materials include an elaborate BRCA-P study website (containing a study summary, call to action, and contact sheet in Spanish), shareable social media graphics (in English and Spanish), flyers (in English and Spanish), and study summary sheets (in English and Spanish). To promote diversity in our trials, we have partnered with two patient advocacy organizations (FORCE and TigerLily Foundation) who focus on providing information on cancer prevention and upcoming clinical trials to minority populations.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:
- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:
- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

This trial is currently in the recruitment phase and no results are available at this moment. However, mutations in *BRCA1* or *BRCA2* affect at least one in 400 women in the industrialized world. They are associated with up to 87% lifetime risk for the development of breast cancer, and a 15% to 50% lifetime risk for the development of ovarian cancer. There is now a widespread awareness that a positive family history of breast and/or ovarian cancer, particularly when early onset, could be due to the presence of a deleterious *BRCA1* or *BRCA2* germline mutation. As a result, affected women with a family history now commonly receive genetic testing. This is also being increasingly performed for women diagnosed with breast cancer before age 60 where their tumors exhibit '*BRCA1*-like' features, such as a Triple Negative Breast Cancer phenotype. Genetic

testing is increasingly relevant for their medical management, due to important therapeutic options that include consideration of mastectomy and incorporation of platin-based chemotherapy or parp inhibitors. Importantly, the identification of a mutation in cancer patients usually leads to 'cascade testing' of unaffected relatives to ascertain whether they harbor a pathogenic *BRCA* mutation. This practice increases the numbers of *BRCA1/2* mutation carriers who are unaffected by cancer.
+
Since both ovarian cancer and breast cancer can occur at young ages in women carrying a *BRCA1* mutation, they are usually advised to undergo prophylactic bilateral salpingo-oophorectomy (PBSO) at about age 40 (after completion of their families – NCCN guidelines) in order to prevent ovarian cancer.

However, early PBSO compromises bone health and may require ongoing monitoring of bone mineral density throughout life and treatment with bone-protective therapies. Available non-surgical chemopreventive options such as aromatase inhibitors (AIs) are often associated with significant menopausal symptoms, and a further decline in bone health. Alternative, non-hormonal chemopreventive strategies are thus urgently required.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

Nothing to report for US.

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Global

- Slow recruitment at some activated sites: proactive measures to motivate sites to enroll participants, such as communication via trial PI. Additionally, in Australia a recruitment campaign was already launched last year. Further advertisement and contact strategies will be initiated in the upcoming weeks in order to draw attention to the trial and thus boost enrollment. Further, also in Austria, Germany and Spain advertisement campaigns are being initiated. Additionally, in Austria the local Investigator (PI, Dr Singer) is following up personally with the Austrian sites to discuss potential issues and solutions. On a global level, ABCSG did hold an Investigator Meeting and a dedicated Investigator emergency TC to discuss the lack of enrollment and to underline to crucial point of getting enrollment started or increased. All country sponsors and Investigators are aware of the situation and are very involved in following up to address the respective local situation.

- Due to the ongoing pandemic, many active sites may experience a prolonged enrollment phase. To ensure continued drug supply, Amgen, the pharmaceutical partner, and drug provider was consulted, who has agreed to extend the recruitment phase until Dec 2023, thereby safeguarding the global drug supply for the extended treatment time.
- Slow activation in some countries such as US or UK. Ongoing efforts from ABCSG team to support these countries such as Teleconferences, provision of created trial documents and workflows. The UK should come on board shortly, while activation in the US is likely being pushed to 2022.

Activation / Recruitment delays:
Issue:
The ongoing COVID-19 pandemic has limited on-site staff, monitor and research team availability which may lead to a slowdown in site activation. We also expect delays/hesitance in participation from prospective participants since the general public cannot anticipate the behavior of the virus over the next few months. In countries that are already active (Austria, Australia, Spain and Israel), sites will reduce enrollment of participants as needed until the situation calms down and site staff is available / participants are not put at risk anymore. In countries where submission is already performed to EC / CA, such as UK the study / site activation may be delayed.

Resolution:
While it is difficult to predict how the COVID-19 pandemic will impact research practices across all countries in the next few months, the ABCSG, as the global coordinator, is in ongoing correspondence with active sites and with global partners and will offer assistance to all participating groups in order to have oversight, activate sites according to the local practice of respective participating countries and to provide harmonized information to all as needed, considering that local sponsors maintain responsibility to adhere with local regulations and laws and to ensure participant safety while on-site.

United States:
We have regular discussions with trial leadership and arrange timely follow-up to optimize trial conduct in the US. There have been ongoing efforts from ABCSG team to support US through regular teleconferences to monitor trial documents and workflows.

Administrative & COVID-19 related delays:
Issue:
1. Delays in MoU and Contract execution
2. Adapting US reporting systems to ABCSG's reporting systems

Resolution:
1. We have encountered unanticipated delays in contract finalization in the US: Our teams at DFCI and Alliance have regularly followed up with the NCI, ABCSG and the global study leadership to ensure timely contract agreement and finalization. We recently learned that the MoU has been reviewed by the NCI. Pending agreement between ABCSG and NCI, we anticipate that the contract will be signed and executed during Q4 of 2021.
2. The Alliance and NCI have devoted considerable effort to adapt our systems to harmonize participant registration, drug distribution, data collection, specimen collection and

processing, and all trial related activities with the ABCSG. Such coordinated efforts will ensure smooth trial conduct at all sites. The Alliance has conducted several system optimization and testing sessions with ABCSG's team to address challenges in system adaptation. We anticipate that system harmonization will also occur during Q4 of 2021.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Due to the persisting COVID-19 pandemic, study progress is still significantly affected. Slower recruitment and extended trial activation timelines in some countries have resulted in a prolonged enrollment phase and an increase in trial associated costs.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

There have been no changes in use or care of human subjects.

Significant changes in use or care of vertebrate animals

Not Applicable

Significant changes in use of biohazards and/or select agents

There are no changes in the use of study agent, denosumab.

6. **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

  This trial is currently in the recruitment phase and no results are available at this moment. The trial description is available on the ABCSG (https://www.abcsg.org/), BCT (https://www.breastcancertrials.org.au/home) and EMA (https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-002505-35/AT) homepages. Participant recruitment website is in development in the US.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

  Nothing to report

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

  Nothing to report

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report for the US

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change".

Name:	**Judy E. Garber, MD MPH**
Project Role:	Principal Investigator
No change	

Name:	**Nizar Bhulani, MD MPH**
Project Role:	Research Scientist/Project Manager – Dana-Farber Cancer Institute
No change	

Name:	**Marie Wood, MD**
Project Role:	Site Principal Investigator – University of Vermont
Research Identifier:	
No change	

Name:	**Geoffrey Lindeman, MBBS PhD**
Project Role:	Principal Investigator – ANZ Clinical Trials
No change	

Name:	**Sarah-Jane Dawson, PhD**

Project Role: Co-Investigator – ANZ Clinical Trials
No change

Name: **Bianca Capaldo**
Project Role: Research Officer – ANZ Clinical Trials
No change

Name: **Joy Tsai, MD**
Project Role: Co-Investigator – Massachusetts General Hospital
Research Identifier:
Nearest Person Month Worked: 1.2 CM for the period September 15, 2020 – September 14, 2021
Contribution to Project:
Dr. Tsai is responsible for all aspects of conducting this study including coordination of multi-site HR-pQCT enrollment, ensuring subject safety, budget planning, and communication with regulatory committees. She is also be responsible for data acquisition, data analysis, and preparation of manuscripts. She will have final responsibility of upholding the scientific and ethical integrity of the protocol.

Name: **Benjamin Leder, MD**
Project Role: Co-Investigator – Massachusetts General Hospital
Research Identifier:
Nearest Person Month Worked: 0.70 CM for the period September 15, 2020 – September 14, 2021
Contribution to Project:
Dr. Leder fulfilled the role of Dr. Tsai during this period in all the activities related to the project actively participating in decision making related to scientific, safety, and compliance issues.

Name: **Hang Lee, PhD**
Project Role: Co-Investigator – Massachusetts General Hospital
Research Identifier:
Nearest Person Month Worked: 0.40 CM for the period September 15, 2020 – September 14, 2021
Contribution to Project:
Dr. Lee supported Dr Leder in all the activities related to the project.

Name: **Michael Bruce**
Project Role: Research Assistant – Massachusetts General Hospital
Research Identifier:
Nearest Person Month Worked: 0.9 CM for the period September 15, 2020 – September 14, 2021
Contribution to Project:
Mr. Bruce participates in all aspects of the study protocol and assists with IRB correspondence and interactions with other HR-pQCT sites.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report for the US.

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Organization Name: ***Alliance for Clinical Trials in Oncology***
Organization Location: Chicago, IL
Partner's Contribution: The Alliance has worked with Dana-Farber Cancer Institute and other partner organizations like ABCSG to streamline processes for trial activation and set up in the US.

Organization Name: ***Mayo Clinic***
Organization Location: Rochester, MN
Partner's Contribution: The Mayo Clinic will serve as a central repository for all the human tissue and specimens collected during the trial in the US.

Organization Name: ***Forms Vision***
Organization Location: Hollandse Kade 13, 1391 JD Abcoude, Netherlands
Partner's Contribution: Implementation of an XML Web Service which enables ABCSG-50 study sites to complete randomization of subjects in ABCSG-50 through the US based RandoNode system.

Organization Name: ***Health Communication Core (HCC)***
Organization Location: Boston, MA
Partner's Contribution: The HCC will develop and host the trial website for the duration of the study.

Organization Name: ***FORCE: Facing Our Risk of Cancer Empowered***
Organization Location: Tampa, FL
Partner's Contribution: Force is a patient advocacy organization that would support participant recruitment by sharing trial relevant information on their platform.

Organization Name: ***TigerLily Foundation***
Organization Location: Stone Ridge, VA
Partner's Contribution: TigerLily Foundation is a patient advocacy organization that would support participant recruitment by sharing trial relevant information on their platform.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to* ***https://ers.amedd.army.mil*** *for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.*

9. APPENDICES: *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*