The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) is conducting a 5-year international multicentre double-blind placebo-controlled trial investigating the effects of exemestane, a steroidal aromatase inhibitor (AI), on breast cancer incidence in postmenopausal women at increased risk of developing breast cancer -- the MAP.3 (Excel) trial. We are proposing a companion study to this trial to examine the long-term effects of this agent on bone.

1.0 Background

1.1 Aromatase Inhibitors for Breast Cancer Prevention

Aromatase inhibitors (AIs) are a new class of endocrine therapy for breast cancer. These compounds inhibit aromatase (estrogen synthetase), an enzyme responsible for the conversion of androgens to estrogens. This conversion is the final step in the estrogen synthesis pathway. Blocking this conversion decreases circulating estrogen, reduces formation of the cancer-causing catechol metabolites of estrogen, and prevents stimulation of the estrogen receptor. Because of these properties, these agents are currently being investigated for use in advanced breast cancer and for the primary prevention of breast cancer in postmenopausal women at increased risk of developing breast cancer.

Currently, three AIs are approved in Canada and the US for the treatment of advanced breast cancer -- two reversible non-steroidal AIs (anastrozole and letrozole) and one irreversible steroidal AI (exemestane). These agents inhibit in vivo aromatization by >98% [1-3]. They also appear more efficacious than tamoxifen as adjuvant therapy [4-8]. The structures of the non-steroidal and steroidal AIs are different. The non-steroidal AIs (anastrozole and letrozole) bind reversibly to the p450 portion of the aromatase enzyme, whereas the steroidal AI (exemestane) binds irreversibly to the substrate-binding pocket. Exemestane has demonstrated anti-tumor effects in patients who have had no response to previous non-steroidal AI therapy [9]. In a

comparison study of exemestane, anastrozole and letrozole versus megestrol acetate as second-line hormonal therapy for postmenopausal women with advanced breast cancer, exemestane demonstrated improved survival times compared to the non-steroidal AIs as well as megestrol [10]. Unlike results reported for anastrozole [11] and letrozole [12], the median survival time had still not been reached for exemestane at 28 months [13]. Furthermore, exemestane produced objective responses in post-menopausal women with metastatic breast cancer after failure of treatment with non-steroidal AIs [9,14].

1.2 Effect of Aromatase Inhibitors on Bone

Because of their ability to almost completely deplete estrogen levels in the circulation, chronic use of AIs in postmenopausal women has the potential to adversely affect bone by increasing bone resorption and the risk of osteoporosis. Osteoporosis is a major health issue, affecting one in four women over the age of 50 in North America[15, 16]. Established osteoporosis risk factors for women include advanced age, postmenopausal status, Caucasian or Asian descent, late menarche or early menopause, low peak bone mass, and family history of osteoporosis or fracture[17-21]. The lifetime risk of any osteoporotic fracture for an average 50 year-old Caucasian woman is >40%[22, 23]. Osteoporotic fractures result in functional disabilities, pain, loss of independence, lower health-related quality of life, and are associated with increased mortality [24-27]. The potential adverse effect of AIs on bone is especially important as women who may be using AIs for breast cancer prevention are postmenopausal and are already at increased risk of osteoporosis and fractures.

Preliminary data showed that the non-steroidal AI letrozole increased markers of bone resorption in healthy post-menopausal women[28], as well as in women with previous DCIS, LCIS or benign breast disease[29]. Eastell et al examined changes in biomarkers of bone turnover after one year of

treatment and bone mineral density (BMD) after 2 years of treatment in a subgroup of 308 women participating in the Anastrozole or Tamoxifen Alone or in Combination (ATAC) breast cancer adjuvant therapy trial[30]. Anastrozole was associated with significant BMD loss and a small increase in bone turnover, whereas tamoxifen (and the combination) was associated with increased BMD and decreased remodeling. The overall ATAC trial, which involved 9366 postmenopausal women, reported a significantly higher incidence of fractures in women taking anastrozole compared to those taking tamoxifen (11.0% versus 7.7%, $p < 0.0001$) after a median follow-up of 68 months[31].

1.3 Effect of Exemestane on Bone

Exemestane is a third generation steroidal AI, structurally related to the natural substrate androstenedione. Its principal metabolite, 17-hydroexemestane, is androgenic. The effect of exemestane on bone may be different from the non-steroidal AIs because of the androgenicity of 17-hydroexemestane.

In preclinical models, exemestane and 17–hydroexemestane have positive effects on bone metabolism. Using mature female Sprague Dawley rats (an established animal model of postmenopausal osteoporosis), our group demonstrated that the adverse bone turnover changes associated with loss of estrogen can be reversed with exemestane[32]. Administration of exemestane or 17-hydroexemestane to ovariectomized (OVX) rats resulted in a significant reduction of both bone resorption (pyridinoline) and formation (osteocalcin) markers, to levels seen in non-OVX control rats[32, 33]. In contrast, letrozole-treated OVX rats had bone turnover markers similar to those seen in OVX rats[34, 35]. In addition, administration of exemestane or 17-hydroexemestane to OVX rats demonstrated a significant dose-dependent protection against BMD reduction at both the lumbar spine and the total hip. Lumbar spine BMD in rats given

exemestane was 99.7% of BMD in intact controls and 11% higher than in OVX rats (P <.0001). Total hip BMD in rats given exemestane was 99.9% of the BMD in intact controls and 7.1% higher than in OVX rats (P <.001). In contrast, letrozole did not protect against the loss of BMD associated with the loss of estrogen[35].

In a recent study by Lonning and colleagues, there were no statistically significant difference in changes in lumbar spine BMD when comparing women with breast cancer taking exemestane versus those taking placebo for 2 years[36]. There was a small 1.24% decrease in femoral neck BMD in the exemestane group, which is not clinically significant based on commonly observed coefficients of variation in the femoral neck[37]. In addition, early evidence from the Intergroup Exemestane Study (IES) that randomized women to exemestane or tamoxifen (after two or three years of adjuvant treatment with tamoxifen) indicated that therapy with exemestane did not lead to significantly more fractures that tamoxifen: respectively, 3.1% versus 2.3% (p=0.08) at a medial of 30.6 months follow up[4]. In summary, exemestane may have a better bone profile than non-steroidal AIs.

1.4 Measurements of Bone Strength

The current gold standard for measuring bone strength in the clinical setting is the measurement of BMD by Dual-energy X-ray Absorptiometry (DXA), as BMD has been shown to be the best skeletal independent predictor of fractures[38-40]. For one standard deviation (1SD) decrease of BMD at the spine and the hip, there is a 2.3 times and a 2.6 times increase in risk for spine and hip fractures, respectively[41-43]. Bone strength, however, depends on both the material composition (such as bone mineral content or BMD) and the structural properties (such as size, shape, and microarchitecture) of bone. Recent data suggest that bone loss with the loss of estrogen at and after menopause is associated with a compensatory increase in periosteal

apposition which partially preserves bone strength[44]. There is an inverse relationship between serum estradiol levels and periosteal apposition: the lower the serum estradiol level, the greater the periosteal apposition. In pubertal boys, androgen production also increases periosteal apposition, bone diameter and cortical thickness. Ideally, to measure bone strength or changes in bone strength, a combination of BMD and bone geometric parameters should be used. High-resolution peripheral quantitative computed tomography (pQCT) is a new technology that can determine both bone geometric parameters (such as cortical thickness, trabecular thickness, trabecular separation and trabecular number), and BMD (such as total, cortical and trabecular volumetric BMD)[45]. It has very low radiation (similar to the radiation of a DXA scan) and is currently used in osteoporosis treatment trials as the primary endpoint.

2.0 Rationale

Recent data suggest that exemestane may have better efficacy for the primary prevention of breast cancer than non-steroidal AIs. Based on animal models and preliminary clinical data, exemestane may also have less adverse effects on bone because of the androgenicity of its principal metabolite, 17-hydroexemestane. Currently, the NCIC CTG is conducting a 5-year international multicentre double-blind placebo-controlled trial investigating the effects of exemestane for the primary prevention of breast cancer in at risk postmenopausal women. To determine whether this drug is a good and safe choice for breast cancer prevention, we will need to establish its effect on bone in postmenopausal women who are already at increased risk of osteoporosis. If exemestane is shown to have a neutral effect on bone, perhaps due to its steroidal properties and androgenic effects, and is effective in preventing breast cancer, it may be a safe choice for postmenopausal women at increased risk of developing breast cancer. If

exemestane is shown to have a detrimental effect on bone as suggested by Lonning et al[46, 47], its risks and benefits for breast cancer prevention will need to be assessed in this population.

What we are interested in is the effect of exemestane on bone strength. While BMD is the gold standard for measurement of bone strength in the clinical setting, bone geometry plays an important role in bone strength as well[48, 49]. Both the loss of estrogen and the androgenic effects of 17–hydroexemestane can theoretically increase periosteal apposition, thereby increasing bone strength. Thus, we are proposing a companion study to examine the long-term effects of exemestane on bone geometry and BMD in postmenopausal women at increased risk of developing breast cancer.

3.0 Research Objectives

Our primary objective is to examine the effect of exemestane in women without osteoporosis participating in the MAP.3 trial on total volumetric BMD at the distal radius at 2 years.

Our secondary objectives are to determine:

1) The effect of exemestane on total volumetric BMD at 1 year, and cortical and trabecular volumetric BMDs by pQCT at 1 and 2 years at the distal radius and the distal tibia, and total volumetric BMD at 2 years at the distal tibia**;**
2) The effect of exemestane on cortical thickness, the trabecular thickness, trabecular number and trabecular separation at both the distal radius and the distal tibia at 1 and 2 years; and
3) Effects of exemestane on lumbar spine (L1-L4) and total hip BMDs by DXA at 1 and 2 years;
4) The effect of exemestane on bone strength index at 1 and 2 years.

Our primary hypothesis is that exemestane does not induce significant loss of volumetric BMD at the distal radius. Our secondary hypotheses are that exemestane does not induce significant loss of bone strength in postmenopausal women at increased risk of developing breast cancer at 2

years. While there may be mild decreases in BMD scores at the lumbar spine and the total hip by DXA at 2 years with exemestane, there will be compensatory changes in bone structure and geometry such that bone strength index may not be significantly affected.

4.0 Methods

4.1 Study Design

The NCIC CTG MAP.3 trial is a 5-year international, multicentre, randomized double-blind, placebo controlled study of exemestane (25mg daily) versus placebo in 4,560 postmenopausal women at increased risk of developing breast cancer (Please see **Appendix 1.1** for lay summary of the study.) Currently, there are slightly more than 1500 women recruited worldwide. The main study does not have funding for a bone component (except for the collection of clinical fractures as a safety endpoint); that is why we are applying for peer-review funding for the assessment of bone parameters in this population. This companion study will involve a subset of 300 women without osteoporosis participating in MAP.3.

Only centres with access to the high-resolution pQCT scanner, X-treme CT, will participate in this companion study. X-treme CT has been recently shown to have high reproducibility (coefficient of variation between 0.7-1.5% for volumetric BMD and 2.5-4.4% for trabecular architecture) for assessing bone density and microarchitecture at the distal radius and the distal tibia[45]. It also has the ability to detect age- and disease-related changes [45]. Currently, there is one in Toronto, Canada, one in University of California in San Francisco, and one in Mayo Clinic in Rochester, Minnesota. Thus, the MAP.3 centers in Toronto (University Health Network, Women's College Hospital, and Mount Sinai Hospital), the University of California at Davis and the Mayo Clinic center will participate in this substudy. (These centers have done well in terms of recruitment of subjects. Over the past year or so, they have recruited

approximately 100 women in Toronto, 160 women at UC Davis and 20 women at the Mayo Clinic.) Women being randomized to MAP.3 at these participating centres who meet our inclusion and exclusion criteria **(Appendix 2.1)** will be approached for informed consent **(Appendix 2.2)** to participate in this companion study. All eligible women will be approached until recruitment for this companion study is complete. This approach will maintain a balance between the two arms of the trial.

Women who are leaving the study for any reason will be asked to have their pQCT and DXA scans at the time of exiting the study, unless these measurements were performed with the past 6 months. Reasons for withdrawal can include development of breast or other cancers, permanent stopping of study medications for any reason, development of fragility fractures or osteoporosis, and other unexpected personal reasons.

4.2 Study Population

As part of the main MAP.3 protocol, all women will have had a BMD measurement within 1 year prior to randomization. Those who do not have osteoporosis and have a T-score above -2.0 at the lumbar spine, total hip and femoral neck will be considered for this companion study. We chose a BMD cutoff of T-score = -2.0 because postmenopausal women (especially those age 65 and over) who have BMD lower than a T-score of -2.0 are currently recommended to consider pharmacological therapies for their bones[15, 50]. Pharmacological therapies are confounders of the true change in bone, if any, with exemestane. In addition, if women have ANY of the following exclusion criteria, they are not eligible for this companion study. These criteria are to ensure safety of the participants and to enhance internal validity of the study:

1. Women with osteoporosis;
2. Women with T-score of -2.0 or below at the lumbar spine (L1-L4), total hip or femoral neck;

3. Women with a fragility fracture after age 40;
4. Women who have been on any bone drug, such as hormone replacement therapy, bisphosphonates, teriparatide, parathyroid hormone, sodium fluoride, strontium, calcitonin and high dose vitamin D (more than 2000iu of vitamin D_3 daily), in the past 3 months;
5. Women who have ever been on a bisphosphonate for more than 6 months;
6. Women who have ever been on strontium for more than 1 month;
7. Women who are on chronic oral steroids (the equivalent of 5mg of prednisone a day or higher for more than 2 weeks within the past 6 months and will likely require ongoing therapy);
8. Women with Paget's disease, Cushing's disease, hyperparathyroidism, uncontrolled hyperthyroidism or other metabolic bone diseases;
9. Women with inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, lupus, psoriatic arthritis, or hepatitis.
10. Women with malabsorption syndromes such as untreated celiac disease.
11. Women with decompensated diseases of the liver, bowel, kidney, pancreas, lung, or heart.

4.3 Intervention

A. Participant Assignment and Blinding:

Based on the MAP.3 main protocol, participants in this companion study will be randomly assigned to 25mg of exemestane daily versus a placebo pill daily using a central randomization process at NCIC CTG (**Appendix 1.1**). This companion study is double-blinded; neither the participants nor the study investigators/staff will be aware of the participant assignments.

It is possible that changes in BMD and bone geometry measurements could lead to changes in behaviour on the part of the participant or study physician/staff and may introduce bias. To prevent this, BMD and bone geometric measurements made in this substudy will not be available

to participants or study staff until the end of the study period. Results will, however, be reviewed by a central International Society of Clinical Densitometry (ISCD) certified densitometrist, and a letter will be generated to notify study staff of any significant changes necessitating a change in care for the participant (See Safety section).

B. Calcium and Vitamin D supplementation:

All participants in this companion study will be assessed for dietary calcium and vitamin D intake at baseline and yearly using standardized forms (**See Appendix 2.3).** They will receive calcium and vitamin D supplementation so that their estimated daily intake will approximate recommended levels (1200-1500mg Ca, 800iu Vitamin D) for postmenopausal women. Centres unable to use the calcium calculator will provide standardized supplementation in the amounts of 500-650 mg calcium and 400 IU vitamin D daily to each study participant in this companion study.

4.4 Data Collection

Participants will be followed for a total of 2 years from randomization (baseline). After the baseline visit, follow-up will occur at 1 year and 2 years (**See Appendix 2.4, Data Collection Schedule)**.

A. Bone Specific Variables

In addition to the outcome measures in this companion study and the baseline data collected in the main MAP.3 study, we will collect data that will allow us to do the following:

1. Verify the comparability of two treatment groups, e.g. patient demographics, health behaviors, medical history, diet, etc.
2. Assess the generalizability of the study cohort, e.g. age, ethnicity, socio-economic status, etc.
3. Ensure the health of our participants is not being compromised.

The extra variables include alcohol use, fracture history, balance and risk of falls questions, family history of osteoporosis and fractures, and dietary intake of calcium and vitamin D, if possible. Study staff will collect these variables during follow-up visits using standardized case report forms (CRFs) **(Appendices 2.3, 2.5).**

Fractures sustained within this study will be confirmed with radiological reports. Patients who complain of new back pain that are suspicious of vertebral fractures will have lateral spine X-rays for confirmation. Details of how the fracture was sustained, when it was sustained, and the fracture site will be collected on standard CRFs (**Appendix 2.6**). A committee consisting of at least 2 experts in osteoporosis and fractures will conduct fracture adjudication. Fractures will be divided into fragility fractures versus traumatic fractures.

B. pQCT Measurements

High-resolution pQCT assessments will be performed by experienced technologists at the 3 research centers (University Health Network, University of San Francisco and Mayo Clinic in Rochester), using the X-treme CT (Scanco, Switzerland). In general, the acquisition of these scans takes approximately 30mins, with scan times of 5-10minutes per site. The technologists will follow standard protocols established by Scanco for the positioning of the limb and the acquisition of data. Repeat scans at follow-up should be done on the same equipment, preferably using the same technologist. All the scans will be sent to University Health Network for central processing and analysis by a single experienced technologist according standard protocols. This technologist has scanned and analyzed more than 400 postmenopausal women in the past few months. The 3 pQCT centers will also perform daily and weekly quality control measurements as per standard protocol. Scans will have to be repeated if the 5th rod in the daily phantom exceeds 1% deviation from the established baseline mean. In addition, we will ship around a

standard daily phantom to all three sites and the centers will scan this phantom 10 times at the beginning of the study and at the end of the study. This will assess the variability in measurements between the sites and potential drift of the equipment over the study period.

C. DXA Measurements

Similarly, DXA measurements will be performed by experienced technologists at the participating centers, using either Hologic or Lunar densitometers. In general, the acquisition of these scans will take approximately 15-20minutes, with scan times of 1-3 minutes per site. The technologists will follow standard protocols from the manufacturers for positioning and acquisition of the data. Repeat scans at follow-up should be done on the same equipment, preferably using the same technologist. These scans will also be sent to University Health Network for central processing and analysis by a single experienced ISCD-certified technologist and reviewed by an ISCD densitometrist according to standard protocols. University Health Network Bone Density Laboratory is already serving this function for other NCIC trials, as well as other peer-reviewed funded studies. Recent quality control data from this laboratory showed coefficient of variations of 0.89% for the lumbar spine (L1-L4) and 1.09% for the total hip for the Hologic QDR 4500/ Delphi A when thirty-two volunteers with T-scores ranging from -2.9 to 4.1 were scanned twice with on-and-off the scanning table and repositioning in between scans. These results are consistent with other published data.

The 3 DXA centers will perform daily and monthly quality control measurements using methods described by Bonnick et al [51]. The quality control logs over the study period will be reviewed as part of quality assessment of the bone density scans in the study. In addition, we will ship around a standard Hologic morphometric spine phantom to all three sites and the centers will scan this phantom 10 times at the beginning of the study and at the end of the study. This again

will assess the variability in measurements across the sites and the potential drift in equipment over the study period.

4.5 Outcome Definition

The primary outcomes of interest are the percentage change in total volumetric BMD at the distal radius from baseline to 2 years. This percentage change is defined as the ratio of the change in volumetric BMD from baseline to the end of second year to the baseline BMD. Secondary outcomes include the difference in percentage changes in cortical and trabecular volumetric BMDs by pQCT at the distal radius and the distal tibia, as well as areal BMDs by DXA at the lumbar spine (L1-L4) and total hip, the difference in percentage changes in bone structure and geometry (cortical thickness, trabecular thickness, trabecular number and trabecular separation), and the difference in bone strength indices from baseline to 1 year and from baseline to 2 years between the two groups.

The calculation of bone strength indices will follow the protocol by Schneider et al[52]. Using pQCT scans obtained, we will measure the periosteal diameter, the medullary diameter, and the cortical thickness of the distal radius. The total cross-sectional area, the medullary area, and the cortical area will be calculated on the assumption that the bone is cylindrical (area = diameter^2 x $\pi/4$). Cross-sectional moment of inertia will be calculated based on ([periosteal diameter/2]^4 - [medullary diameter/2]^4) x $\pi/4$. The section modulus is an estimate of the ability of the distal ulna to withstand bending forces and will be calculated as the cross-sectional moment of inertia (CSMI) divided by half the periosteal diameter. Previous cadaveric studies have shown that the CSMI in this region is highly correlated with the strength of the bone[53].

4.6 Sample Size/Power Calculations:

Our primary objective is to show that the two-year reduction in total volumetric BMD at the distal radius is *not increased* by a clinically important amount in the exemestane group. Specifically, we calculate the percent reduction for each subject between baseline and two years and then compare the means of these percentages between groups. Let D be the true difference in the mean percent BMD reduction between the two study groups: D = [% Change on Exemestane] - [% Change on Placebo]. Our sample size calculations are based on using this value D to show that exemestane is not inferior to placebo with respect to BMD loss at this site. The sample size calculation for a noninferiority design requires the choice of a non-inferiority boundary (δ), here the maximum value for D that would be consistent with a conclusion that exemestane is not non inferior to placebo. Jones has suggested that a δ should be about half the size of the clinically important difference that would be chosen in a comparative trial[54]. The value 8% can be considered a clinically significant percentage change, since a 3-5% per year change is considered clinically significant for an individual. Thus, we choose δ=4%. There is no published longitudinal X-treme CT data to use as a source for the standard deviation of the two-year percent change, although several current osteoporosis treatment trials are using this technique for the assessment of bone geometric parameters as the primary endpoint. We used results from Boutroy et al[45]on the mean (254 mg HA/cm^3) and between-subject standard deviation (62 mg HA/cm^3) for total density, and the correlation between baseline and two year BMD in our own Vitamin K study (r=0.9) to estimate the variance of the percent change using the delta method. The null hypothesis for this study is H_0: D> 4%. We computed the sample size under the alternative hypothesis that relative to placebo, exemestane does not increase bone loss at 2 years in postmenopausal women at increased risk of developing breast cancer (D=0).

With $\alpha = 5\%$ and 90% power, 128 subjects per arm will give 90% power to reject the hypothesis of a clinically important difference in changes in volumetric BMD at the distal radius site. Another way to consider this study design is that 125 subjects per arm will give a 90% probability that the 95% confidence interval for D will exclude the clinically unimportant value of 4%.

Based on an assumption of 10% withdrawal rate (missing assessment or lost to follow-up) and a 5% drop out rate (stopping study medications due to adverse events or developing conditions contraindicated in this study) during the first two years of follow-up, we estimate that we will need to recruit 150 patients per group (total of 300 participants).

4.7 Data Analysis

All analyses will operate on the principle of intention to treat. Significance will be assessed at a level of $\alpha=0.05$ for primary and secondary outcomes. Baseline characteristics, secondary diagnoses not related to the study and medication use will be summarized for each treatment group at baseline and 2 years. In the case of withdrawals, we will ask that they return at the two year mark for final pQCT and DXA measurements if appropriate (i.e., if they are not taking any bone altering medications or they have not developed a condition that is known to affect BMD); if this is not possible or appropriate, we will attempt to get final pQCT and DXA measurements at the time of withdrawal and the observed changes in BMDs and geometric parameters will be extrapolated to give predicted 2 year outcomes. Where patients have only a baseline BMD, we will make various assumptions about the missing data (e.g., it is ignorable; or missing changes in the treatment group were relatively large) and test the sensitivity of the results to these assumptions. We will summarize patient characteristics and reasons for withdrawals by treatment

group. We will also determine whether participants who withdraw from the study differ from those who remain in terms of factors relating to the primary outcome of interest.

Analysis of the primary and secondary outcomes:

The primary objective of this study is to show that at 2 years exemestane causes a percent decrease in total volumetric BMD at the distal radius that is no more than an absolute 4% larger than the percent decrease seen in subjects using placebo. As outlined in section 4.6, this analysis will use a one-sided test of the null hypothesis H_0: D> 4%. The choice of a non-inferiority boundary (δ) is a somewhat subjective one. To aid in the interpretation of the results for those who might use a different δ, an upper one-sided 95% confidence interval for D will be presented. The upper end of this confidence interval indicates (with 95% confidence) the largest amount of increased BMD loss among subjects on exemestane that is consistent with the data from the trial. Because the main MAP.3 study is still blinded at 2 years, we will have the unblinded analyses performed by Dr. Tomlinson (and his group) who is unrelated to the main study. Investigators involved in the care of patients will not have access to individual patient data.

Similar confidence interval approach used for the primary outcomes will be used to analyze these secondary outcomes -- that is, we will construct one-sided confidence limits for the difference in these outcomes between placebo and exemestane groups and compare these limits with accepted clinically significant differences for these outcomes to assess whether exemestane has no clinically significant impact on these outcomes.

The percentage change in cortical and trabecular volumetric BMDs, and areal BMDs at 1 year, as well as bone structural indices at 1 and 2 years, are secondary endpoints and will be analyzed the same way as the 2-year change in total volumetric BMD at the distal radius.

If there is evidence of a "drift" in DXA or pQCT calibrations, sensitivity analyses of the primary and secondary outcomes will use values corrected for the drift. This can be done by performing a least squares fit of the true to the observed densities of the phantoms and using this factor to correct the observed values at that particular centre. These values will be corrected according to the calibration scan performed closest in time to the affected scans.

5.0 Safety Issues:

High-resolution pQCT scans and BMD scans by DXA have very low radiation. Each set of scans is similar to radiation exposure of 1/5 of a chest X-ray, or to 1 – 1 ½ times the daily background radiation on earth. Thus, these scans pose minimal to no risk to study subjects. For safety of the subjects and to minimize fracture risk, the central laboratory at University Health Network reviewing these scans will inform the center involved when there are participants who drop 10% or more BMD at the lumbar spine (L1-L4), total hip or femoral neck or when participants' T-scores fall to or below -2.5 at 1-year follow-up. These participants (either by the ≥10% BMD drop or T-score ≤ -2.5 criteria) as well as those who sustain a clinical low-trauma fracture during the study period at the spine or in any long bones (clavicle, humerus, radius, ulna, femur or tibia) will be withdrawn from this companion study and will be counseled with respect to treatment options. However, these participants will be allowed to stay in the MAP.3 main study for the duration of the main study.

6.0 Adverse Events

All adverse events (AEs) and serious adverse events (SAEs) as defined by the Food and Drug Administration (FDA) in the United States will be recorded and analyzed as part of the main study. An arms-length safety committee will monitor all SAEs throughout the study.

7.0 Personnel

Dr. Cheung, the principal applicant, is Associate Professor in the Departments of Medicine and the Clinical Epidemiology and Health Care Research Program at the University of Toronto. She is currently holding a 5-year CIHR / Ontario Women's Health Council Career Scientist Mid-Career Award in postmenopausal health. She directs the University Health Network Bone Density Laboratory, which serves as a central review for a number of peer-reviewed funded studies. She has been a key member of the Osteoporosis Canada Clinical Guidelines committee, the Ontario Women's Health Council Strategic Working Group on Osteoporosis, and the Canadian Task Force for Preventive Health Care clinical practice guidelines on the prevention and management of postmenopausal osteoporosis. She is a site-PI and the bone substudy chair for MAP.3. Dr. Cheung will be responsible for the overall design, conduct, analyses and the preparation of the manuscript for this companion study.

Dr Goss is Professor of Medicine at Harvard Medical School and the international chair of the NCIC CTG MAP.3 study as well as the international chairman of four other international trials of aromatase inhibitors in postmenopausal women with early stage and advanced breast cancer. He is the principal and co-investigator of sub-studies of bone metabolism in the NCIC CTG MA27 and NCIC CTG MA17 trials respectively. In his laboratory, Dr Goss has conducted several studies in the preclinical setting of bone metabolism with exemestane and the non-steroidal aromatase inhibitors anastrozole and letrozole. He has also conducted a study in postmenopausal volunteers on the effects of exemestane, letrozole and anastrozole on biochemical markers of bone metabolism.

Dr. Richardson is a PhD epidemiologist and Assistant Professor in Community Health & Epidemiology at Queen's University in Kingston, Ontario. She is the Project Coordinator for

clinical trials of various agents in breast cancer chemoprevention at NCIC CTG, including the MAP.3 trial. In this role, she is responsible for the overall conduct of the MAP.3 trial. She will ensure that data from the main study and this companion study are successfully integrated, and will be a member of the steering committee of this companion study.

Drs. Tile (co-investigator, Toronto site), Pruthi (Additional Author, Rochester site) Eisen (co-investigator, Sunnybrook Regional Cancer Centre site), and Robbins (Collaborator, Davis site) are experienced researchers in women's health. They have a strong track record in recruitment of postmenopausal subjects and have participated in large women's health clinical trials such as RUTH, STAR, WHI. They have high standards for the conduct of these studies and follow good clinical practice guidelines. They will be in charge of patient recruitment, assessment and overseeing the conduct of this substudy at their site.

Drs. Sharmila Majumdar and Sundeep Khosla (collaborators, UCSF and Rochester) are experts in the field of non-invasive assessment of bone strength and bone microarchitecture. They run high quality research laboratories for both pQCT and DXA measurements. They will be lending their expertise and that of their research group for the conduct of this companion study.

Dr. Tomlinson is Assistant Professor in the Department of Public Health Sciences at the University of Toronto. He is an expert biostatistician in randomized controlled trials (RCTs) and non-inferiority/equivalence studies and will be lending his expertise to this project.

8.0 Steering Committee and Quality Control

A Steering Committee consisting of Drs. Cheung, Goss, Richardson, Pruthi and Robbins will be established to: review issues around recruitment and retention; monitor data quality via random chart reviews; monitor quality of BMD and quality control of participating pQCT and DXA laboratories; develop consensus on arising issues; and advise the principal investigator on study

related issues. The committee will meet or have teleconferences at least semi-annually for the first 2 years and annually for the rest of the study, and as needed to address specific issues.

9.0 Feasibility

The MAP.3 study is recruiting steadily (~1500 women over the past 2 years) but will likely need another 2-3 years to complete recruitment of the main study. The Toronto, Rochester and Davis sites are some of the more productive recruitment sites in the study. They have a total of ~200 subjects enrolled currently, and estimate they will enroll another 600 in the next couple of years. All the sites have plans in place to ramp up recruitment. Dr. Cheung has been successful in recruiting over 2 years 440 postmenopausal women for a single-center prevention study. From experience, the investigators estimate that of the 600 women estimated to be recruited over the next couple of years between all the participating sites, half of them will be eligible and willing to participate. Thus, we believe achieving a 300 women sample size for this companion study is do-able amongst the participating centers.

10.0 Timeline (Appendix 2.7)

This is expected to be a 4.75-year study – 3months for startup (phantom quality control assessments using phantoms, training of technologists and study coordinators etc), 2 years for recruitment, 2 years for follow-up and half a year for data cleaning, analyses and preparation of manuscript.

11.0 Confidentiality

All participant data will be kept strictly confidential. All CRFs and test results are only linked to a study participant number. All data will be stored in locked cabinets and password protected computers at NCIC Clinical Trials Centre and at University Health Network. Participants will not be identifiable from any results published or presented as a result of this companion study.

12.0 Relevance

This is the first study to examine in detail the effects of exemestane on bone strength in a population of postmenopausal women without breast cancer. Development of third generation AIs is one of the most significant advances in treatment of estrogen positive breast cancers. Whether this is also true in the preventative setting depends to a large extent on its tolerability and side effect profile. The findings of this companion study will provide useful definitive clinical information on the effects of exemestane on bone strength in postmenopausal women, a population already at risk for osteoporosis. Identifying the effects of exemestane on bone is critical and will impact how it is used, both in the adjuvant and preventative setting.

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Questions and Answers

When Considering Participation in the ExCel Research Study

What is the ExCel research study?
The ExCel research study is a phase III breast cancer prevention clinical trial. It is a new and important international clinical trial designed to determine whether a special type of medication can prevent breast cancer in healthy postmenopausal women who have an increased risk for developing breast cancer.

The ExCel research study is coordinated by the National Cancer Institute of Canada Clinical Trials Group in cooperation with healthy women and cancer centers in the United States, Canada and Spain. The NCIC CTG is funded by the Canadian Cancer Society.

More than 4,500 women will take part in the ExCel research study.

Why is this study being done?
In 1998, tamoxifen was identified as the first drug treatment available to women for the prevention of breast cancer. However, tamoxifen can cause a number of serious side effects in women, including cancer of the uterus and blood clots. Therefore, women need to seriously consider both the risks and benefits of tamoxifen use before accepting it.

Scientific evidence suggests that the treatment being tested in the ExCel research study (exemestane) may also help prevent breast cancer and with fewer side effects. However, the only way to find out for sure is to test it on healthy women who, for a number of reasons, may have a greater than average risk of developing breast cancer.

If successful, we may have another option for breast cancer prevention that has fewer serious side effects than tamoxifen.

What is the design of the ExCel study?
Women eligible for the study will be randomly assigned to one of two treatment groups and all women will take one pill per day for five years.

- If you are in Group A, you will get 1 tablet of **exemestane** per day.
- If you are in Group B, you will 1 tablet of placebo per day (an inactive substance that does not have any of the medicine being studied in the trial).

What is the medication used in this trial and why?
After menopause, when the ovaries stop making estrogen, the body continues to make estrogen from skin, muscle and fat. Even though it is only present at low levels, it continues to be very important in the development of breast cancer.

Exemestane is one member of a class of drugs called aromatase inhibitors. Aromatase inhibitors limit the body's ability to produce estrogen. Estrogen plays a key role in the development and growth of most types of breast cancer and inhibition of estrogen may prevent breast cancer in many women.

Exemestane is approved by the U.S. Food and Drug Administration (FDA) and Health Canada and is marketed by Pfizer, Inc. as Aromasin®. It is currently used for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.

How long will the study last?
The study will enroll participants for two years and the results should be available in four to five years.

Questions and Answers

When Considering Participation in the ExCel Research Study

Who can participate?
Every clinical trial has a set of inclusion and exclusion criteria which are used to ensure that subjects who enter this study are medically appropriate candidates for this therapy. For the safety of the subjects, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other women with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

You may be able to participate in ExCel if:

- you are 35 years of age or older
- you are postmenopausal (not having monthly periods)
- you are at increased risk for developing breast cancer. Some of the factors that can increase your risk are:
  - age
  - family history of breast cancer
  - number of breast biopsies
  - age at first menstrual period
  - age at time of first live birth

Unfortunately women who fit certain exclusion criteria cannot participate in the study. Some of the key exclusion criteria are:

- premenopausal
- taking hormone replacement therapy
- diagnosed with primary invasive breast cancer

What can I expect if I join ExCel?
Before beginning any treatment, you will have a regular health examination that will include some routine blood tests. The research staff will measure your blood pressure, take your pulse, record your height and weight, and check your breasts, lungs, heart and abdomen. You will have a mammogram (if you have not had one done within the past 12 months) and a bone mineral density x-ray test, to measure the thickness of your bones (if you have not had one in the past year).

If you are eligible and you choose to participate, you will read and sign a consent form that explains the ExCel research study in more detail. Then you will be randomly assigned to one of two treatment groups and will take one pill per day for five years.

You will have two follow-up visits during the first year – at six and 12 months – and then an annual follow-up visit during years two through five for clinical evaluation. During these visits you will have routine blood tests and a mammogram. You will also be asked to complete some questionnaires at your follow-up appointments about your overall health and quality of life. During the study, your doctor will watch you closely to see if you have side effects from the study drug or any other medications that you may be taking.

Why is ExCel a placebo-controlled clinical trial?
In this study, there is a one in two chance that you will receive only placebo (an inactive substance). You may have concerns about taking part in the study because of this. However, this is the best way we have to see if a new therapy is effective, and to clearly see the potential side effects and impact on quality of life.

Three other breast cancer prevention studies have already been done. These studies all compared tamoxifen to placebo. All three of these studies have shown that certain groups of women who took tamoxifen greatly lowered their chance of getting breast cancer. These groups were women 35 to 59 years old who had an above average risk of developing breast cancer and women older than 60 years old who had an average or high risk of developing breast cancer.

Because of its side effects, tamoxifen has only been approved by the FDA for preventing breast cancer in women who are at "high risk." For example, tamoxifen caused endometrial cancer, stroke, blood clots and eye problems (cataracts) especially in older women who were past menopause. It also caused increased symptoms in menopausal women, such as hot flashes, vaginal discharge and genital itch.

The benefit of tamoxifen is best seen in young women before menopause. It is less helpful to women who have past menopause.

The American Society of Clinical Oncology (ASCO) has noted the side effects of tamoxifen. They also noted that the tamoxifen clinical trials have not clearly shown that this drug has a good effect on overall health and helps to lower the rate of death from breast cancer. ASCO has therefore recommended the use of a placebo in breast cancer prevention clinical trials to help ensure studies provide clear information about the potential benefits of treatments being tested.

What does it mean to participate in a *randomized, double-blind* study?
If you decide to participate, you will be **randomized** into one of the study groups described. Randomization means that you are put into a group by chance. It is like flipping a coin. Neither you nor your doctor can choose what group you will be in. You will have a one in two chance of being placed in either group.

This study is a **double-blind** study, which means that neither you nor the doctor will know if you are taking **exemestane** or **placebo**. In an emergency, if the treatment needs to be identified it will be.

What protections do I have?
Before and during a cancer prevention trial, you have several important rights:

- informed consent: you have the right to know all you need to make a thoughtful decision about joining a study.
- changing your mind: you have the right to leave the study at any time.
- medical monitoring: you have the right to have your health watched throughout the study.
- removal from harm: you will be taken off the study if doctors learn that an agent may harm you.

How is the safety of participants ensured? Is the trial monitored?
Participant safety is central to the clinical trial process and very important to ExCel investigators. The clinical trial process involves many safeguards to ensure that a participant's well-being is protected at all times.

There are strict requirements about who can join the trial. The health care team in each center will closely monitor participants' health and watch for any side effects.

There is an independent Data Safety and Monitoring Committee (DSMC) that will provide oversight of the trial. The DSMC includes medical and cancer specialists, biostatisticians and lay people. The DSMC will meet every six months to review the safety data from all participants. In addition, the DSMC is available to review the trial safety data, any time, at the request of the NCIC CTG trial team.

All centers will also be audited by the NCIC CTG to ensure they are following the protocol and working within the *Good Clinical Practice* guidelines.

Will I need to see my regular doctor?
Participating in a clinical study does not replace your regular medical care. You should continue to see your regular doctor. If you are accepted into the study, it will be important for your doctor to know about your participation.

What is exemestane used for?
High levels of estrogen, especially in postmenopausal women, can increase the risk of breast cancer because estrogen plays a key role in the development and growth of some types of breast cancer. Even when the ovaries stop making estrogen after menopause, the body still continues to produce it in low levels. Exemestane stops the production of estrogen and its supply to pre-cancerous and cancerous cells, therefore, preventing them from growing.

Exemestane is a treatment being used successfully in women with breast cancer and it has been shown to be highly effective in preventing the disease from returning. It also prevents the occurrence of new cancer in the opposite breast, suggesting that it may prevent the disease in healthy women.

Exemestane is approved by the FDA and Health Canada and is marketed by Pfizer, Inc. as Aromasin®. It is currently used for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy.

What are the common side effects of exemestane?
Exemestane is well-tolerated and side effects associated with this treatment are generally predictable and manageable. However, as with most medications, including over the counter preparations, prescription drugs and drugs used in research studies, exemestane may cause side effects in some women.

The known symptoms for exemestane are related to the suppression of estrogen and may include hot flashes; low grade nausea is seen occasionally. Few women stop taking exemestane due to side effects.

Why can't premenopausal women participate in ExCel?
Exemestane is one member of a class of drugs called aromatase inhibitors. Exemestane, given alone, is not recommended in premenopausal women for two reasons:

1) Aromatase inhibitors work against breast cancer by suppressing the body's ability to produce estrogen. In postmenopausal women, estrogen is still produced in the body's fat, skin and muscle and it can be fully suppressed by the inhibitors.

   In premenopausal women, estrogen production comes mainly from the ovaries and the inhibitors cannot adequately suppress this.

2) By partially, but inadequately, suppressing estrogen from the ovaries, the inhibitors cause a reflex stimulation by hormones from the pituitary gland in the brain. This over stimulates the ovaries, and can cause ovarian cysts, pain and discomfort. It can also result in an increase in fertility and an unwanted pregnancy.

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐ **Participant Initials** ☐☐☐

INCLUSION/EXCLUSION WORKSHEET

Participant is INCLUDED because she:

	Yes	No	N/A*
A1. Meets the MAP.3 main study inclusion/exclusion criteria _____	☐	☐	☐
A2. Does not have osteoporosis_____	☐	☐	☐
A3. Has T-scores that are –1.9 or higher at the lumbar spine (L1-L4), total hip and femoral neck (*note*: a T-score of –2.0 or lower at any ***one*** of the three sites excludes the participant)_____	☐	☐	☐
A4. Available for follow-up – (to have BMD/pQCT scans at the same site _____	☐	☐	☐

Participant is EXCLUDED because she has:

	Yes	No	N/A*
B1. Sustained a fragility fracture after age 40 (Fragility fracture is defined as a fracture sustained with minimal trauma, often from a standing height or less without external force, such as a slip and fall on a slippery surface when walking. Fractures sustained from car accidents or sports injury are not considered fragility fractures.)	☐	☐	☐
B2. Been on any bone drug in the past three months. Drugs not covered in the main study criteria include: hormone replacement therapy (except Vagifem® and Estring®, or estrogen creams no more than 3 times per week, as per MAP3 criteria), bisphosphonates (such as Etidronate (Didrocal®), Alendronate, (Fosamax®), Risedronate (Actonel®), Ibandronate (Boniva®), Zoledronic acid (Zometa®), Clodronate (Bonefos®), Pamidronate (Aredia ®), Teriparatide (Forteo ®), sodium fluoride, strontium, calcitonin (Miacalcin ®) and high doses of vitamin D (equivalent to 2000 IU/day of vitamin D3)_____	☐	☐	☐
B3. Been on any bisphosphonate for more than 6 months total or on strontium for more than 1 month total during her lifetime_____	☐	☐	☐
B4. Been on chronic oral steroids (the equivalent of 5mg of Prednisone daily or higher for more than 2 weeks within the past 6 months and will likely require ongoing therapy- Inhaled steroids are permissible)_____	☐	☐	☐
C1. Paget's disease, Cushing's disease, hyperparathyroidism, uncontrolled hyperthyroidism or other metabolic bone diseases _____	☐	☐	☐
C2. Inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, lupus, psoriatic arthritis, hepatitis _____	☐	☐	☐
C3. Malabsorption syndromes such as untreated celiac disease _____	☐	☐	☐
C4. Advance disease of the liver, bowel, kidney, pancreas, lung or heart_____	☐	☐	☐

Interviewer notes:_____

_____

_____

_____

_____

*N/A = question was not asked (e.g. participant was excluded and did not want to answer further questions)

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐ **Participant Initials** ☐☐☐

FOLLOW-UP

Reason for follow-up:

☐ Interviewer needs to review inclusion/exclusion criteria → Specify question: _____

Participant: ☐ is perimenopausal

☐ wants to think about joining this companion study

☐ may discontinue medication → Specify: _____

☐ is currently not available, but may be in future

☐ other: _____

Date of follow-up	Notes	Interviewer's initials

APPOINTMENT SCHEDULING

Preferred dates and times: _____

_____

_____

_____

_____

Participant is scheduled for:	☐ **full baseline visit**
Date (Day/Month/Year)**:**	/ /
Appointment time:	
Researcher:	

Insert Hospital Letterhead

EFFECTS OF EXEMESTANE ON BONE STRENGTH IN POSTMENOPAUSAL WOMEN AT INCREASED RISK OF DEVELOPING BREAST CANCER (MAP.3Bone Strength Study)

A Companion Study to NCIC CTG Trial MAP.3 (Excel)

Consent to Allow the Evaluation of Bone Geometry and Bone Mineral Density (Optional)

Because you are enrolled in the Study of Exemestane Versus Placebo in Postmenopausal Women at Increased Risk of Developing Breast Cancer (NCIC CTG MAP.3, also called Excel), you may choose to participate in a companion research study that will measure the effect of this medication on bone. This is an optional part of the Excel study and refusal to take part in this companion study will not affect participation in the main study.

You are being asked to take part in a research study. Before agreeing to participate in this study it is important that you read and understand the following explanation of proposed procedures. The following information describes the purpose, benefits, discomfort, risks and precautions associated with this study. It also describes your right to refuse to participate or withdraw from the study at any time. In order to decide whether you wish to participate in this research study, you should recognize enough about its risks and benefits in order to make an informed decision.

Please ask the study doctor or study staff to explain any words you do not understand before signing this consent form. Make sure all of your questions have been answered to your satisfaction before signing this document.

WHY IS THIS COMPANION STUDY BEING DONE?

Exemestane blocks the effects of estrogen in our bodies. After menopause, the strength of bones slowly declines. Estrogen is important to the maintenance of bone health in postmenopausal women. The purpose of this optional part to the MAP.3 (Excel) research study, called a 'companion study', is to evaluate the effects of exemestane on the thinning of bones (osteoporosis).

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Women from across Canada and the US who are participating in the main MAP.3 trial are eligible for participation in this companion study. Approximately 300 women enrolled in MAP.3 will participate in this study. This companion study will run for the first 2 years that you are in MAP.3 and will not require any additional visits.

WHAT IS INVOLVED IN THE COMPANION STUDY?

If you decide to participate in this study you will be asked:

- To have bone geometry (peripheral Quantitative Computer Tomography (pQCT)) scans of your wrist and ankle on 3 separate occasions, (at baseline, 1 year and 2 years).
- To have bone mineral density scans of your lumbar spine and 1 hip on 3 separate occasions (at baseline, 1 year and 2 years).
- To take calcium and vitamin D supplements based on your dietary intake.
- To provide any previous fracture history or family history of fractures and/or osteoporosis.
- To have your height measured yearly for the duration of the study

pQCT Measurement:

If you agree to take part in this substudy, you will be asked to have your bone geometry assessed by peripheral quantitative computer tomography (pQCT) measurements of your forearm and ankle before you begin MAP.3. Only one forearm and one ankle will be tested. You will be asked to have pQCT measurements of your forearm and ankle again at your 1-year and 2-year visits.

Bone Mineral Density Measurement:

If you decide to participate, one measurement of bone mineral density of your spine and hip will be done before you begin the MAP.3 study. This measurement is called 'dual-energy x-ray absorptiometry', or DXA.

While you are taking part in MAP.3Bone Strength Study, you will have one measurement of bone mineral density of your hip and spine at year 1 and year 2. You will not be informed of the results of these measurements. An independent doctor, not related to the study, will examine all the scans and will notify study staff and you if you develop osteoporosis or if there is significant bone loss. You will then be taken out of this companion study and counseled on treatment options. If you are removed from the companion study, you will not have to leave the main Excel study.

Calcium and Vitamin D:

If you agree to take part in this companion study and are a suitable candidate, you will be given daily calcium and Vitamin D supplements in standard doses (to be taken by mouth) to help prevent osteoporosis. These supplements will be provided to you free of charge.

HOW LONG WILL I BE IN THIS COMPANION STUDY?

The companion study will run for the first 2 years you are in MAP.3. You can refuse to participate in this companion study or stop taking study medications at any time. However, if you decide to stop participating in this companion study, you should talk to

your study doctor first. You will be asked to have a final assessment of BMD, and bone geometry.

WHAT ARE THE RISKS OF THE STUDY?

Having a pQCT scan takes approximately 10 minutes and involves a very small amount of x-rays, approximately 20% of the dose used for a routine chest X-ray, similar to that experienced with a bone mineral density scan. The entire procedure is painless and is done while you are sitting up on a cushioned chair.

Having a DXA scan is also painless and involves lying down for 10-20 minutes on a cushioned machine that produces very small amounts of x-rays. For this test you may be required to remove or adjust some clothing or jewelry that may contain metal objects. The amount of radiation is less than 10% of the dose used for a routine chest x-ray.

There are no known described risks or side effects to the measurement of bone mineral density with DXA or with measurement of bone geometry by pQCT.

Vitamin D and Calcium will be provided to all women in this companion study. Side effects from calcium and Vitamin D are rarely seen but may include: stomach upset or constipation.

WHAT IF I STOP PARTICIPATION IN THIS COMPANION STUDY

If you decide to stop participation in this substudy you are still eligible to stay in the main study.

If you are removed from the companion study due to a drop in bone density or developing a fragility fracture, or for any other reason, you will be counseled on treatment options for your bones. You will not be required to leave the main study should this happen.

ARE THERE BENEFITS TO TAKING PART IN THE COMPANION STUDY?

If you agree to take part in this companion study, there may or may not be direct medical benefit to you. The information learned from this companion study may benefit other women at increased risk for developing breast cancer who decide to take exemestane in the future.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. No identifying information will be transferred outside of this hospital. We cannot guarantee absolute confidentiality.

Organizations that may inspect your medical records and receive information from your medical records for quality assurance and data analysis are:

- National Cancer Institute of Canada Clinical Trials Group (NCIC CTG),
- The research group at University Health Network in Toronto that is coordinating this companion study
- The Research Ethics Committees who oversee the ethical conduct of this study

- U.S. Food and Drug Administration (because it oversees the use of new drugs in the U.S.)
- Health Canada (because it oversees the use of new drugs in Canada).

This may include information from the main study (MAP.3) required for completion of case report forms and the results of your BMD studies. In addition, relevant information on adverse and serious adverse events that occur while in the main study (MAP.3) will be used in this companion study. The organizations listed above will keep information about you confidential, to the extent permitted by applicable laws, in the following manner:

- Your name will not be used in any reports about the companion study;
- You will be identified only by a serial number and initials
- Identifying information will be kept behind locked doors.

WHAT ARE THE COSTS?
You will receive no compensation for taking part in this companion study. Taking part may result in added costs to you. You may ask about any expected added costs.

In the case of research-related side effects or injury, medical care will be provided by your doctor or you will be referred for appropriate medical care. Although no funds have been set aside to compensate you in the event of injury or illness related to the study treatment or procedures, you do not waive any of your legal rights for compensation by signing this form.

Calcium and Vitamin D will be given to you free of charge as long as you participate in the MAP.3Bone Strength companion study. If Bisphosphonates become a necessary part of your treatment, your doctor will select the best drug, dose and schedule. You understand that the Bisphosphonates will NOT be provided free of charge by the organizers of the study and that, if they are required, you or your medical insurer will have to cover their costs.

WHAT ARE YOUR RIGHTS AS A PARTICIPANT?
Taking part in this companion study is voluntary. You may choose not to take part or may leave the companion study at any time. Refusing to take part or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you choose not to take part or if you stop participating in this companion study, your participation in the main MAP.3 study will not be affected.

You will be told about new information that may affect your health, welfare, or willingness to stay in this companion study.

You will be given a copy of this signed consent form.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
If you have questions about taking part in this companion study, or suffer a research-related injury, you can talk to your study doctor, Dr. Principal investigator, Hospital name, at (xxx) xxx-xxxx, or your study nurse coordinator, name, at (xxx) xxx-xxxx.

For questions about your rights as a research participant, please call research ethics board at (xxx) xxx-xxxx.

SIGNATURES

I have had the opportunity to discuss this study and my questions have been answered to my satisfaction. I consent to take part in the study and am aware that I may withdraw at any time without affecting my medical care. I have received a signed copy of this consent form. I voluntarily consent to participate in this study.

_____	_____	_____
Participant's Name (please print)	Participant's Signature	Date

I confirm that I have explained the nature and purpose of the study to the participant named above. I have answered all questions.

_____	_____	_____
Name of Person Obtaining Consent	Signature	Date

_____	_____	_____
Name of Doctor	Signature	Date

If this consent process has been done in a language other than that on this written form, with the assistance of a translator, please indicate:
(language)_____

_____	_____
Signature of Translator	Date

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐☐ **Participant Initials** ☐☐☐

4. Calcium and Vitamin D Supplement Dosage Recommended:

Complete the attached dietary assessment in order to determine the amount of vitamin supplementation required (Page 4)

Daily Calcium supplement recommended (1500mg – Total Calcium from all sources) _____
(From page 4)

Daily Vitamin D supplement recommended (800IU – Total Vitamin D from all sources) _____
(From page 4)

Calcium (600 mg) with Vitamin D (400 IU)	_____ tablets daily	_____ bottles dispensed
Calcium (600 mg) without Vitamin D	_____ tablets daily	_____ bottles dispensed
Vitamin D (400 IU)	_____ tablets daily	_____ bottles dispensed
Calcium Citrate (350 mg) without Vitamin D	_____ tablets daily	_____ bottles dispensed

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐☐ **Participant Initials** ☐☐☐

Calcium and Vitamin D Dietary and Supplement Income Assessment

Calcium-Rich Foods 1 cup = 250 ml	**Portion Size**	**Milligrams per Portion**	**Number of Portions for the past 7 days**	**Total Milligrams of Calcium for the past 7 days**	**Vitamin D intake for the past 7 days**
Bread	2 slices	50 mg			
Broccoli, cooked	3/4 cup	50 mg			
Kidney beans, Lima beans, Lentils	1 cup	50 mg			
Orange (fruit, not juice)	1 medium	50 mg			
Tahini	2 Tbsp.	50 mg			
Bok choy or Kale, cooked	1/2 cup	75 mg			
Chickpeas	1 cup	75 mg			
Cottage cheese (regular or low fat)	1/2 cup	75 mg			
Ice cream	1/2 cup	75 mg			
Parmesan cheese	1 Tbsp.	75 mg			
Almonds	1/4 cup	75 mg			
Baked beans, Soybeans, White beans	1 cup	150 mg			
Ice milk, Frozen yogurt (reg. or low fat)	1/2 cup	150 mg			
Pancakes or Waffles, made with milk	3 medium	150 mg			
Pudding, made with milk	1/2 cup	150 mg			
Soft and semi-soft cheese such as feta, mozzarella, camembert (reg. or low fat)	1 1/4" cube	150 mg			
Soup, made with milk	1 cup	150 mg			
Tofu, made with calcium	3 oz.	150 mg			
Firm cheese such as cheddar, swiss, gouda (reg. or low fat)	1 1/4" cube	250 mg			
Processed cheese slices (reg. or low fat)	2 slices	250 mg			
Salmon or Sardines, canned with bones	1/2 can	250 mg			
Yogurt, fruit flavoured (reg. or low fat)	3/4 cup	250 mg			
Milk - skim, 1%, 2%, whole, buttermilk or chocolate **[1 cup contains 100 IU Vitamin D]**	1 cup	300 mg			
Calcium-fortified beverages (e.g. soy, orange juice, rice)	1 cup	300 mg			
Skim milk powder	1/3 cup	300 mg			
Yogurt, plain (reg. or low fat)	3/4 cup	300 mg			
TOTAL Calcium and Vitamin D intake from Food FOR 7 DAYS					

TOTAL Calcium and Vitamin D Intake ÷ 7 (TOTAL TAKEN PER DAY IN FOOD)		

Is participant taking any supplements that contain calcium or vitamin D? ☐ Yes ☐ No

	Calcium (mg)	Vitamin D (IU)
If yes, how much does the participant take per day?	_____	_____
TOTAL CALCIUM AND VITAMIN D TAKEN PER DAY (From all Sources)	_____	_____

Use this information to complete the amount of supplementation required on the previous page

Calcium supplement recommended (1500mg – Total Calcium from all sources) _____
(Transfer to page 3)

Vitamin D supplement recommended (800IU – Total Vitamin D from all sources) _____
(Transfer to page 3)

Data Collection Schedule

Data Collected	Baseline	1-Year	2-Year	Final Visit
BMD – lumbar spine (L1-L4), left hip	X	X	X	X
PQCT – radius, tibia	X	X	X	X
Bone Specific Medical History: **eg.** Alcohol consumption, family history, falls, fractures, etc.	X			
Current Medical history: **eg.** Changes in lifestyle, falls, fractures		X	X	X
Dietary Assessment	X	X	X	
Dispense Calcium and Vitamin D	X	X		
Height, Weight measurement	X	X	X	X

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐☐ **Participant Initials** ☐☐☐

CASE REPORT FORM – BASELINE

Date of Visit: ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

Date Informed Consent Obtained: ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

Does the participant meet all Inclusion/Exclusion criteria for the MAP.3 main study? ☐ Yes ☐ No

Does participant meet all Inclusion/Exclusion criteria for MAP.3Bone Strength study companion Study? ☐ Yes ☐ No

1. MEASUREMENTS:

Date of X-treme pQCT (Radius and Tibia): ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

Date Scan mailed to UHN: ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

Date of Bone Densitometry (Hip and Spine (L1-L4): ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

Date Scan mailed to UHN: ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

Height ☐☐☐.☐ ☐ inches ☐ cm

Weight ☐☐☐.☐ ☐ lbs ☐ kg

2. OSTEOPOROSIS RISK FACTORS:

2.1 Alcoholic Beverage Consumption: Does participant drink alcoholic beverages?

☐ Yes If YES: How many ***servings*** of wine per week? _____
☐ No How many ***servings*** of beer per week? _____
How many ***servings*** of spirits per week? _____

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐☐ **Participant Initials** ☐☐☐

2.2 Fracture History: Has the participant ever had a fracture at age 40 and over? ☐ Yes ☐ No

If YES: Specify:

	Never	Yes, Once	Yes, Multiple	Don't Know
Vertebrae	☐	☐	☐	☐
Wrist	☐	☐	☐	☐
Hip	☐	☐	☐	☐
Other, Specify:_____	☐	☐	☐	☐

2.3 Falls: During the past 12 months, has the participant fallen and landed on the floor or ground or fallen and landed on an object like a table or stair?

☐ Yes If YES: How many falls in the past 12 months? _____
☐ No

Is the participant presently using any walking assistive device?

☐ Yes If YES: What type of device? _____
☐ No

Has the participant fainted, passed out, or blacked out in the last 12 months?

☐ Yes ☐ No

2.4 Family History: Is there a family history of osteoporosis in the participant's family?

☐ Yes If YES: Who? ☐ Parent ☐ Sibling ☐ Both ☐ Unknown
☐ No
☐ Unknown

Has anyone in the participant's family ever broken a hip after the age of 40?

☐ Yes ☐ No ☐ Unknown

2.5 Surgical Menopause: Has the participant had a hysterectomy?: ☐ Yes ☐ No

If YES please provide date of surgery: ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

Were Ovaries removed?: ☐ No ☐ Yes, one ovary
☐ Yes, both ovaries

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐☐ **Participant Initials** ☐☐☐

3. Bone Medication Use:

Past and current treatments	**Never**	**Previously**	**Currently**	**Duration of Use** (No of months)	**Date Stopped** (month /year)
Calcium	☐	☐	☐	_____	_____
Vitamin D	☐	☐	☐	_____	_____
Calcitonin	☐	☐		_____	_____
Strontium	☐	☐		_____	_____
Fluoride	☐	☐		_____	_____
Other, specify below:	☐	☐	☐	_____	_____

4. Calcium and Vitamin D Supplement Dosage Recommended:

Complete the attached dietary assessment (Page 4) in order to determine the amount of vitamin supplementation required

Daily Calcium supplement recommended (Approx. 1500mg minus Total Calcium from all sources) (From page 4) _____

Daily Vitamin D supplement recommended (Approx. 800IU minus Total Vitamin D from all sources) (From page 4) _____

Calcium 600 mg with Vitamin D 400 IU _____ tablets daily _____ bottles dispensed

Calcium 650 mg _____ tablets daily _____ bottles dispensed

Vitamin D 400 IU _____ tablets daily _____ bottles dispensed

Note: Supplements Available

A) Jamieson Super Calcium (600 mg Calcium + 400 IU Vitamin D) – 75 tablets/bottle
B) Jamieson MegaCal (650 mg Calcium) – 100 tablets/bottle
C) Jamieson Vitamin D (400 IU vitamin D) – 90 tablets/bottle

A combination of the above supplements may be used to provide a daily calcium intake between 1200-1500 mg and a daily vitamin D intake between 400-800 IU.

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐☐ **Participant Initials** ☐☐☐

Calcium and Vitamin D Dietary and Supplement Income Assessment

Calcium-Rich Foods 1 cup = 250 ml	**Portion Size**	**Milligrams per Portion**	**Number of Portions for the past 7 days**	**Total Milligrams of Calcium for the past 7 days**	**Vitamin D intake for the past 7 days**
Bread	2 slices	50 mg			
Broccoli, cooked	3/4 cup	50 mg			
Kidney beans, Lima beans, Lentils	1 cup	50 mg			
Orange (fruit, not juice)	1 medium	50 mg			
Tahini	2 Tbsp.	50 mg			
Bok choy or Kale, cooked	1/2 cup	75 mg			
Chickpeas	1 cup	75 mg			
Cottage cheese (regular or low fat)	1/2 cup	75 mg			
Ice cream	1/2 cup	75 mg			
Parmesan cheese	1 Tbsp.	75 mg			
Almonds	1/4 cup	75 mg			
Baked beans, Soybeans, White beans	1 cup	150 mg			
Ice milk, Frozen yogurt (reg. or low fat)	1/2 cup	150 mg			
Pancakes or Waffles, made with milk	3 medium	150 mg			
Pudding, made with milk	1/2 cup	150 mg			
Soft and semi-soft cheese such as feta, mozzarella, camembert (reg. or low fat)	1 1/4" cube	150 mg			
Soup, made with milk	1 cup	150 mg			
Tofu, made with calcium	3 oz.	150 mg			
Firm cheese such as cheddar, swiss, gouda (reg. or low fat)	1 1/4" cube	250 mg			
Processed cheese slices (reg. or low fat)	2 slices	250 mg			
Salmon or Sardines, canned with bones	1/2 can	250 mg			
Yogurt, fruit flavoured (reg. or low fat)	3/4 cup	250 mg			
Milk - skim, 1%, 2%, whole, buttermilk or chocolate **[1 cup contains 100 IU Vitamin D]**	1 cup	300 mg			
Calcium-fortified beverages (e.g. soy, orange juice, rice)	1 cup	300 mg			
Skim milk powder	1/3 cup	300 mg			
Yogurt, plain (reg. or low fat)	3/4 cup	300 mg			
TOTAL Calcium and Vitamin D intake from Food FOR 7 DAYS					

TOTAL Calcium and Vitamin D Intake ÷ 7 (TOTAL TAKEN PER DAY IN FOOD)		

Is participant taking any supplements that contain calcium or vitamin D? ☐ Yes ☐ No

	Calcium (mg)	Vitamin D (IU)
If yes, how much does the participant take per day?	_____	_____
TOTAL CALCIUM AND VITAMIN D TAKEN PER DAY (From all Sources)	_____	_____

Use this information to complete the amount of supplementation required on the previous page

Calcium supplement recommended (1200-1500mg – Total Calcium from all sources) _____
(Transfer to page 3)

Vitamin D supplement recommended (400-800IU – Total Vitamin D from all sources) _____
(Transfer to page 3)

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐ **Participant Initials** ☐☐☐

MEDICAL HISTORY – FOLLOW UP FORM

Date of Visit: ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

1. MEASUREMENTS:

Date of X-treme pQCT (Radius and Tibia): ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

Date Scans mailed to UHN: ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

Date of Bone Densitometry (Hip and spine (L1-L4): ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

Date Scans mailed to UHN: ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

Height ☐☐☐.☐ ☐ inches ☐ cm

Weight ☐☐☐.☐ ☐ lbs ☐ kg

2. MEDICAL HISTORY FOLLOW UP:

2.1 Alcoholic Beverage Consumption:

Has participant's alcoholic beverage consumption changed in the last 12 months?

☐ Yes **If YES:** How many ***servings*** of wine per week? _____

☐ No How many ***servings*** of beer per week? _____

How many ***servings*** of spirits per week? _____

2.2 Smoking:

Has the participant's cigarette smoking changed in the last 12 months?

☐ Yes **If YES:** ☐ Started smoking or smokes a different number of cigarettes?

☐ No Current average number of cigarettes per day _____

☐ Stopped smoking?

2.3 Fractures:

Has participant had any fractures since last visit? ☐ No ☐ Yes

If YES: Please specify type of fracture: _____(Complete Fracture Form)

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐ **Participant Initials** ☐☐☐

2.4 Falls/Balance:

During the past 12 months, has the participant fallen and landed on the floor or ground or fallen and landed on an object like a table or stair?

☐ Yes **If YES**: How many falls in the past 12 months? _____

☐ No

Is the participant presently using any walking assistive device?

☐ Yes **If YES:** What type of device? _____

☐ No

Has the participant fainted, passed out, or blacked out in the last 12 months?

☐ Yes ☐ No

3. BONE SPECIFIC MEDICATION:

Has the participant started any bone medication in the last 12 months? ☐ Yes ☐ No
(e.g. bisphosphonates, SERMS, strontium, steroids, etc)

If YES: Please specify type of medication: _____

Should participant be discontinued from MAP.3Bone Strength Study? ☐ Yes ☐ No

4. Calcium and Vitamin D Supplement Dosage Recommended:

Has the participant's diet changed significantly over the past 12 months? ☐ Yes ☐ No

If YES: Please redo the Dietary Assessment form to recalculate the new amount of dietary calcium and vitamin D required.

If NO, dispense same quantity of Calcium and Vitamin D as previous visit.

Calcium 600 mg with Vitamin D 400 IU	_____ tablets daily	_____ bottles dispensed
Calcium 650 mg	_____ tablets daily	_____ bottles dispensed
Vitamin D 400 IU	_____ tablets daily	_____ bottles dispensed

Note: Supplements Available

A) Jamieson Super Calcium (600 mg Calcium + 400 IU Vitamin D) – 75 tablets/bottle
B) Jamieson MegaCal (650 mg Calcium) – 100 tablets/bottle
C) Jamieson Vitamin D (400 IU vitamin D) – 90 tablets/bottle

A combination of the above supplements may be used to provide a daily calcium intake between 1200-1500 mg and a daily vitamin D intake between 400-800 IU. **PROTOCOL**

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐ **Participant Initials** ☐☐☐

5. Continuation//Discontinuation in MAP.3 Bone Strength Study:

Will this subject continue to receive MAP.3 study drug? ☐ Yes ☐ No
If No: Will this subject continue in Follow-up? ☐ Yes ☐ No

Will this subject continue to follow MAP.3 Bone Strength Study protocol? ☐ Yes ☐ No

If subject is discontinuing MAP.3 Bone Strength Study protocol, please indicate reason below:

- ☐ Completed Follow-up Period
- ☐ Intercurrent Illness: *Description:*_____
- ☐ Developed Osteoporosis or experienced a Fragility Fracture; *please complete Investigator Summary Form*
- ☐ Protocol Violation (started exclusion medication): *Type:*_____
- ☐ Removed from MAP.3 Main study: *Reason*:_____
- ☐ Dropped Out of MAP.3 Main study: *Reason:*_____
- ☐ Other: _____
- ☐ Unknown
- ☐ Lost to Follow-Up

Notes:

Site Identification ☐☐☐☐ **Participant Number** ☐☐☐ **Participant Initials** ☐☐☐

Calcium and Vitamin D Dietary and Supplement Intake Assessment

Calcium-Rich Foods 1 cup = 250 ml	Portion Size	Milligrams per Portion	Number of Portions for the past 7 days	Total Milligrams of Calcium for the past 7 days	Vitamin D intake for the past 7 days
Bread	2 slices	50 mg			
Broccoli, cooked	3/4 cup	50 mg			
Kidney beans, Lima beans, Lentils	1 cup	50 mg			
Orange (fruit, not juice)	1 medium	50 mg			
Tahini	2 Tbsp.	50 mg			
Bok choy or Kale, cooked	1/2 cup	75 mg			
Chickpeas	1 cup	75 mg			
Cottage cheese (regular or low fat)	1/2 cup	75 mg			
Ice cream	1/2 cup	75 mg			
Parmesan cheese	1 Tbsp.	75 mg			
Almonds	1/4 cup	75 mg			
Baked beans, Soybeans, White beans	1 cup	150 mg			
Ice milk, Frozen yogurt (reg. or low fat)	1/2 cup	150 mg			
Pancakes or Waffles, made with milk	3 medium	150 mg			
Pudding, made with milk	1/2 cup	150 mg			
Soft and semi-soft cheese such as feta, mozzarella, camembert (reg. or low fat)	1 1/4" cube	150 mg			
Soup, made with milk	1 cup	150 mg			
Tofu, made with calcium	3 oz.	150 mg			
Firm cheese such as cheddar, swiss, gouda (reg. or low fat)	1 1/4" cube	250 mg			
Processed cheese slices (reg. or low fat)	2 slices	250 mg			
Salmon or Sardines, canned with bones	1/2 can	250 mg			
Yogurt, fruit flavoured (reg. or low fat)	3/4 cup	250 mg			
Milk - skim, 1%, 2%, whole, buttermilk or chocolate **[1 cup contains 100 IU Vitamin D]**	1 cup	300 mg			
Calcium-fortified beverages (e.g. soy, orange juice, rice)	1 cup	300 mg			
Skim milk powder	1/3 cup	300 mg			
Yogurt, plain (reg. or low fat)	3/4 cup	300 mg			
TOTAL Calcium and Vitamin D intake from Food FOR 7 DAYS					

TOTAL Calcium and Vitamin D Intake ÷ 7 (TOTAL TAKEN PER DAY IN FOOD)		

Is participant taking any supplements that contain calcium or vitamin D? ☐ Yes ☐ No

	Calcium (mg)	Vitamin D (IU)
If yes, how much does the participant take per day?	_____	_____
TOTAL CALCIUM AND VITAMIN D TAKEN PER DAY (From all Sources)	_____	_____

Use this information to complete the amount of supplementation required on the previous page

Calcium supplement recommended (1200-1500mg – Total Calcium from all sources) _____
(Transfer to page 2)

Vitamin D supplement recommended (400-800IU – Total Vitamin D from all sources) _____
(Transfer to page 2)

Site Identification ☐☐☐☐ Participant Number ☐☐☐ Participant Initials ☐☐☐

INVESTIGATOR SUMMARY FORM – FRACTURE / OSTEOPOROSIS

Date of Event ☐☐ - ☐☐☐ - ☐☐☐☐ **Adverse Event number** ☐☐☐
Day Month Year

REASON FOR FORM:

1. Osteoporosis:

Did participant's T-score fall to (= or below –2.5)?
In the total lumbar spine? ☐ Yes ☐ No
In the total hip? ☐ Yes ☐ No
In the femoral neck? ☐ Yes ☐ No

If yes, please provide date of BMD ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

2. Fracture:

2.1 What type of fracture was it?
☐ Fragility
☐ Non-Fragility
☐ Difficult to determine

2.2 Is a radiology report available? ☐ Yes ☐ No

2.3 Was the participant hospitalized for 24 hours or more? ☐ Yes ☐ No

If yes, please provide date of admission: ☐☐ - ☐☐☐ - ☐☐☐☐
Day Month Year

2.4 Was the fracture caused by a life-threatening event? ☐ Yes ☐ No
If yes, explain _____

2.5 Did the event result in a severe or permanent disability? ☐ Yes ☐ No ☐ Don't know
If yes, explain _____

2.6 What is the anatomical site of the fracture? (Mark all that apply)

☐ Skull
☐ Spine
☐ Arm / Forearm / Elbow
☐ Hand / finger
☐ Clavicle / Scapula / Shoulder
☐ Other _____
☐ Ribs / Sternum
☐ Pelvis / Sacrum
☐ Hip/ Femur
☐ Tibia / Fibula / Patella
☐ Foot / Toe
☐ Wrist
☐ Ankle

Site Identification ☐☐☐☐ Participant Number ☐☐☐ Participant Initials ☐☐☐

2.7 Please provide a brief description of the event below:

_____
_____
_____
_____
_____
_____
_____
_____
_____

3. Will participant be going out of Bone Strength Study? ☐ Yes ☐ No

4. Will participant be going out of main Excel study? ☐ Yes ☐ No

Investigator signature: _____ Date: _____

Printed name: _____

Study Coordinator's signature: _____ Date: _____

Printed name: _____

Study Timeline