K01 Alcohol & Breast Cancer (ABC) Trial

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PROTOCOL TITLE:

Effect of Light Alcohol Intake on Sex Hormone Levels among Postmenopausal Women with ER+ Breast Cancer on Aromatase Inhibitor Therapy: The Alcohol and Breast Cancer (ABC) Trial

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1.0 Objectives*

Alcohol intake raises sex hormone levels, however, it is unknown if that effect persists in postmenopausal women with estrogen receptor-positive (ER+) breast cancer on aromatase inhibitor (AI) therapy, which is an estrogen suppressant. There have been no studies to examine alcohol's effect on sex hormone levels among postmenopausal women with ER+ breast cancer receiving AI therapy. These drugs are only prescribed to postmenopausal women who had ER+ breast cancer, the subtype where alcohol has been found to increase breast cancer incidence. This information is needed for postmenopausal women with estrogen receptor-positive (ER+) breast cancer to make informed decisions about their alcohol intake and its potential effect on adjuvant AI therapy.

To address this issue, we will conduct a pilot randomized controlled crossover trial of 20 postmenopausal women with estrogen receptor-positive (ER+) breast cancer who receive AI therapy and who consume at least one alcoholic drink per week but not more than one drink per day, to assess whether alcohol at low "real-world" levels of intake increases sex hormone levels in the presence of AI's.

We hypothesize that the expected within-person increases in sex hormone levels following light alcohol consumption will not be observed among women using aromatase inhibitor therapy throughout study enrollment.

2.0 Background*

Several controlled feeding studies among premenopausal and postmenopausal women showed that alcohol supplementation for a few weeks acutely increases estrogen and sex hormone-binding globulin (SHBG) levels. However, data on how light intake of alcohol impacts sex hormone levels among women receiving estrogen suppressants is critical for guiding postmenopausal women with estrogen receptor-positive (ER+) breast cancer about the safety of alcohol intake.

In a cross-sectional study of 490 postmenopausal breast cancer survivors (Wayne S. *Cancer Epidemiol Biomarkers Prev*. 2008;17(11):3224-3232.), alcohol intake and sex hormone levels were strongly associated despite the relatively low range of alcohol intake in study participants. Tamoxifen use dampened the association between alcohol intake and dehydroepiandrosterone sulfate (DHEAS) levels, and among participants with ER+ tumors, there was no association between alcohol intake and sex hormone-binding globulin (SHBG).

Although alcohol intake raises sex hormone levels, it is unknown if that effect persists on aromatase inhibitor therapy, in part because the mechanism underlying alcohol's effect on sex hormone levels is not well understood. Despite the potential

risks of alcohol intake on hormone levels, a cancer diagnosis is not associated with long-term changes in daily alcohol intake. Furthermore, there have been discrepant findings on the association between alcohol intake and breast cancer recurrence and survival. Some studies have found that alcohol intake is not associated with a higher rate of breast cancer mortality, and it may even lower the rate of all-cause mortality.

There have been no studies to examine alcohol's effect on sex hormone levels among postmenopausal women with estrogen receptor-positive (ER+) breast cancer receiving aromatase inhibitor therapy. This information is needed for them to make informed decisions about their alcohol intake and its potential effect on adjuvant aromatase inhibitor therapy. Therefore, we will conduct a pilot randomized controlled crossover trial to assess whether alcohol at low "real-world" levels of intake increases sex hormone levels in the presence of aromatase inhibitor therapy.

3.0 Inclusion and Exclusion Criteria*

We aim to identify postmenopausal women with estrogen receptor-positive (ER+) breast cancer who typically consume at least one alcoholic drink per week but not more than two servings per day and are currently prescribed aromatase inhibitors including anastrozole (Arimidex®), letrozole (Femara®), and exemestane (Aromasin®). These drugs are only prescribed to postmenopausal women who have been diagnosed with estrogen receptor positive (ER+) breast cancer, the subtype where alcohol has been found to increase breast cancer incidence.

Inclusion Criteria:

- ER+ breast cancer
- Female sex at birth
- Postmenopausal, either natural or induced
- Self-reported consumption of at least one alcoholic drink per week but not more than two servings per day
- Currently prescribed aromatase inhibitors including anastrozole (Arimidex®), letrozole (Femara®), and exemestane (Aromasin®)
- Documented liver function test results below 1.5X the upper limit of normal within 12 months of screening

Exclusion criteria:

- Self-reported consumption of more than two drinks per day, a previous or current history of alcohol abuse based on standard questionnaires (AUDIT≥8), or consumption of 4 or more drinks in one day within the last 6 months
- Currently undergoing cytotoxic chemotherapy or radiation planned in the next two months
- Any surgery planned in the next two months
- Alcohol flushing syndrome
- Current use of any pharmaceutical agent contraindicated with alcohol, including warfarin, dual antiplatelet therapy, and metronidazole
- Hemoglobin A1c>8% or a fasting glucose result above 180 mg/dL within 6 months of screening

- Unable to speak or understand English
- Unable to understand and provide informed consent, as judged by the study team
- Uncertain ability to complete the protocol, as judged by the study team

We will not include adults unable to consent, individuals who are not yet adults, pregnant women, or prisoners.

4.0 Study-Wide Number of Subjects*

Not Applicable. This is a single-site pilot trial.

5.0 Study-Wide Recruitment Methods*

Not Applicable. This is a single-site pilot trial.

This pilot study is funded by very limited project funds from Dr. Mostofsky's K01 award and comprises a total of 20 women – a small enough total to be readily completed at a single center. Dr. Mostofsky, a research collaborator at BIDMC, will conduct recruitment herself at the BI oncology clinics. As a result, expansion beyond BIDMC is not currently feasible on the project's NIH-funded budget.

6.0 Multi-Site Research*

Not Applicable. This is a single-site pilot trial.

7.0 Study Timelines*

- Each participant will be involved in the study for ten weeks from the date of her screening visit.
- We anticipate that it will take one year from the date of IRB approval to recruit and enroll enough women so that 20 women will have completed all study visits.
- We anticipate that it will take 2 years from the date of IRB approval to complete the interviews, clean the data and prepare the primary analyses.

8.0 Study Endpoints*

We will examine within-person changes in blood levels of estradiol, testosterone, dehydroepiandrosterone sulfate (DHEAS), and sex hormone-binding globulin (SHBG) after three weeks of one serving of white wine daily compared to levels after three weeks of one serving of white grape juice daily.

At visits 1, 2, 3, and 4, the BIDMC Clinical Research Center (CRC) nurses will obtain a fasting blood sample. Within 72 hours, Quest Diagnostics will measure hepatic function, a complete blood count, and following visits 2 and 4, they will conduct a lipid panel. On our weekly phone check-ins, we will ask about recent health events such as unscheduled hospitalizations or any symptoms that have developed since the last meeting.

9.0 Procedures Involved*

This is an unblinded randomized controlled crossover trial to examine whether 3 weeks of light alcohol consumption causes a short-term change in sex hormone levels compared to levels following 3 weeks of white grape juice consumption among postmenopausal women with estrogen receptor-positive (ER+) breast cancer taking an aromatase inhibitor. In this design, participants are compared to themselves at different times, with the sequence of the two treatment arms assigned by randomization. In other words, half of the women will be randomized to consume one serving of white wine every day for three weeks followed by one serving of white grape juice every day for three weeks, and half of the women will be randomized to three weeks of white grape juice followed by three weeks of white wine. To prevent a potential carryover effect of the drink in the first period affecting hormone levels in the second treatment period, we will ask participants to refrain from drinking any alcohol or grape juice for two weeks before starting each treatment arm. The women will know when they are supposed to drink the wine and when they are supposed to drink the grape juice.

Recruitment:

We will present the trial protocol and eligibility criteria at a meeting for the six medical oncologists and three nurse practitioners who provide outpatient care at the BIDMC BreastCare Center and ask for their assistance to recruit patients from their practice who may be eligible and interested in participating in our trial.

We will review medical records for patients receiving care in the BreastCare Center or Healthcare Associates (HCA), BIDMC's primary care practice, to see if they meet the eligibility criteria, and contact their health provider about their fitness to participate. Unless their provider recommends otherwise, we will mail an invitation letter to patients who appear to be eligible and ask them to contact us if interested. If they do so and remain interested, we will arrange a screening visit. We will also call participants who have received letters and have upcoming clinical appointments to remind them of the study and to determine if they would like to arrange a screening visit in conjunction with that appointment. We will also continue to place flyers and brochures in the BreastCare Center so that women who are interested in the study can reach out to us.

We are submitting a request for a waiver of HIPAA authorization to obtain protected health information for potentially eligible women receiving care at the BIDMC BreastCare Center to confirm eligibility. Institutions will register eligible

participants in the Clinical Trials Management System (CTMS) OnCore as required by DF/HCC Policy REGIST-101.

Screening Visit:

If a referred patient is interested in learning more about the study, we will invite her to meet with a member of the research team in a private room at the BIDMC BreastCare Center. The study team member will explain the study, obtain informed consent, and confirm eligibility. An MD is not required for the consent process. No study procedures will be performed prior to obtaining informed consent. If the patient has not had liver function measured in the past 12 months, we will conduct a liver function test at their screening visit. If a hemoglobin A1c or fasting glucose test is not available, we will refer them to their physicians until we can document clinical control. We will obtain information on medical history, including an assessment of their usual frequency of alcohol consumption (using the Alcohol use Disorders Identification Test (AUDIT), the type of aromatase inhibitor therapy prescribed, and demographic and medical characteristics,

Aromatase inhibitors are only prescribed to women who are postmenopausal, either naturally or artificially induced. If any women report that they are pre-menopausal, sexually active, and not using an effective form of contraception, we will counsel them that these medications are teratogenic and they will be referred back to their providers. Participants found ineligible will be thanked for their time but they will not be invited for the baseline visit (Study Visit 1). Either the primary investigator (Dr. Kenneth Mukamal) or another physician involved in the study will review the screening results to confirm eligibility. Eligible participants will begin a two-week run-in period in which they will refrain from alcohol and grape juice (washout period 1).

Study Visit 1 (Baseline):

If the participant confirms that she did not drink alcohol or grape juice for the past two weeks, she will return for visit 2 after fasting for 12 hours. The BIDMC CRC nurses will draw 100 mL (approximately 7 tablespoons) of blood for real-time processing of a basic metabolic panel and safety monitoring (complete blood count and hepatic panel). We will store the remaining sample for analyzing sex hormone levels as soon as all participants complete the study. The CRC nurses will conduct the blood draw, specimen processing, and transportation to Quest Diagnostics in accordance with their pre-specified procedures.

The CRC research nurses will conduct safety monitoring at each study visit. Using their standard protocols, they will perform repeated measurements of vital signs, including height (at baseline), weight, systolic and diastolic blood pressure, and heart rate. They will measure supine blood pressure as the average of the final 2 of 3 measurements following at least five minutes of rest using an automated cuff device calibrated at least monthly. They will measure weight with the participant wearing light clothing and standing on a digital scale with handrails.

Using the REDCap randomization module, we will randomly allocate women to a sequence of either white grape juice followed by white wine or to a sequence of white wine followed by white grape juice. One drinking period consists of 3 weeks of one serving (5 oz≈14 g alcohol) of white wine consumption daily and the other drinking period consists of 3 weeks of a calorically equivalent serving (6 ounces) of (alcohol-free) white grape juice. At the beginning of the white wine drinking period, the participants will receive one 3L box and one 500 mL box of Bota Box Chardonnay, a commercially available white wine that is 13% alcohol by volume for the three weeks of one serving (5 ounces) of white wine consumption daily. At the beginning of the white grape juice drinking period, the participants will receive one 96-ounce bottle and one 64-ounce bottle of Welch's 100% White Grape Juice for the three weeks of a calorically equivalent serving (6 ounces) of (alcohol-free) white grape juice each day. There will be no blinding of the alcoholic beverages; all participants will know when they have been randomized to drink the white wine and when they have been randomized to drink the grape juice.

After obtaining IRB approval, we will work with the CRC to finalize the plans to purchase, store and transfer the white wine and white grape juice to participants. We will distribute the three-week supply of wine or grape juice and a standardized labeled measuring cup to ensure that participants consume the correct amount each day. We will give the participants an information sheet, advising them to refrain from all alcohol and grape juice except their assigned drink and to maintain their typical patterns of diet and activity throughout the study. For the three weeks of white wine intake, we will advise participants to drink their daily serving at a time when they will not drive or operate machinery in subsequent hours. We will also provide a paper calendar for participants to record their daily alcohol and grape juice intake and tell them that we will review this calendar with them on our weekly phone calls.

Study Visit 2:
At the end of the 3-week drinking period, the participant will come to the BIDMC CRC, and a nurse will draw 90 mL (approximately 6 tablespoons) of blood for safety measures and sex hormone levels. They will also take vital signs and measure weight. We will ask participants to bring leftover drinks to this visit so that we can measure the remaining amount as an indicator of adherence. We will ask participants to refrain from drinking any alcohol or grape juice for the next two weeks (washout period 2).

Study Visit 3:
At the end of the 2-week washout period, the participant will come to the BIDMC CRC, and a nurse will draw 90 mL (approximately 6 tablespoons) of blood for safety measures and sex hormone levels. They will also take vital signs and measure weight. We will then distribute the second beverage to consume daily for the following 3 weeks.

Study Visit 4:

At the end of the 3-week drinking period, the participant will come to the BIDMC CRC, and a nurse will draw 90 mL (approximately 6 tablespoons) of blood for safety measures and sex hormone levels. They will also take vital signs and measure weight. We will ask participants to bring leftover drinks to this visit so that we can measure the remaining amount as an indicator of adherence.

Blood Samples: The nurse will obtain blood samples in the morning after the last day of each 2-week washout period and each 3-week dietary period. We will schedule blood draws for time windows of up to ±4 days of the end of the prior washout or drinking period. If the visit is delayed for up to four days, we will ask participants to continue the protocol (washout, white wine, or white grape juice) for the additional days. At visit 1, the nurse will draw 100 mL (approximately 7 tablespoons) of blood and at visits 2, 3, and 4, the nurse will draw 90 mL (approximately 6 tablespoons) of blood. They will draw one 10 mL tube for each of the 10 assays: complete blood count, hepatic function panel, basic metabolic panel (only at visit 1), DHEAS, FSH, LH, SHBG, estradiol, testosterone, and progesterone. This amount is in accordance with the BIDMC Committee on Clinical Investigations (CCI) Blood Volume Safety Guidelines.

The CRC staff will centrifuge the blood samples for the complete blood count, hepatic function panel, basic metabolic panel, and sex hormones for 15 min at 2000x g and 4°C between 15 and 30 min after collection. They will aliquot the plasma and serum in labeled 250 µl cryovials and store the samples at -80°C in CRC freezers. The CRC will send blood samples to Quest Diagnostics. The safety measurements will be conducted within 72 hours of collection. At the end of the study, they will send frozen samples from each visit to Quest Diagnostics for analysis of sex hormones. The CRC nurses will conduct the blood draws, specimen processing, and transfer to Quest Diagnostics in accordance with the CRC's established protocols to maintain the quality of the specimens and to protect the privacy of the participants.

Safety and Adherence: A member of the research team will call participants once per week to ask about any changes in health, to remind the participant to complete the weekly online questionnaire about lifestyle factors, and to address any questions that they may have about their participation in the study. A safety monitor will oversee patient safety by regularly monitoring participants' vital sign and body measurements from clinic visits, lab results for liver function, complete blood count, and triglycerides and responses to questions from the weekly check-in calls about any changes in health, and they will follow up with any participant whose results are concerning.

We will assess adherence by asking participants to return unused drinks so that we can measure how many drinks the participant consumed, at least from the provided drinks. Throughout the ten weeks of the trial, participants will complete weekly REDCap online questionnaires about lifestyle factors over the prior week. We will also ask participants about their alcohol intake. Depending on participant preference

and feasibility, participants may report daily alcohol intake using the REDCap alcohol timeline follow-back assessment or they may opt to respond to a daily REDCap-secured survey that will be texted to them every evening. If participants report more than the assigned amount of wine during any study visit including the final visit, on a questionnaire, or during a phone call with study staff, Dr. Kenneth Mukamal will speak with them to determine if any evidence of alcohol use disorder or at-risk drinking is present, and all such participants will be referred for counseling. Those with no such evidence of problem drinking will remain in the study with continued monitoring.

As an objective marker of alcohol adherence, we will pool some of the remaining blood samples across participants. After the sex hormone analyses are complete, the staff at the Brigham Research Assay Core who conducted the sex hormone analyses will one pooled sample from several participants following the wine phase and one pooled sample from several participants following the grape juice phase. We will send the two samples to Quest Diagnostics to estimate average phosphatidyl ethanol levels as an objective marker of adherence to the study protocol—the average phosphatidyl ethanol levels by treatment period across several individuals, with no individual results for each participant. The purpose is to estimate an objective marker of alcohol adherence, and not to test any new scientific hypotheses. We plan to report the average phosphatidyl ethanol levels in our findings on the study.

To minimize risk, we have established clear and conservative entry criteria for interested participants. In particular, we require that all participants are current drinkers and that they typically consume at least one alcoholic drink per week but no more than two servings per day. This level, and the intervention dose of one drink per day, are explicitly within the limits of consumption for women diagnosed with breast cancer established by the American Society of Clinical Oncology.

We will establish a formal safety monitor. This role may be filled by Dr. Steven Come or by a breast cancer specialist to whom he may delegate this role. The safety monitor will oversee patient safety by regularly monitoring participants' lab results and responses to questions from the weekly check-in calls about any changes in health. They will assess the severity, expectedness, and relationship to the intervention for any self-reported symptoms or lab results and document adverse events. In addition, we will set up an independent data safety and monitoring board (DSMB) that will meet every 6 months to evaluate the safety and utility of continuing the pilot trial.

If a participant experiences an adverse event, she will be directed to her treating oncologist. We will also notify the IRB, as appropriate (see section 12).

We aim to assure data quality and protect the confidentiality of participant data by using REDCap electronic data capture tools. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies.

We are submitting drafts of the study materials with this application for protocol approval, and we will convert these data collection tools to forms in the REDCap database.

Screening Eligibility Checklist: The study staff will complete this measure with the participant during the screening visit and by reviewing medical records. This assessment includes the Alcohol Use Disorders Identification Test (AUDIT). At the screening visit, we will also collect contact information.

Clinical Research Center Visit form: We will collect information about anthropomorphic data, blood samples, and responses to questions about medical history, lifestyle factors, alcohol intake, and changes in medications during the study.

Weekly Check-In Call: The study staff will call participants once per week and ask them if they "had any reason to speak to or visit your health practitioner since we last spoke?" If the participant responds that there have been reasons to seek care, the study staff will ask for details. The study staff will also ask if "there any other changes to your health that you want us to know about?" and if the participant reports any changes, the study staff will ask for details. This information will be relayed for the safety monitor to review in the secure REDCap system. We will use the structure of the alcohol timeline follow-back survey to assess daily alcohol and grape juice intake since the prior check-in call. We will ask participants to record their daily intake on their paper diary that we gave them at Visit 1.

Weekly REDCap Survey: Participants will complete an online weekly survey through the REDCap system. If they would prefer to complete this survey by phone, a member of the study staff will conduct this survey as an interview by phone and enter the data into REDCap on the participant's behalf. The survey also includes the short version of the Centre for Epidemiological Studies Depression Scale (CES-D 10), a Pain Intensity Scale using a visual analog scale to rate overall pain from 0 to 100, and in two of the weekly assessments, participants will complete the Pittsburgh Sleep Quality Index (PSQI) about their sleep quality over the prior month.

As indicated in the table of assessment times below, we will collect information about eligibility at the screening visit, and at visits 1, 2, 3, and 4, we will collect information about body measurements, vital signs, blood samples, and alcohol intake. In the weekly questionnaires, participants will provide information about alcohol intake, lifestyle factors, and any concerns. We will schedule blood draws for time windows of up to ±4 days of the end of the prior washout or drinking period. If the visit is delayed for up to four days, we will ask participants to continue the protocol (washout, white wine, or white grape juice) for the additional days. Similarly, we will schedule weekly calls for up to 4 days before or 4 days after the target schedule date.

	Screening	Washout 1	Washout 1	Visit 1	Drinking Period	Drinking Period	Drinking Period	Visit 2	Washout 2	Washout 2	Visit 3	Drinking Period	Drinking Period	Drinking Period	Visit 4	# Assessments
Study Day	0	1-7	8-14	15	15-21	22-28	29-35	36	36-42	43-49	50	51-57	58-64	65-71	72	
Window Allowance (Days)		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	
Type of Visit	Clinic	Phone	Phone	Clinic	Phone	Phone	Phone	Clinic	Phone	Phone	Clinic	Phone	Phone	Phone	Clinic	
Payment				$20				$30			$30				$50	
Admin, Body Measurements, and Vitals																
Consent, contact information	X															1
Eligibility: e.g., Alcohol use Disorders Identification Test (AUDIT) and hepatic panel if none in the past 12 months*	X															1
Randomization				X												1
Verification of consent and documentation				X				X			X				X	4
Height				X												1
Weight, waist circumference				X				X			X				X	4
Vital signs- blood pressure, heart rate				X				X			X				X	4
Distribute drink				X							X					2
Measure leftover drink								X							X	2
Pay participant, reimburse parking				X				X			X				X	4
Blood Draw																
Hepatic panel	*			X				X			X				X	4
Complete blood count with differential				X				X			X				X	4
Basic metabolic panel (fasting)				X												1
Lipid panel								X							X	2
Estradiol and estrone				X				X			X				X	4
Sex hormone binding globulin (SHBG)				X				X			X				X	4
Dehydroepiandrosterone sulfate (DHEAS)				X				X			X				X	4
Testosterone				X				X			X				X	4
Weekly Call																
Health events		X	X		X	X	X		X	X		X	X	X		10
Other health changes		X	X		X	X	X		X	X		X	X	X		10
Alcohol and grape juice timeline follow-back		X	X		X	X	X		X	X		X	X	X		10
Weekly REDCap Questionnaires																
Pittsburgh Sleep Quality Index (PSQI)							X							X		2
Depressive Symptoms (CES-D-10)		X	X		X	X	X		X	X		X	X	X		10
Overall pain (visual analog scale)		X	X		X	X	X		X	X		X	X	X		10
Open text-any questions, concerns, comments		X	X		X	X	X		X	X		X	X	X		10

10.0 Data and Specimen Banking*

We will store the blood samples for sex hormone levels from each study visit in a −80 °C freezer at BIDMC until all participants complete the study. Only members of the study staff will have access to the specimens.

Each specimen will be labeled with a study identifier. The crosswalk file linking these subject identifiers to participants' private health information will be stored in separate computer files with password protection, and results will be presented only in aggregate.

Once the trial is complete, we will adhere to all required regulations regarding data dissemination. As outlined in the Notice of NIAAA Data-Sharing Policy for Human Subjects Grants Research Funded by the National Institute on Alcohol Abuse and Alcoholism (https://grants.nih.gov/grants/guide/notice-files/NOT-AA-18-010.html), NIAAA uses an established informatics infrastructure, hosted and managed by the National Institute of Mental Health (NIMH) to enable the sharing and use of data collected from human subjects. The NIMH Data Archive (https://data-archive.nimh.nih.gov/) stores and disseminates data from funded clinical trials, and we will work with the NDA to create a compatible data structure and appropriately tagged fields and strip all identifiers from submitted datasets. We anticipate that data submitted to the NDA will become available to the general public 2 years after the completion of the proposed K01 award, as specified by NIAAA. Because of the limited size (20 subjects, single-center) of the proposed trial, all costs associated with data submission will be subsumed by effort allocated to the Principal Investigator and by budgeted costs at the BIDMC Clinical Research Center.

11.0 Data Management* and Confidentiality

We will present descriptive statistics on the proportion of people screened who were eligible and ineligible, and the number randomized. We will describe the health characteristics and self-reported adherence of the completers and non-completers based on the available data.

We will construct linear mixed models to examine within-person changes in levels of estradiol, testosterone, DHEAS, and SHBG from grape juice to white wine, including a random subject intercept and fixed effects for treatment and sequence. We will assess the potential for a carryover effect by evaluating a cross-product term for treatment and sequence. We will use a logarithmic transformation for skewed distributions of the sex hormone levels.

We will use Markov Chain Monte Carlo (MCMC) multiple imputation. For each treatment arm, we will use the SAS "proc mi" procedure to generate 10 multiply imputed datasets that incorporate appropriate variability across the imputations. We will use the SAS "proc mianalyze" procedure to combine the results from the imputed data sets to properly reflect the uncertainty due to missing values.

Our primary analysis will use an intention-to-treat (ITT) approach, classifying participants according to their assigned treatment arms regardless of adherence to study protocol. In a sensitivity analysis, we will use a per-protocol approach in which a participant's follow-up will be terminated at the time, if any, at which they cease to follow the protocol, and we will adjust for pre-randomization and post-randomization factors that may predict adherence.

Our primary endpoint is free estradiol (estradiol divided by SHBG). We should have excellent power to assess effects of alcohol on DHEAS but reasonable power to detect effects on estrone sulfate, although, as a pilot study with an intentional goal of training and career development, power is but one dimension on which to evaluate the merits of the trial. We have used standard formulae to estimate the minimum detectable difference for 2-period crossover trials (http://hedwig.mgh.harvard.edu/sample_size/js/js_crossover_quant.html). Using the 4-week results of a similar crossover trial of alcohol on changes in estrone sulfate and DHEAS, and using the dosage of 15 gm/day that most closely approximates the dosage proposed in this application, we can estimate the proportional changes anticipated with varying degrees of power, as shown below at a two-sided 0.05 significance level. Based upon data presented in that trial, we estimate the SD of within-person differences to be 42% for estrone sulfate and 13% for DHEAS.

Power	Minimum Detectable Difference	
	Estrone sulfate (ng/dl)	DHEAS (ng/dl)
50%	19%	6%
80%	28%	9%
90%	32%	10%

For comparison, the increases in estrone sulfate in previous trials of alcohol were 15-21% in a trial of premenopausal women and 7-22% in a trial of postmenopausal women.

The comparable effects on DHEAS were 4-7% and 5-9%. Thus, we appear to have adequate power to detect effects of the expected size from previous crossover trials. Moreover, we have particularly strong power to exclude virtually all clinically significant increases (e.g., increases of 10% or larger) in DHEAS.

Our results would also provide all necessary information to power a more definitive trial of estrone and other estrogens.

We aim to assure data quality and protect the confidentiality of participant data. We will keep all electronic data behind secure firewalls and all paper forms in locked files accessible by authorized personnel only. Subject identifiers will be stored in separate computer files with password protection, and results will be presented only in aggregate. We will use REDCap (Research Electronic Data Capture) tools hosted at BIDMC. REDCap is a secure, web-based application designed to support data capture for research studies. REDCap provides advanced de-identification options that can be used when exporting data, such as removing known identifier fields, removing invalidated text fields, notes fields, or date fields, date shifting, and hashing of the record names. It also includes a randomization module. REDCap utilizes a third-party vendor, Twilio, to send an SMS message with a REDCap survey link. Subjects can click on the link and be directed to a REDCap survey on their phone.

During all phases of a study, we aim to ensure that all data are carefully measured and recorded. We will use prepared phone scripts for recruitment, appointment reminders, and weekly check-in calls to provide information about the study and its procedures and to obtain study responses in as consistent a manner as possible. Our manual of operations will include details on where to obtain patient information, how to record the data, how to classify and report adverse events, and whom to contact with questions so that all members of the study team record information in a consistent manner throughout the trial.

All study staff will be trained and certified in privacy protection, the Health Insurance Portability and Accountability Act (HIPAA), and the ethical conduct of clinical research. Study team members will meet regularly for study training and to make sure that all questions are asked similarly.

We will check the consent form and any paper forms for completeness, and double-enter the data to minimize errors.

Our REDCap database will have data validation rules and required fields to minimize the risk of incorrect and missing information. To ensure that the data are accurate and complete, we will create study-specific flow sheets for each study visit to ensure that the data collected is consistent at each study visit. Prior to initiating the study, the PI or her designee will hold a session to train Clinical Research Center staff in the conduct of the study. The study team will enter data in real time directly into the REDCap database rather than completing paper forms and manual data entry. This includes baseline information such as inclusion and exclusion criteria, randomization arm, measures of adherence to the drinking and washout periods, visit data such as vital signs and blood draw details, medication changes, adverse events, and other measures.

We will use standardized procedures for measuring vital signs and obtaining blood samples, and we will use validated measures for assessing the frequency of alcohol intake to increase the likelihood that the data is accurate and complete.

We will call participants once a week to make sure that they have access to their drinks, that they are adhering to the protocol, and that they complete the study assessments.

Quest Diagnostics will conduct specimen analyses for safety markers (hepatic panel, complete blood count with differential, fasting basic metabolic panel, and lipid panel). We will follow standard laboratory practices regarding sample chain of custody and sample confidentiality. This lab is approved by the Harvard Catalyst organization, and it is used by the BIDMC Clinical Research Center because they provide high-quality research and clinical data.

We will label all specimens with the date and time of the blood draw and two subject identifiers using labels from the Quest Diagnostics ordering system to minimize the risk of mislabeling specimens. We will send the samples for safety monitoring assays to Quest Diagnostics within 72 hours of collection. Prior to transport to the Quest Diagnostics laboratory, samples will be processed according to the laboratory guidelines for sample submission.

We will obtain laboratory results about the safety measures from the Quest eResults system and manually enter the data into the study database. We will retain paper copies of the reports and periodically conduct audits to compare the entered data with the paper copies to ensure that it was accurately entered in the study database.

The Brigham Research Assay Core (BRAC) will conduct specimen analyses for sex hormones. We will centrifuge the samples for sex hormone assays and freeze the serum in aliquots at -80°C. At the end of the study, we will bring the samples to the BRAC. They will use liquid chromatography–mass spectrometry to measure estradiol, estrone, and testosterone, and they will use chemiluminescence to measure sex hormone binding globulin (SHBG) and dehydroepiandrosterone sulfate (DHEAS). We will follow their sampling, storage, and transport procedures.

We will obtain laboratory results about the sex hormone measures from the Freezerworks database on the BRAC web portal system and manually enter the data into the study database. We will retain paper copies of the reports and periodically conduct audits to compare the entered data with the paper copies to ensure that it was accurately entered in the study database.

Only members of the research team, including the CRC nurses, will have access to the data and specimens. Quest Diagnostics will transmit results through their secure

eResults system with study-specific account access. We will download results and enter the data into our study-specific REDCap database.

12.0 Provisions to Monitor the Data to Ensure the Safety of Subjects*

We will follow the NIAAA guidelines for administration of alcohol, including attention to informed consent; selecting participants that have no known increased risk of alcohol dependence; great attention to confidentiality; restriction to participants who regularly consume alcohol rather than alcohol-naïve individuals; exclusion of pregnant women; low alcohol exposure for the intervention period of 3 weeks; access to medical backup services; and compensation for participation.

Dr. Mukamal, a practicing primary care internist, Dr. Steven Come, an oncology internist, or an oncology internist identified by Dr. Come will oversee data safety. They will monitor laboratory results from the scheduled visits on a real-time basis for all participants. They will ensure comprehensive monitoring and entry of all safety-related data in the REDCap electronic research management system, distinguishing between serious adverse events, non-serious adverse events, and unanticipated problems following the BIDMC's IRB guidelines. The study team will meet every month to discuss the ongoing health and safety of participants.

At all clinic visits, we will measure vital signs and body measurements. A member of the research team will call participants once per week to ask about any reasons to speak to or meet with a health practitioner and any other health changes. At all visits and on all weekly calls, we will encourage participants to contact us about any health concerns or questions.

We will also obtain lab assays for a hepatic panel, lipid panel, and complete blood count. We will discontinue enrollment and immediately refer for treatment any participant who

- Develops liver function test abnormalities greater than 2X the upper limit of normal or
- Experiences 15% change in their white blood count, hemoglobin level, or platelet count that results in values outside the normal range or
- Experiences a doubling of their triglyceride levels that results in values outside the normal range

following the three weeks of consuming white wine.
Participants who report any excess use of their assigned beverage per week will receive additional intensive surveillance by telephone, and we will discontinue enrollment if excessive alcohol use persists.

If participants report more than the assigned amount of wine during any study visit including the final visit, on a questionnaire, or during a phone call with study staff, Dr. Kenneth Mukamal will speak with them to determine if any evidence of alcohol use disorder or at-risk drinking is present. If there is evidence of problem drinking, they will be immediately referred for treatment. Addiction specialists, including

psychopharmacologists and clinical social workers, practice within the Healthcare Associates multidisciplinary clinic and are available on-call at all times.

We will report adverse events as follows:

1. **Unexpected fatal or life-threatening adverse events** will be reported to the BIDMC institutional review board (the Committee on Clinical Investigations - CCI) and the BIDMC General Clinical Research Center (GCRC) Research Subject Safety Office (RSSO) by telephone or in person within **one business day** of notification, and followed by a formal written report within **seven calendar days**.
2. All other **expected and unexpected serious adverse events** will be reported to the CCI and the GCRC RSSO within **seven calendar days**.
3. We will also provide the GCRC RSSO with an **annual** summary of **adverse events** (including anticipated, non-serious adverse events), delineated by category and number in addition to that provided to the CCI.

Any serious adverse event will lead to a cessation of enrollment until the relationship between the adverse event and the study conduct is determined.

The study team will meet at least once per month to discuss the information collected from the CRC visits, lab results, weekly calls and REDCap surveys, and any calls from participants about other concerns or health changes. We will discuss the safety of trial enrollment and any concerns and whether we should propose any changes to the protocol.

In addition to this intense safety oversight, we will develop an independent Data and Safety Monitoring Board (DSMB) comprised of a general internist or oncologist with expertise in clinical trial conduct, an alcohol expert (who may also be a physician), and a biostatistician. The DSMB will meet every 6 months during the trial and more frequently as needed. We will notify the DSMB immediately if any unexpected life-threatening or fatal adverse events occur. They will provide reports after each meeting outlining the safety of the trial and delineate any plans for interruption or discontinuation of the trial.

The content of the Data and Safety Monitoring Reports will include details such as

a. Number of participants screened, reasons potential participants excluded, the number enrolled
b. Frequency, mean, min/max of all laboratory safety assays, e.g., elevations in liver function tests, severe neuropsychiatric disturbances, or changes in vital signs
c. Quality and completeness of the study data: frequency of missing or erroneous data, and frequency of outliers
d. Safety data by treatment period, including frequency of adverse events, serious adverse events, and any data that allows for comparisons of safety among alcohol and non-alcohol dietary periods, e.g., clinical laboratory data, treatment retention, and reasons for participant dropout.

e. Individual participant data will be available for DSMB review as needed. In the assessment of serious adverse events, the DSMB will review each case, including treatment group assignment.

The DSMB will stop the trial if there is evidence of any of the following conditions:
a. Clear evidence of harm
b. No likelihood of demonstrating treatment benefit (futility)
c. Overwhelming evidence of the benefit of treatment

We have no reason to anticipate that alcohol is beneficial for sex hormone levels. Rather, we are testing whether the constant use of aromatase inhibitor therapy throughout study enrollment lowers the impact of alcohol consumption on within-person changes in sex hormone levels. If the results of the lab results indicate that the low alcohol intake is harmful as defined by the DSMB, the DSMB will stop the trial.

13.0 Withdrawal of Subjects*

We may decide to terminate a subject's participation in the trial without regard to the subject's consent if
a. there is a concern that the alcohol intake is causing an unacceptable level of risk
b. the subject is not adhering to the study protocol
c. the subject is not meeting at arranged times despite repeated attempts, or because
d. the inclusion/exclusion criteria are no longer met (e.g. a new surgery is scheduled to take place during trial participation or a new medication is initiated and alcohol is contraindicated to its use).

We will reassure participants that they are free to discontinue participation in the study at any time for any reason without fear of penalty or loss of medical care or loss of any benefits to which they may otherwise be entitled. In the event of early termination/withdrawal from the study, a member of the study staff will conduct an exit interview to identify the reasons for terminating participation, and we will recommend that the participant follow up with their health care providers if they report and medical or psychological reasons for discontinuing participation. We will document the date of study withdrawal, whether the withdrawal of the subject resulted from a decision by the subject or by the investigator, and the reasons for the withdrawal. If appropriate, we will request the return of any remaining beverages and provide payment for any visits completed on the day of termination.

If a participant chooses to withdraw from the study, the data collected up to the time of withdrawal will continue to be used, but the participant will no longer be contacted and no further data will be collected.

14.0 Risks to Subjects*

Because alcohol will only be provided for three weeks to participants, we do not anticipate any measurable or clinically meaningful increase in the potential long-

term risks related to alcohol consumption, including any measurable risk in chronic disease. The potential risks to study participants from use of alcohol for three weeks include risks related to temporary sedation (such as the use of machinery immediately after drinking), gastrointestinal upset, flushing (in cases of genetic intolerance to alcohol or use of specific medications), and a potential worsening of liver disease among people with pre-existing liver disease. In addition, alcohol is an addictive substance, although the risk of precipitating alcohol misuse among women already consuming alcohol safely is likely low. For both arms, the assigned beverage contains ~120 calories and can cause weight gain if not balanced by decreases in the caloric content of the diet.

The only other risks related to this study are procedural and include discomfort or anxiety answering questions about medical history and pain and temporary slight discoloration of the skin after blood draws.

Specifically, potential risks associated with study participation include anxiety related to completing the questionnaires, temporary discomfort and slight discoloration of the skin after blood draws, and feeling ill after drinking a serving of wine or grape juice. However, all participants will be postmenopausal women with estrogen receptor-positive (ER+) breast cancer who regularly consume alcohol, so these risks seem less likely than if we were recruiting from the general population. There is a potential risk of psychological harm due to inadvertent disclosure of medical information. However, we will record information behind a secure firewall using the REDCap system.

Completing the online questionnaires, phone check-ins and interviews could lead to the unforeseeable risk of a breach of confidentiality if someone other than the research team obtained access to the data. However, the screening and enrollment lists, lab results, interview responses, and questionnaires will all be entered and stored in the secure REDCap system with features to export de-identified datasets for analysis. The consent forms will include participant names, but the signed forms will be stored in a locked cabinet.

Aromatase inhibitors are only prescribed to women who are naturally or artificially (e.g. hysterectomy) postmenopausal. Therefore, no women will join the study pregnant or become pregnant during their participation in the study.

There are no known risks to others who are not subjects.

15.0 Potential Benefits to Subjects*

As we will indicate in the informed consent form, there are no clinical benefits to participation.

As we indicated in the informed consent form, there are no direct benefits to participation.

16.0 Vulnerable Populations*

Not Applicable. We will not include pregnant women, prisoners, children, or impaired adults.

17.0 Community-Based Participatory Research*

Not Applicable. This trial does not involve community-based participatory research.

18.0 Sharing of Results with Subjects*

We will assure participants that the line of communication is open and provide participants with the research team's contact information should they have follow-up questions. When the study first becomes available in its entirety through public access, we will contact participants by phone or email, based on their preference, to inform them about how they can look for published study results, and we will share the study's official name and Protocol ID number so they may search public databases.

19.0 Setting

Screening visits will take place at the Beth Israel Medical Center BreastCare Center:

Joseph M. and Thelma Linsey BreastCare Center
330 Brookline Avenue
Shapiro Clinical Center, 4th Floor
Boston, MA 02215

Subsequent visits will take place at the Beth Israel Deaconess Medical Center Clinical Research Center, located in the Clinical Research Center on East Campus:

Clinical Research Center
330 Brookline Avenue
Gryzmish Building, 8th Floor
Boston, MA 02115

After the blood samples are prepared at the clinical research center, safety measures will be sent for analysis to:

Quest Diagnostics LLC
200 Forest Street, 3rd Floor, Suite B
Marlborough, MA 01752-3023

Sex hormone blood samples will be prepared at the clinical research center and stored at BIDMC. At the end of the study, these frozen samples will be sent for analysis to:

Brigham Research Assay Core
221 Longwood Avenue
RFB Room 477
Boston, MA 02115

There is no community advisory board for this research. This is a single-site pilot trial, so no study visits for this research will take place outside of this organization.

20.0 Resources Available

All members of the study team have experience conducting clinical trials and have training in the safety, privacy, and integrity laws about the conduct of clinical research.

Dr. Kenneth J Mukamal is the primary investigator of this trial and co-mentor of the NIH/NIAAA K01 career development award funding this study (K01AA027831). He is Associate Professor of Medicine at Beth Israel Deaconess Medical Center (BIDMC). His primary research interests are investigating the role of dietary and lifestyle factors—particularly alcohol intake—on the incidence and prognosis of cardiovascular and neurovascular disease. As a general internist and clinical investigator, he has vast experience conducting studies on the health effects of alcohol. He has conducted a randomized trial of alcohol among patients at high cardiovascular risk at BIDMC that informs the design and conduct of this trial. Dr. Mukamal served as a member of the BIDMC IRB for approximately fifteen years and he is attuned to the importance of safety and confidentiality concerns.

Dr. Steven Come is Associate Professor of Medicine at Harvard Medical School and a treating physician at the Beth Israel Deaconess Medical Center's Breast Cancer Program. He is a collaborator on the career development award. As a physician providing care to breast cancer patients and a clinical researcher of chemotherapy, Dr. Come will be the liaison between the BreastCare Center team and the study staff to identify eligible women with estrogen receptor-positive (ER+) breast cancer from the BreastCare Center who may be interested in participating and to monitor the safety of the trial participants. Dr. Come may delegate some of these recruitment and monitoring responsibilities to other oncologists at the BreastCare Center, such as Dr. Jaymin M. Patel.

Dr. Julie E. Buring is Professor of Medicine at Brigham and Women's Hospital (BWH) and Professor of Epidemiology at the Harvard T.H. Chan School of Public Health. She is the primary mentor on the career

development award that is funding this study (K01AA027831). Dr. Buring has been involved in the design, conduct, analysis, and interpretation of several randomized clinical trials and large-scale cohort studies. Dr. Buring serves as Chair of the Institutional Review Board at Harvard Medical School, and she is both familiar with and dedicated to the responsible conduct of research.

Dr. Elizabeth Mostofsky is the NIAAA K01 career development awardee for the grant that is funding this trial. She has been involved in conducting small clinical trials and will devote a large proportion of her time to the design and conduct of this trial with close mentorship from Drs. Buring, Mukamal, and Come. This pilot study is funded by very limited project funds from Dr. Mostofsky's K01 award and comprises a total of 20 women – a small enough total to be readily completed at a single center. Dr. Mostofsky, a research collaborator at BIDMC, will conduct recruitment herself at the BI oncology clinics. As a result, expansion beyond BIDMC is not currently feasible on the project's NIH-funded budget.

After obtaining IRB approval, we will work with the CRC to finalize the plans to purchase, store, and transfer the white wine and white grape juice to participants. All alcohol and grape juice transfers, blood draws, and physical exams will take place with oversight of the experienced staff at the BIDMC Clinical Research Center with frequent consultation with Drs. Buring, Mukamal, and Come.

BIDMC follows over 5,000 women with breast cancer who account for over 8,000 visits yearly, of whom over 3,500 are likely to be ER+, of whom a vast majority are likely to be taking an aromatase inhibitor and hence potentially eligible for our trial. By working closely with oncologists in the BIDMC BreastCare Center, we are highly likely to identify, recruit, and enroll 20 women to complete the study. If we face challenges with recruitment, we will apply for an IRB amendment to broaden our recruitment to other audiences. Since the trial is only 10 weeks and participants complete both treatment arms that involve low levels of consumption, it is feasible to complete this trial in the timeline proposed.

The proposed trial is a primary aim of a career development award funded by the National Institute on Alcohol Abuse and Alcoholism (K01AA027831), which provides 80% of my effort. Therefore, completing this trial is of utmost importance, and it will be Dr. Mostofsky's focus during the timeline of the trial.

We aim to primarily recruit participants from the Joseph M. and Thelma Linsey BreastCare Center. The oncology team includes six attending physicians and three nurse practitioners who provide care to more than 4,000 patients per year.

The BIDMC Clinical Research Center is located on the BIDMC East Campus. The staff will provide their experience and assistance with advertising the study and recruiting participants, and their licensed nursing staff will conduct the weight

measurements, storage and distribution of the wine and grape juice, the blood draws, the blood sample preparation for freezing, and shipment of the blood samples to Quest Laboratories.

Dr. Kenneth J. Mukamal is a general internist and clinical investigator at BIDMC with extensive experience conducting observational and interventional studies on the effects of alcohol consumption. Dr. Steven Come is an oncologist in the BIDMC BreastCare Center where we will primarily recruit participants for this trial. Dr. Mukamal, Dr. Come, and any physician to whom they delegate safety monitoring responsibilities will review the results of the safety measures and classify them according to severity, relation to the study intervention, and whether it had been expected or not.

Before engaging with potential study participants, we will meet with staff members, from oncologists to CRC nurses and research assistants, to ensure that they are familiar with the study protocol and safety measures. As described in section 12.0, we have a formal plan to ensure that the study staff knows whom to contact with questions or concerns about safety or other protocol issues and how to contact a study physician if needed.

21.0 Prior Approvals

On December 17, 2021, we received notification from the FDA that our study does not require an IND. The letter is included in our application packet.

22.0 Recruitment Methods

We will present the trial protocol and eligibility criteria at a meeting for the six medical oncologists and three nurse practitioners who provide outpatient care at the BIDMC BreastCare Center and ask for their assistance to recruit patients from their practice who may be eligible and interested in participating in our trial.

We will review medical records for patients in the BreastCare Center with upcoming appointments to confirm eligibility. We will notify the BreastCare Center health providers about their upcoming visits with potentially eligible patients so that they may target their recruitment efforts toward their patients who are potentially eligible to participate.

The BreastCare Center health practitioners will describe our study to these patients and ask the patient if they are interested in being contacted to learn more about participation in the trial. If the patient agrees to be contacted and a study team member and the patient are available at that time, we will meet the participant at the BreastCare Center to discuss the study at that time. If the patient agrees to be contacted but is not available at that time, we will mail them an IRB-approved letter

with information about the study and contact information for them to speak to someone on the study team. If they contact us, we will arrange a screening visit. Otherwise, we will contact them within a week of receiving the letter to ask them if they have any questions and are interested in meeting for a screening visit. We will also place flyers and brochures in the BreastCare Center so that women who are interested in the study can reach out to us.

This application includes the

- Brochure for the BreastCare Center study staff, including the inclusion/exclusion criteria, a figure of the study design, and the study team contact information so that they can tell us about potentially eligible participants
- Flyer for the BreastCare Center waiting room
- Telephone Script for Recruitment
- Invitation letter, including a study information sheet with frequently asked questions

We will provide parking vouchers to participants who plan to drive to BIDMC. In addition, we will compensate participants for their time and effort at the end of each study visit, with a total of $130 for completing all 10 weeks of the study ($20 for Visit 1 (Baseline), $30 for Visit 2, $30 for Visit 3, and $50 for Visit 4). These levels of compensation are designed to provide some minimal compensation for the time and inconvenience of these visits without providing any undue incentive to join the study, a particularly important consideration in studies of alcohol.

We will pay participants using a pre-paid debit card called ClinCard® that is administered by the company Greenphire to manage all payments associated with participation in study visits and travel related to participation in the study. We will add the money to the card after each completed visit. Participants may use this card at any store that accepts credit cards, or they can use a bank machine to remove cash. However, there may be fees drawn against the balance of the card for cash withdrawals and inactivity.

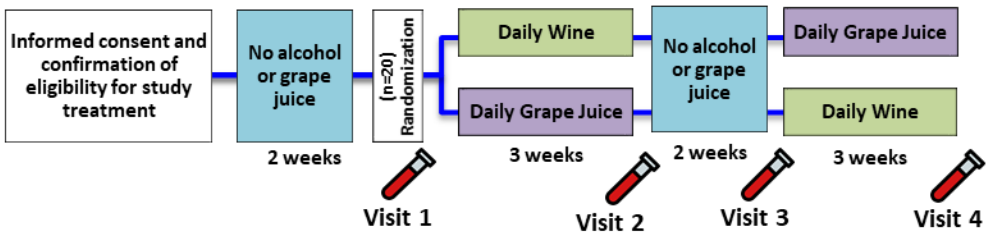
23.0 Local Number of Subjects

We will screen and enroll participants until we have 20 participants who have completed the ten weeks of the study.

BIDMC follows over 5,000 women with breast cancer who account for over 8,000 visits yearly, of whom over 3,500 are likely to be ER+ and hence potentially eligible for our trial.

We plan to contact as many as 100 participants to ensure that at least 20 women complete the study. This pilot study is funded by very limited project funds from

Dr. Mostofsky's K01 award and comprises 20 women – a small enough total to be readily completed at a single center.



24.0 Provisions to Protect the Privacy Interests of Subjects

We will protect subjects' privacy interests by keeping all data behind secure firewalls and in locked files accessible by authorized personnel only. We will record all questionnaire and interview responses and all anthropometric measurements, lab results, and study staff notes using REDCap (Research Electronic Data Capture). REDCap is a secure web application designed to support data capture for research studies. It includes features for HIPAA compliance including real-time data entry validation (e.g., for data types and range checks), a full audit trail, user-based privileges, de-identified data export mechanism to statistical packages, and integration with Beth Israel directories. Access to study data in REDCap will be restricted to the members of the study team with authentication through institutional credentials.

Subject identifiers will be stored in separate computer files with password protection, and results will be presented only in aggregate. In addition, current/future employees involved with the proposed study routinely must agree not to disclose any information to which he or she might have access, regardless of his or her perception about its confidentiality, as part of annual training. All BIDMC employees also complete training in the responsible conduct of research.

We will explain to potential participants that we are working closely with Dr. Come and other health practitioners from the BIDMC BreastCare Center to ensure their safety. All visits will take place in a private room, and we will remind them that they can stop participating at any time with no concern of this withdrawal affecting their clinical care. At all visits and phone calls, we will remind the participants that they can reach out to us at any time with questions or concerns.

We are submitting a request for a waiver of HIPAA authorization to disclose protected health information for anyone recommended by the BreastCare Center oncologists and nurse practitioners. We will access the patient's recent medical records to confirm their eligibility for this trial. The research team will access participant information through the REDCap database. This secured database will be hosted by BIDMC behind the firewall of will be the centralized source of all

study data and administrative details for the screening process and the enrollment and conduct of the trial. Only authorized members of the study team will be able to access this information, and they will not share their login credentials with other personnel working on the study.

25.0 Compensation for Research-Related Injury

The treating hospital will offer the care needed to treat injuries directly resulting from taking part in this research. These treatments may be billed to the participant or to their insurance company. There are no plans to pay the participant or to provide other compensation for the injury, such as lost wages or lost time from work.

If the participant is injured as a direct result of participation in this study, the participant will be offered the necessary care to treat their injury. The participant or their insurance company will be billed for medical care and/or hospitalization related to this injury. The participant will be responsible for co-payments, deductibles, and co-insurance. There are no plans to pay the participant or to provide other compensation for the injury, such as lost wages or lost time from work.

26.0 Economic Burden to Subjects

There are no costs to participants for completing the study. We will provide white wine, white grape juice, and a measuring cup. We will also provide parking passes for participants who plan to drive to the Beth Israel Medical Center Clinical Research Center.

27.0 Consent Process

Once a potential participant meets with study staff at the BIDMC BreastCare Center, we will obtain and document written informed consent to complete the screening process and if eligible, to be randomized for the crossover trial. We will follow all guidelines described in the Standard Operating Procedures for Human Subjects Research (CON-100). We will make sure that the informed consent process is conducted by a member of the study team who is trained in human subject protections, trained on the protocol, and listed on the Delegation of Authority Log.

We will conduct the consent process in a private room at the BreastCare Center to ensure participant privacy and to make sure that they feel comfortable asking questions. We will remind participants that they can stop participating at any time and for any reason, and cessation will not have any impact on their medical care in any way. After explaining the study, asking the participants to carefully review the consent form, and discussing any

questions that they may have, the patient will sign the informed consent form. The study team member will document the informed consent date and time and they will confirm that they explained the research to the participant, ensured that the patient understood the expectations of participating, and that the patient freely consented to participate. This process will take approximately 30 minutes.

At each visit, the CRC staff will ask the participant whether they would like to continue to participate in the study.

We will restrict inclusion to participants who can speak and understand English because we do not have sufficient funding to prepare materials and conduct visits in other languages, and we need to be sure to identify any health and safety concerns that may arise during the study.

We are submitting an application for a partial waiver of HIPAA authorization to review medical records of potentially eligible BreastCare Center patients in order to confirm eligibility. At the screening visit, we will obtain written consent to complete the screening process and potentially enroll in the trial.

This trial does not involve subjects who are not yet adults (infants, children, teenagers).

This trial does not involve cognitively impaired adults.

This trial does not involve adults unable to consent.

28.0 Process to Document Consent in Writing

Following policy #CON-100, we will obtain and document the informed consent of each woman who participates in the trial. A member of the study team who is trained in human subjects protections and trained on the protocol will make sure that the potential participant voluntarily confirms her willingness to participate in research, after having been informed of all aspects of the research that are relevant to her decision to participate. The trained research staff will meet with the prospective participant in a private room and discuss the IRB-approved informed consent document, and make sure that the person clearly understands the range of risks, the potential benefits, and the voluntary nature of participating in the research. The study staff will remind the potential participant that she has the right to decline participation and to withdraw from the research without negatively affecting their subsequent medical care in any way at any time after the research has begun.

She will be given time to consider participating in the research and to ask questions. If the prospective participant chooses to participate, she will sign and date the informed consent document, and the person obtaining informed

consent will also sign and date the document. We will provide a copy of the signed and dated document to the participant and we will retain the signed and dated document in a locked file cabinet.

We will obtain written documentation of informed consent using the consent form submitted with this IRB application.

This application includes a draft of our consent form for written consent to participate in the study, and the last page includes a checklist for ensuring that the informed consent process is conducted in accordance with policy #CON-100.

29.0 Drugs or Devices

This trial does not involve the administration of drugs or the use of any devices. Our application includes the FDA's letter on December 17th, 2021 confirming that an Investigational New Drug Application (IND) is not required for our study.

Research Consent Form
Dana-Farber/ Harvard Cancer Center
BIDMC/BCH/BWH/DFCI/MGH/Partners Network Affiliates

Protocol Title: Effect of Light Alcohol Intake on Sex Hormone Levels among Postmenopausal Women on Aromatase Inhibitor Therapy

DF/HCC Principal Investigator(s) / Institution(s): Kenneth J Mukamal / Beth Israel Deaconess Medical Center

Main Consent

INTRODUCTION AND KEY INFORMATION

All research is voluntary. It is your choice whether you take part in this research or not. If you decide to participate, please sign and date at the end of this form. We will give you a copy and you can refer to this consent form at any time.

The following is a short summary of this research study to help you decide whether you would like to be a part of this study. More detailed information is provided later in this form.

For purposes of this research, you will be referred to as a "participant."

1. Why am I being invited to take part in a research study?

You are invited to take part in in this research study, because you are a postmenopausal woman with estrogen receptor-positive (ER+) breast cancer who takes an aromatase inhibitor.

2. Why is this research being done?

The purpose of this study is to assess whether light alcohol intake increases sex hormone levels in the presence of standard breast cancer therapy.

3. Who is supporting this research?

A grant from the National Institutes of Health (K01AA027831) is supporting this research by providing funds for the staffing, supplies, and participant payments.

4. What does this research study involve and how long will it last?

This research study involves 10 weeks of participation, including 3 weeks consuming one serving of white wine daily, 3 weeks consuming one serving of

white grape juice daily, and 2 weeks of drinking neither alcohol nor grape juice before each of these 3-week drinking periods.

The names of the study exposures involved in this study are:

- White wine
- White grape juice

The research study procedures include one screening visit to obtain informed consent, four study visits with blood draws, and ten weekly phone calls and online questionnaires over the ten weeks of the study. Throughout the study, you should refrain from all alcohol and grape juice except your assigned drink and maintain your typical patterns of diet and activity throughout the study.

At the beginning of each 3-week drinking period, we will provide the white wine or white grape juice that you will need for the study. You will be asked to consume one serving per day of the study intervention (white wine) for three weeks and one serving per day of the study comparator (white grape juice) for three weeks, with each drinking period preceded by two weeks of no alcohol or grape juice consumption. You will not be followed after the ten-week study ends.

Alcohol consumption can affect coordination, motor skills, and cognition, i.e., the ability to think, judge, and reason. Driving after drinking alcohol increases the risk of vehicular accidents. After drinking alcohol, you should not drive, operate heavy machinery or engage in any activities that require you to be alert and/or respond quickly and you should not participate in activities that may be dangerous to yourself or to others.

It is expected that about 20 women will take part in this research study.

Information about you and your health is personal and private. Generally, it cannot be obtained without your written permission. By signing this form, you are providing that permission, and your information may be obtained and used in accordance with this informed consent and as required or allowed by law. This means that researchers may obtain information regarding your past medical history, as well as specimens and samples from previous health care providers such as hospitals and labs.

5. What are the risks to participating in this study?

There are risks to taking part in any research study. We want to make sure you know about a few key risks right now. More detailed information is provided in the "What are the risks or discomforts of the research study?" section.

There is a risk that you could have side effects from the white wine.

Some of the most common side effects that the study doctors know about are:

- Feeling tired immediately after drinking white wine
- Upset stomach after drinking white wine
- Discomfort or anxiety answering questions
- Pain and slight skin discoloration after blood draws

6. Will being in this study benefit me in any way?

We do not know if taking part in this study will benefit you. This study may help researchers learn information that could help people in the future and help postmenopausal women with estrogen receptor-positive (ER+) breast cancer make informed decisions about their alcohol intake.

7. What are my options?

Instead of being in this research study, you have other options which may include the following:

- Decide not to participate in this research study
- Participate in another research study

If you choose not to participate, are not eligible to participate, or withdraw from this research study, this will not affect your present or future care and will not cause any penalty or loss of benefits to which you are otherwise entitled.

We encourage you to take some time to think this over, to discuss it with other people and your primary doctor, and to ask questions at any time.

A. WHY IS THIS RESEARCH STUDY BEING DONE?

This research study is a pilot study, which is the first time investigators are examining the effect of light alcohol consumption on sex hormones among postmenopausal women with estrogen receptor-positive (ER+) breast cancer taking an aromatase inhibitor. In this experimental study, you will be asked to drink white wine and white grape juice, which are not consumed as the standard of care. The U.S. Food and Drug Administration (FDA) has not approved alcohol as a treatment for any disease.

In this research study,

- We are studying the effect of 3 weeks of drinking one serving of white wine compared to 3 weeks of drinking one serving of white grape juice. We are conducting this study to understand whether drinking one serving of alcohol per day increases sex hormone levels such as estrogen while taking an aromatase inhibitor that aims to suppress levels of these hormones.
- Alcohol intake raises sex hormone levels, however, it is unknown if that effect persists in postmenopausal women with estrogen receptor-positive (ER+) breast cancer taking an aromatase inhibitor. There have been no studies to examine alcohol's effect on sex hormone levels among postmenopausal women with estrogen receptor-positive (ER+) breast cancer. These drugs are only prescribed to postmenopausal women who had estrogen receptor-positive (ER+) breast cancer, the subtype where alcohol has been found to increase breast cancer incidence. This information is needed for breast cancer survivors to make informed decisions about their alcohol intake and its potential effect on adjuvant AI therapy.
- Previous studies have shown that alcohol increases sex hormone levels. Tamoxifen, a drug that blocks estrogen's action on breast cells, dampened the association between self-reported alcohol over the past month or year and some hormones (DHEAS) but strengthened the association between alcohol and other hormones (SHBG).

B. WHAT IS INVOLVED IN THE RESEARCH STUDY?

You will be "randomized" into one of the study drinking sequence groups: white wine followed by white grape juice or white grape juice followed by white wine. Randomization means that you are assigned one of these sequences by chance. It is like flipping a coin.

You will have an equal chance of being placed in any of the following sequence groups:

- 3 weeks of daily white wine followed by 3 weeks of daily white grape juice
- 3 weeks of daily white grape juice followed by 3 weeks of daily white wine

Before the research starts (screening visit):
After signing this consent form, you will be asked to undergo some screening tests or procedures to find out if you can be in the research study. Many of these tests and procedures are likely to be part of regular cancer care and may be done even if it turns out that you do not take part in the research study. If you have had some of these tests or procedures recently, they may or may not have to be repeated.

- **Medical history**, which includes questions about your health, current medications, and lifestyle factors
- **Typical alcohol intake**, including questions about how often you drink alcohol and how much you drink each time
- **Blood tests:** If you have not had liver function measured in the past 12 months, the nurse will draw 10 mL (less than 1 tablespoon) of blood to measure your liver function levels.

If you do not meet the eligibility criteria, you will not be able to participate in this research study. If these assessments show that you are eligible to participate in the research study, you will be asked to refrain from drinking alcohol and grape juice for two weeks.

Study Treatment Overview:

- **Drinking Periods:** Each study treatment cycle lasts 3 weeks during which time you will be taking the study drink (white wine or white grape juice) one time per day. There are two drinking periods during this 10-week study.
- **Washout Periods:** Before both of the 3-week drinking periods, you will be asked to refrain from drinking all alcohol and grape juice.

Visit 1: During this visit, we will conduct a clinical exam and blood draw and we will give you the drink and measuring cup for you to use over the next three weeks.

This visit will involve the following:

- **Clinical Exams:** You will have a physical exam (height, weight, waist circumference, blood pressure, and heart rate) and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Blood tests:** We will obtain a blood sample after fasting for 12 hours. The nurse will draw 100 mL (approximately 7 tablespoons) of blood to monitor your health (liver function, blood count, basic metabolic panel) and to measure your sex hormone levels.

Visit 2: During this visit, we will conduct a clinical exam and blood draw and we will ask you to refrain from drinking alcohol and grape juice for the next two weeks.

This visit will involve the following:

- **Clinical Exams:** You will have a physical exam (weight, waist circumference, blood pressure, and heart rate) and you will be asked questions about your general health and specific questions about any

problems that you might be having and any medications you may be taking.
- **Blood tests:** The nurse will draw 90 mL (approximately 6 tablespoons) of blood to monitor your health (liver function and blood count) and to measure your sex hormone levels.

Visit 3: During this visit, we will conduct a clinical exam and blood draw and we will give you the drink for you to use over the next three weeks.
This visit will involve the following:
- **Clinical Exams***:* You will have a physical exam (weight, waist circumference, blood pressure, and heart rate) and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Blood tests:** The nurse will draw 90 mL (approximately 6 tablespoons) of blood to monitor your health (liver function and blood count) and to measure your sex hormone levels.

Visit 4: During this visit, we will conduct a clinical exam and blood draw.
This visit will involve the following:
- **Clinical Exams***:* You will have a physical exam (weight, waist circumference, blood pressure, and heart rate) and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Blood tests:** The nurse will draw 90 mL (approximately 6 tablespoons) of blood to monitor your health (liver function and blood count) and to measure your sex hormone levels.

Research Consent Form

Dana-Farber/ Harvard Cancer Center
BIDMC/BCH/BWH/DFCI/MGH/Partners Network Affiliates OHRS Version: 1.31.2020

Research Study Plan:

		Screening	Washout 1	Washout 1	Visit 1	Drinking Period 1	Drinking Period 1	Drinking Period 1	Visit 2	Washout 2	Washout 2	Visit 3	Drinking Period 2	Drinking Period 2	Drinking Period 2	Visit 4	# Assessments
	Study Day	0	1-7	8-14	15	15-21	22-28	29-35	36	36-42	43-49	50	51-57	58-64	65-71	72	
	Window Allowance (Days)		±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	
	Type of Visit	Clinic	Phone	Phone	Clinic	Phone	Phone	Phone	Clinic	Phone	Phone	Clinic	Phone	Phone	Phone	Clinic	
	Payment				$20				$30			$30				$50	
Admin, Body Measurements, and Vitals																	
	Consent, , contact information	X															1
	Eligibility: e.g. Alcohol use Disorders Identification Test (AUDIT) and liver function test, if none in the past 12 months*	X															1
	Randomization				X												1
	Verification of consent and documentation				X				X			X				X	4
	Height				X												1
	Weight, waist circumference				X				X			X				X	4
	Vital signs- blood pressure, heart rate				X				X			X				X	4
	Distribute drink				X							X					2
	Measure leftover drink								X							X	2
	Pay participant, reimburse parking				X				X			X				X	4
Blood Draw																	
	Hepatic panel	*			X				X			X				X	4
	Complete blood count with differential				X				X			X				X	4
	Basic metabolic panel (fasting)				X												1
	Lipid panel								X							X	2
	Dehydroepiandrosterone sulfate (DHEAS)				X				X			X				X	4
	Sex hormone binding globulin (SHBG)				X				X			X				X	4
	Estradiol				X				X			X				X	4
	Testosterone				X				X			X				X	4
Weekly Call																	
	Health events		X	X		X	X	X		X	X		X	X	X		10
	Other health changes		X	X		X	X	X		X	X		X	X	X		10
Weekly REDCap Questionnaires																	
	Timeline follow-back (or daily REDCap text)		X	X		X	X	X		X	X		X	X	X		10
	Pittsburgh Sleep Quality Index (PSQI)							X							X		2
	Depressive Symptoms (CES-D-6)		X	X		X	X	X		X	X		X	X	X		10

	Overall pain (visual analog scale)		X	X		X	X	X		X	X		X	X	X		10
	Open text-any questions, concerns, comments		X	X		X	X	X		X	X		X	X	X		10

Planned Follow-up

We will not follow up with you after the 10-week study ends, but we will provide our contact information in case you have any questions after the study ends and we will ask for your permission to contact you to update you on the results of this study.

You can stop participating in the research study at any time, however, the FDA requires that any information collected up to the point of your withdrawal not be removed from the study.

C. WHAT ARE THE RISKS OR DISCOMFORTS OF THE RESEARCH STUDY?

There are risks to taking part in any research study. In this study, there may be side effects from the wine or grape juice, from giving blood samples, and from completing interviews.

There is a great deal of variability among side effects and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the 10-week study to keep track of blood pressure, heart rate, liver function, blood count, and triglycerides. If you experience side effects, they may go away after you stop taking the wine or grape juice. Some side effects can be mild, but other unexpected side effects can be long-lasting and may never go away. Some may be life-threatening or fatal.

Risks Associated with White Grape Juice and White Wine

Likely

- Feeling tired immediately after drinking white wine

Occasional

After drinking white wine, you may experience the following side effects:

- Upset stomach
- Turning red or "flushing" after drinking white wine (in cases of genetic intolerance to alcohol or use of specific medications)
- Worsening of liver disease among people with pre-existing liver disease.

- For both the wine and grape juice drinking periods, the daily drinks contain approximately 120 calories and can cause weight gain if not balanced by decreases in the caloric content of the diet.

Rare

- Alcohol is an addictive substance, although the risk of causing alcohol misuse is low among women who already typically drinking small amounts each week

Non-Physical Risks

The questionnaires used in this study may be upsetting. If you find the questionnaires upsetting, you may speak with the research doctor or ask to be referred for additional emotional support. You may also skip any question that you do not wish to answer.

It is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.

D. WHAT WILL HAPPEN IF I AM REMOVED FROM THE STUDY OR DECIDE TO END MY PARTICIPATION IN THE RESEARCH?

You may be taken off the research study for any reason including:

- It is considered to be in your best interest
- The study treatment or procedures are found to be unsafe or ineffective
- If you have any problems following study treatments and procedures
- Your condition worsens
- A decision is made to end the study
- Or for other unforeseen reasons that make it necessary to stop your participation in the research study

You can also choose to stop participating in the research study at any time. Tell the research doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop. Leaving the research study will not affect your medical care outside of the research study.

It is important to tell the research doctor if you are thinking about stopping so that you and your research doctor can discuss what follow-up care and testing could be most helpful for you.

It is important to note that although you may withdraw from study participation, the FDA requires that any information collected up to the point of your withdrawal not be removed from study records. Additionally, the research doctor may consult public records after you have withdrawn from the study.

If you agree to allow your blood and data to be kept for future research with identifying information that could link your sample to you, you may withdraw your permission at any time. We ask that you contact the study team and let them know you are withdrawing your permission for your identifiable blood and data to be used for future research.

E. WHAT ARE THE BENEFITS OF THIS RESEARCH STUDY?

Taking part in this research study may or may not benefit you. We hope the information learned from this research study will provide more information about the effect of light alcohol intake on sex hormone levels in the presence of aromatase inhibitor therapy.

F. WILL I BE PAID TO TAKE PART IN THIS RESEARCH STUDY?

The study sponsor will provide parking vouchers if plan to drive to the Clinical Research Center. In addition, you will be compensated for your time and effort at the end of each study visit, with a total of $130 for completing all 10 weeks of the study ($20 for Visit 1 (Baseline), $30 for Visit 2, $30 for Visit 3, and $50 for Visit 4).

This research study will use a service called ClinCard® by the company Greenphire to manage all payments associated with your participation in study visits, your time and travel related to participation in the study. Additional information about the service will be provided to you in a separate document.

G. WHAT ARE YOUR COSTS?

Taking part in this research study will not lead to added costs to you or your insurance company. You will not be charged for the white wine, white grape juice, physical exams, and blood draws.

H. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS RESEARCH STUDY?

If you think you have been injured as a result of taking part in this research study, tell the person in charge of this research study as soon as possible. The research doctor's name and phone number are listed in this consent form.

The treating hospital will offer you the care needed to treat injuries directly resulting from taking part in this research. These treatments may be billed to you or your insurance company. You will be responsible for deductibles, co-payments, and co-insurance. There are no plans to pay you or give you other compensation for the injury.

You do not give up any of your legal rights by signing this form.

We will need to collect certain personal information about you for insurance or payment reporting purposes, such as your name, date of birth, gender, social security number, or Medicare identification number and information related to this research study. We may be required to report this information to the Centers for Medicare & Medicaid Services. We will not use this information for any other purpose.

If you go to the Emergency Room or to another hospital or doctor it is important that you tell them that you are in this research. If possible, you should give them a copy of this consent form.

This trial does not involve treatment for a medical condition. You or your insurance company will be responsible for the cost of medical treatment.

I. WHOM DO I CONTACT IF I HAVE QUESTIONS ABOUT THE RESEARCH STUDY?

If you have questions about the study, please contact the research doctor or study staff as listed below:

- Kenneth Mukamal, MD MPH: (617) 754-1409
- Elizabeth Mostofsky, ScD: (617) 432-4023

For questions about your rights as a research participant, please contact a representative of the Office for Human Research Studies at Dana-Farber Cancer Institute (617) 632-3029. This can include questions about your participation in the study, concerns about the study, a research related injury, or if you feel/felt

under pressure to enroll in this research study or to continue to participate in this research study.

J. RETURN OF RESEARCH RESULTS

Tests done on samples in this research study are only for research and have no clear meaning for your health care. For this reason, your study doctor will not share the results with you.

K. CLINICALTRIALS.GOV

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

L. FUTURE USE OF DATA AND SPECIMENS

Your personal information and/or biospecimens collected during this study may be stored and used for future research. Any personal identifiers will not be removed before they are shared so that the information or samples can be linked back to you by authorized personnel.

You will not be asked to provide additional informed consent for the use of your identifiable information or samples in future research.

M. CONFIDENTIALITY

We will take measures to protect the privacy and security of all your personal information, but we cannot guarantee the complete confidentiality of study data.

Medical information created by this research study will not become part of your hospital medical record and will not be forwarded to your primary doctor. Trial information will be stored in your study file and it may also become part of a research database.

The study team may publish the results of this research study and when we do, we may be asked to make the data we collect available to other researchers. We will not include information that identifies you in any publications or to the researchers who request the data to do additional research.

Your anonymized specimens may also be placed into one or more publicly-accessible scientific databases. Through such databases, researchers from around the world will have access to anonymized samples or data for future research.

There is a risk that anonymized research data that is shared with outside collaborators may be re-identified. When anonymized data and specimens are shared with outside collaborators agreements limit what the outside collaborators can do with the information to help prevent re-identification.

N. FINANCIAL DISCLOSURES

It is possible that certain researchers on this study may have earned money from, or own some publicly-traded stock in, the company that makes or is developing the study intervention. The amount of money that a researcher may earn and still take part in research is limited by the Harvard Medical School Faculty of Medicine Policy on Conflicts of Interest and Commitment. If you have further questions, please speak with a member of the study team or contact the Dana-Farber Cancer Institute Office of Research Integrity at 617-432-4557 or researchintegrity@dfci.harvard.edu.

O. CERTIFICATE OF CONFIDENTIALITY (COC)

To help protect your privacy, we have been issued a Confidentiality Certificate from the National Institutes of Health (NIH). With this Certificate, the researchers on this study cannot be forced (for example, by court subpoena) to disclose information that may identify you in federal, state, or local civil, criminal, administrative, legislative or other proceedings.

Disclosure will be necessary upon request of a United States federal or state government agency sponsoring the project that will be used for audit or program evaluation purposes or to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family or even the research doctor from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider, or employer learns about your participation and obtains your consent to receive research information, then we cannot use the Certificate

of Confidentiality to withhold this information. This means that you and your family must actively protect your own privacy.

The Certificate of Confidentiality cannot be used to prevent disclosure to state or local authorities when there is a duty to report concerns of abuse, neglect, self-harm, or a danger to others.

To help protect your privacy, Beth Israel Deaconess Medical Center has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS). With this Certificate, Beth Israel Deaconess Medical Center cannot be forced (for example, by court subpoena) to disclose information that may identify you in federal, state, or local civil, criminal, administrative, legislative or other proceedings.

Disclosure will be necessary upon request of a United States federal or state government agency sponsoring the project that will be used for audit or program evaluation purposes or to meet the requirements of the federal Food and Drug Administration (FDA).

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family or even the research doctor from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider, or employer learns about your participation and obtains your consent to receive research information, then Beth Israel Deaconess Medical Center cannot use the Certificate of Confidentiality to withhold this information. This means that you and your family must actively protect your own privacy.

The Certificate of Confidentiality cannot be used to prevent disclosure to state or local authorities when there is a duty to report concerns of abuse, neglect, self-harm, or a danger to others.

P. PRIVACY OF PROTECTED HEALTH INFORMATION (HIPAA AUTHORIZATION)

The Health Insurance Portability and Accountability Act (HIPAA) is a federal law that requires Dana-Farber/Harvard Cancer Center (DF/HCC) and its affiliated research doctors, health care providers, and physician network to protect the privacy of information that identifies you and relates to your past, present, and future physical and mental health conditions ("protected health information"). If

you enroll in this research study, your "protected health information" will be used and shared with others as explained below.

1. **What protected health information about me will be used or shared with others during this research?**

   - Existing medical records, including mental health records.
   - New health information created from study-related tests, procedures, visits, and/or questionnaires

2. **Why will protected information about me be used or shared with others?**

   The main reasons include the following:
   - To conduct and oversee the research described earlier in this form;
   - To ensure the research meets legal, institutional, and accreditation requirements;
   - To conduct public health activities (including reporting of adverse events or situations where you or others may be at risk of harm); and
   - To provide the study sponsor with information arising from an adverse event or other event that relates to the safety or toxicity of the drug(s) used in the study and for the purpose of this or other research relating the study drug(s) and their use in cancer;
   - To better understand the diseases being studied and to improve the design of future studies; and,
   - Other reasons may include for treatment, payment, or health care operations. For example, some medical information produced by this research study may become part of your hospital medical record because the information may be necessary for your medical care. (You will also be given a notice for use and sharing of protected health information.)

3. **Who will use or share protected health information about me?**

   - DF/HCC and its affiliated research doctors and entities participating in the research will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance will be able to use and share your protected health information.

4. With whom outside of DF/HCC may my protected health information be shared?

While all reasonable efforts will be made to protect the confidentiality of your protected health information, it may also be shared with the following entities:

- Outside individuals or entities that have a need to access this information to perform functions relating to the conduct of this research such as analysis by outside laboratories on behalf of DF/HCC and its affiliates (for example, data storage companies, insurers, or legal advisors).
- The sponsor(s) of the study, its subcontractors, representatives, business partners, and its agent(s): National Institute on Alcohol Abuse and Alcoholism (NIAAA
- Other research doctors and medical centers participating in this research, if applicable
- Federal and state agencies (for example, the Department of Health and Human Services, the Food and Drug Administration, the National Institutes of Health, and/or the Office for Human Research Protections), or other domestic or foreign government bodies if required by law and/or necessary for oversight purposes. A qualified representative of the FDA and the National Cancer Institute may review your medical records.
- Hospital accrediting agencies
- A data safety monitoring board organized to oversee this research, if applicable

Some who may receive your protected health information may not have to satisfy the privacy rules and requirements. They, in fact, may share your information with others without your permission.

5. For how long will protected health information about me be used or shared with others?

- There is no scheduled date at which your protected health information that is being used or shared for this research will be destroyed because research is an ongoing process.

6. Statement of privacy rights:

- You have the right to withdraw your permission for the research doctors and participating DF/HCC entities to use or share your protected health information. We will not be able to withdraw all the information that already has been used or shared with others to carry out related activities

such as oversight, or that is needed to ensure the quality of the study. To withdraw your permission, you must do so in writing by contacting the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"

- You have the right to request access to your protected health information that is used or shared during this research and that is related to your treatment or payment for your treatment, but you may access this information only after the study is completed. To request this information, please contact the researcher listed above in the section: "Whom do I contact if I have questions about the research study?"

Q. DOCUMENTATION OF CONSENT

My signature below indicates:

- I have had enough time to read the consent and think about participating in this study;
- I have had all of my questions answered to my satisfaction;
- I am willing to participate in this study;
- I have been told that my participation is voluntary and I can withdraw at any time

Signature of Participant
or Legally Authorized Representative

Date

Relationship of Legally Authorized Representative to Participant

Research Consent Form
Dana-Farber/ Harvard Cancer Center
BIDMC/BCH/BWH/DFCI/MGH/Partners Network Affiliates OHRS Version: 1.31.2020

To be completed by person obtaining consent:

Adult Participant

The consent discussion was initiated on _____ (date).

Signature of individual obtaining consent: _____

Printed name of above: _____

Date: _____

☐ A copy of this signed consent form will be given to the participant or legally authorized representative.

☐ 1) The participant is an adult and provided consent to participate.

☐ 1a) Participant (or legally authorized representative) is a non-English speaker and signed the translated Short Form in lieu of English consent document:

☐ *As someone who understands both English and the language used by the participant, I interpreted and/or witnessed, in the participant's language, the researcher's presentation of the English consent form. The participant was given the opportunity to ask questions.*

Signature of Interpreter/Witness: _____

Printed Name of Interpreter/Witness: _____

Date: _____

☐ 1b) Participant is physically unable to sign the consent form because:

☐ The participant is illiterate.

☐ The participant has a physical disability.

☐ Other (please describe): _____

The consent form was presented to the participant who was given the opportunity to ask questions and who communicated agreement to participate in the research.

Signature of Witness: _____

Printed Name of Witness: _____

Date: _____

☐ 2) The participant is an adult who lacks capacity to provide consent and his/her legally authorized representative:

☐ 2a) gave permission for the adult participant to participate

☐ 2b) did not give permission for the adult participant to participate

DFCI Protocol Number: 21-698	Approved Date (DFCI IRB Approval): 04/18/2022
Date Posted for Use: 06/23/2022	

Informed Consent Documentation

To be signed by the person obtaining informed consent.

Date of Informed Consent: ☐ Initial Consent ☐ Re-consent

Participant Identifier: Protocol #:

Was a witness present? ☐ Yes* ☐ No *Witness Name:

- The content of the informed consent document was fully explained.
- The participant was given adequate time to review the consent form and received an explanation of the content of the informed consent document.
- The participant had an opportunity to ask questions and all of the participant's questions regarding the study were answered to their satisfaction.
- The participant completed all sections of the informed consent document, and signed and dated the informed consent document.
- The participant received a signed and dated copy of the informed consent document.

Additional comments:

By signing below, I attest that the informed consent process was conducted as indicated above..

Signature:	Date:
Printed Name:	