Moderate Alcohol and Cardiovascular Health Trial (MACH15)

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Funded by: National Institute on Alcohol Abuse and Alcoholism

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STATEMENT OF COMPLIANCE

The Moderate Alcohol and Cardiovascular Health Trial (MACH15) will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the Terms of Award.

The Principal Investigator will assure that no deviation from, or changes to, the protocol will take place without prior agreement from the funder and documented approval from the appropriate Institutional Review Board (IRB) or Ethics Committee, except where necessary to eliminate an immediate hazard(s) to the trial participants.

All personnel involved in the conduct of this trial have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this trial are informed about their obligations in meeting the above commitments.

Principal Investigator: Kenneth J. Mukamal, MD, MPH

Signed: _____ Date: 30 June 2017

Title:	**Moderate Alcohol and Cardiovascular Health Trial (MACH15)**

Précis:

The Moderate Alcohol and Cardiovascular Health Trial (MACH15) is a multicenter, worldwide, randomized clinical trial of ~15 g of alcohol daily versus abstention, using a balanced parallel design and single-blind assessment of all outcomes among approximately 7,800 participants aged 50 years and older with above-average cardiovascular risk. Intervention will average 6 years in duration with a common close-out date. Following recruitment and pre-screening, participants will attend a screening visit followed by a two-week abstention washout period, a baseline visit and randomization, and subsequent visits at 3 months, 6 months, 12 months, and then annually until close-out.

Objectives:

Primary Trial Objective: To determine the effects of one serving of alcohol (~15 g) daily compared to no alcohol intake on the risk of incident cardiovascular disease among adults at above-average cardiovascular risk.

Secondary Trial Objective: To determine the effects of one serving of alcohol (~15 g) daily compared with no alcohol intake on the risk of incident diabetes among participants free of diabetes at baseline.

Endpoints

Primary Outcome:
Time from baseline to a composite endpoint comprised of the first occurrence of a non-fatal myocardial infarction, non-fatal ischemic stroke, hospitalization for angina, coronary/carotid revascularization, or all-cause mortality.

Secondary Outcomes:
1.   Time from baseline to a composite endpoint comprised of the first occurrence of a non-fatal myocardial infarction, non-fatal ischemic stroke, hospitalization for angina, coronary/carotid revascularization, or cardiovascular death.
2.   Progression among normoglycemic and pre-diabetes individuals to American Diabetes Association (ADA)-defined diabetes.

Tertiary Outcomes:
1.   Time from baseline to a composite endpoint comprised of the first occurrence of a non-fatal myocardial infarction, non-fatal ischemic stroke, or cardiovascular death.

2. Time from baseline to the first occurrence of each of the components of primary outcome (5 outcomes).
3. Time from baseline to cardiovascular death.
4. Progression among normoglycemic individuals to ADA-defined prediabetes.

Population:	Adults aged 50 and older at above-average cardiovascular risk
Phase:	Phase III
Number of Clinical Sites Enrolling Participants:	~20 clinical sites worldwide (North and South America, Asia, Australia, Europe, Africa)
Description of Trial Agent:	Alcohol arm: One U.S. serving (~15 g) daily of beer, wine, or spirits for ~6 years Abstention arm: No alcohol intake for ~6 years
Trial Duration:	Enrollment duration: Years 1-4 (7 Vanguard sites), Years 2-4 (All sites) Average duration per participant: 6 years Analysis and Presentation: Years 9-10
Monitoring Plan:	A Data and Safety Monitoring Board will be appointed and be responsible to review data at least every 6 months throughout the trial and ensure participant safety.

1.1 OVERVIEW

The health effects of alcohol consumption have been key public health concerns for millennia. Alcohol consumption is highly prevalent, with remarkably little change in prevalence over the last century, and excessive use is a risk factor for innumerable adverse health outcomes, including cognitive impairment, cancer, cardiomyopathy, cirrhosis, gastrointestinal bleeding, trauma, and social devastation. Although the benefit of avoiding alcohol misuse is well-accepted and uncontroversial, the risks and potential benefits of alcohol consumption when consumed within moderation remain unproven. Observational studies document a lower risk of coronary heart disease and diabetes among moderate consumers relative to abstainers, but they also suggest a higher risk of breast and gastrointestinal cancers, and the possibility of residual confounding of these associations by other characteristics cannot be excluded. No clinical trial has been conducted to test the hypothesis that moderate alcohol consumption lowers risk of cardiovascular disease or diabetes compared to abstention, yet public policy continues to be made regarding safe limits of drinking. A definitive yet feasible clinical trial investigating whether moderate alcohol consumption lowers cardiovascular and diabetes risk is needed; indeed, it was the foremost recommendation of the NIAAA Expert Panel on Alcohol and Chronic Disease Epidemiology.[1]

1.2 BACKGROUND

1.2.1. PREVALENCE OF ALCOHOL USE

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) has defined moderate or low-risk alcohol use as intake of ≤4 drinks on any single day AND ≤14 drinks per week for men and ≤3 drinks on any single day AND ≤7 drinks per week for women. This level of alcohol use is widespread throughout the world; in the U.S., at least half of adults report alcohol use in the last month, most of whom are light or moderate drinkers.[2] The World Health Organization (WHO) estimates that half of all adults worldwide report current or former alcohol consumption, 85% of whom appear to do so without heavy drinking episodes.[3]

Although alcohol intake declines with age, it remains widely common even into older age; in the U.S., 40-60% of adults aged 50 and older report recent drinking within recommended limits.[4] Rates of current drinking among older adults are even higher in Europe and Australasia but lower in Asia.[5] Older adults who drink safely at least occasionally are thus common and represent a particularly attractive group for recruitment into trials of chronic disease.[6]

1.2.2. ALCOHOL AND CARDIOVASCULAR DISEASE

As a consequence of this widespread use, moderate alcohol use is among the most widely studied exposures in the biomedical literature and has been critically reviewed at considerable length by the NIAAA.[7] Epidemiological studies consistently suggest a lower risk of coronary heart disease (CHD) and myocardial infarction (MI) among moderate drinkers than abstainers.[8] In addition to population-based

studies from several populations,[9,10] these have included studies among men and women[11,12] and among middle-aged and older adults.[13,14] Indeed, the association of moderate alcohol intake appears to be similar among individuals at both low and high cardiovascular risk and even among those with prevalent cardiovascular disease (CVD).[15-18] Of note, a cumulative meta-analysis suggests that the best estimate of the association of alcohol and CHD has not changed in almost 20 years.[8]

Meta-analyses have examined the details of the relationship of alcohol consumption and risk of CHD.[19,20] In the most quantitative analysis, which demonstrated a J-shaped dose-response relationship, risk was lowest at 20 g/day (~1.4 drinks per day).[20] Summary relative risks of approximately 0.8 were found, implying that moderate drinking is associated with 20% lower risk of CHD relative to abstention. Thus, consumption of alcohol throughout the range of moderate intake is associated with lower risk of CHD, with strong evidence of lower risk associated with intake of 1-2 drinks per day in both meta-analyses, suggesting that randomized trials of 1 drink (~15 g) daily compared with no or very low intake would fairly test the hypothesis that moderate drinking lowers CHD risk. Of note, the observed descending limb of the alcohol-CHD relationship is steep, with lower risk even with 1-2 drinks per week, implying that the appropriate contrast to daily drinking must be intake as close to abstention as possible.

In general, the specific type of alcoholic beverage type consumed appears to be less important than the consistency with which alcohol is consumed. The beverage most likely to be inversely related to CHD in a given population tends to be the one most widely consumed in that population.[10,21] Two systematic reviews of this topic have concluded that beverage type is relatively unimportant,[22,23] while a recent meta-analysis found similar benefits from beer and wine but not spirits.[24] The effect of alcohol on high density lipoprotein-cholesterol (HDL-C; its major putative mediator) also does not differ by beverage type in short-term controlled experiments.[25] Thus, observational evidence generally supports the hypothesis that it is ethanol intake, *per se*, that is associated with lower risk of CHD. This also concords with how alcohol intake is viewed by NIAAA and other bodies: a limit on total intake without differentiation by beverage type.

Although less well-studied, evidence overall suggests that other coronary outcomes commonly used in clinical trials (e.g., unstable angina, coronary revascularization) demonstrate similar associations with alcohol as does MI. Indeed, several cohort studies have shown similar relationships across all coronary outcomes.[11,14,26-28]

Other vascular outcomes have also been studied extensively in relation to moderate drinking. The association of alcohol consumption with total stroke is complex, given differing associations with the major stroke types of ischemic and hemorrhagic stroke. Further, subtypes within these major stroke types may differ in their associations with alcohol, presumably due to disparate underlying etiologies.[29] Nonetheless, light-moderate drinking has been associated with a lower risk of ischemic stroke of approximately the same magnitude as for CHD, while hemorrhagic stroke appears to have a dose-dependent positive association with alcohol intake.[30] Etiologically, both effects could reflect an antiplatelet effect of alcohol.[31]

The relationship of moderate drinking with blood pressure, an important risk factor for CHD and all forms of stroke, is complex and not entirely consistent even in the hours following consumption.[32] Sex-specific meta-analysis suggests a J-shaped association between alcohol and risk of hypertension among women but a roughly dose-response positive association among men; in neither sex was moderate drinking associated with significantly higher risk.[33]

Moderate alcohol consumption has also been associated with a lower risk of total mortality, chiefly reflecting its inverse association with cardiovascular mortality.[8] The magnitude of this association is again similar to that for CHD, estimated as ~0.83-0.84 in formal meta-analyses.[34]

1.2.3. ALCOHOL AND DIABETES

Beyond CHD, ischemic stroke, and death, observational studies link moderate drinking to lower risk of type II diabetes.[35,36] Meta-analyses suggest that the magnitude of this association might well exceed of CHD, with summary relative risks approaching ~30% lower risk.[35,37] As with CHD, the few studies that have formally examined beverage type suggest generally similar associations across beverage types.[38,39]

1.2.4. ALCOHOL AND CANCER, LIVER DISEASE, AND TRAUMA

Several non-cardiovascular outcomes have strong, plausible relations with moderate drinking, and these bear directly on the safety of any clinical trial of alcohol consumption. Among these, cancer is the most feared and breast cancer the best studied. In observational studies, alcohol consumption appears to have a linear association with breast cancer, with no threshold level of intake.[40] Pooled cohort studies estimate the relative risk to be 1.09 for each 10 g increment in daily intake.[41] Some evidence suggests a similar relationship for other cancers,[42] although the strongest evidence is for oropharyngeal and esophageal cancers that are less common in the U.S. and for which there appears to be substantial synergy between alcohol and cigarette smoking.[43]

Liver cirrhosis, classically associated with long-term heavy drinking, has also been associated with even moderate alcohol intake, although this appears to reflect susceptibility among individuals with predisposing forms of underlying liver disease such as infection with hepatitis viruses.[44] Formal meta-analyses generally suggest threshold effects with risk of cirrhosis significantly increased with intake above 24 g daily.[45]

Trauma and fractures, which contribute enormously to the global burden of illness related to alcohol may also be increased with more moderate drinking, although it is difficult to determine if this reflects true effects of moderate drinking or occasional binge drinking among otherwise moderate consumers.[46] Suicide attempts are related to acute alcohol intake, particularly with heavy drinking but potentially with lower doses as well.[47]

1.2.5. PREVIOUS TRIALS OF ALCOHOL CONSUMPTION

Dozens of trials of moderate drinking over a few weeks have been conducted.[25,36,48-80] Major themes from these trials are reviewed below. However, very few trials have administered alcohol for more than

a few months. Two crossover trials administered alcohol for 16,[81] and 12 weeks,[82] but their design limits their applicability to a long-term randomized clinical trial.

Importantly, a few studies of 3-24 months' duration have now been reported, summarized below. These provide important lessons about the feasibility and design of a long-term randomized trial of alcohol consumption.

An Italian group reported a one-year randomized trial of one glass daily of red wine among 115 diabetic survivors of acute MI.[83] Patients randomized to red wine demonstrated increases in HDL-C and, surprisingly, in echocardiographically-determined left ventricular function. Inflammatory markers and insulin resistance also declined. Although highly-specific biomarkers for alcohol were not reported, trends in nitrotyrosine (a short-term marker of oxidative stress) declined throughout the 12 months, suggesting sustained adherence.

In a 3-month parallel-design trial in Israel comparing wine with a non-alcoholic malt beverage in ~100 non-drinking diabetic adults, Shai et al. found that initiation of wine reduced fasting but not post-load glucose.[84] Sleep improved among those randomized to wine, with no other serious side effects. In a longer follow-up, Shai and colleagues reported results of a 24-month-long randomized trial of diabetic adults, assigning individuals to 150 ml of mineral water, white wine, or red wine daily.[85] Among several notable findings, insulin sensitivity improved in both wine groups relative to mineral water, with consistent improvement across the study period. ALT, AST, bilirubin, and alkaline phosphatase did not differ between the 3 groups.

Shorter trials of alcohol intake on a variety of secondary outcomes are available and suggest some plausible mechanisms for the effects of moderate drinking.[86] The most compelling results of short-term trials of alcohol intake in humans are on levels of HDL-C. This effect of alcohol has been found so consistently and powerfully that HDL-C now provides a plausible biomarker for alcohol consumption, at least at the group level, and has been used to validate questionnaire-based assessments.[87] A meta-analysis of 36 experimental trials of alcohol administration found that intake of 30 g/day (i.e., ~2 drinks) for 4 weeks raised HDL-C by ~4 mg/dl, an 8% increase from pretreatment values.[84] As noted, the effect was similar in studies of beer, wine, spirits, or pure ethanol.

Short-term trials have also examined the effect of alcohol on measures of glucose metabolism and control. In crossover studies, investigators at the U.S. Department of Agriculture (USDA) found that alcohol consumption had no effect on fasting glucose levels but lowered insulin levels, consistent with improved insulin sensitivity.[81] A meta-analysis of feeding studies found that alcohol consumption decreases levels of hemoglobin A1c and (after accounting for publication bias) insulin resistance among non-diabetic individuals, providing strong support for effects of moderate drinking on both incident diabetes and impaired fasting glucose.[88]

Lastly, a 6-month pilot study randomized 39 higher-CVD-risk subjects to either 0 or 15 g of alcohol daily, provided as sugar-free lemonade with or without grain alcohol to test the feasibility of long-term trials of ethanol itself rather than standard alcoholic beverages.[89] In brief, the trial showed no change in any biomarker of alcohol consumption, including HDL-C, GGT, and adiponectin, suggesting that adherence

was suboptimal. Debriefing interviews also suggested poor tolerance of the grain alcohol-based beverage, a finding that strongly supports the use of personalized commercial beverage choice in any long-term trial. In addition, every participant correctly identified their assigned beverage despite their completely identical composition other than alcohol, confirming that true blinding of alcoholic beverages is not feasible in a long-term study among free-living individuals.

In summary, evidence from feeding studies shows that in individuals at above-average CVD risk (such as those with diabetes), individuals can be randomized successfully for as long as 2 years to one commercially-available, palatable alcoholic drink daily versus abstention, with acceptable compliance based upon self-report and effects on glycemic parameters and HDL-C. No adverse safety signals have been identified. On the other hand, the safety and feasibility of testing doses of alcohol above 15 g daily have not been demonstrated.

1.3   RATIONALE

1.3.1. RATIONALE FOR A RANDOMIZED TRIAL

Strong rationale underlies the conduct of a randomized trial comparing moderate drinking with no or very low alcohol intake on cardiovascular disease and diabetes. Most importantly, previous trials have been insufficiently large and long to examine chronic disease outcomes, and hence gold-standard evidence with which to judge the health effects of moderate drinking is completely lacking. In this context, equipoise regarding its effects clearly exists; genuine uncertainty remains in the expert medical community as to whether moderate drinking truly prevents cardiovascular disease, diabetes, or any other health condition.

This state of equipoise is well illustrated by inconsistent guidelines and recommendations regarding drinking. The World Health Organization states that "there is no safe level for drinking alcohol…and that the ideal situation for health is to not drink at all."[90] In contrast, moderate drinking is already recommended by many physicians, especially to higher-risk individuals.[91,92] At the same time, national guidelines on alcohol consumption differ widely and continue to change without consensus. For example, the U.S. Department of Agriculture defines moderate drinking as up to 1 drink daily for women and 2 drinks daily for men.[93] As noted, the NIAAA defines low-risk drinking for women as no more than 3 drinks on any single day and no more than 7 drinks per week; for men, it is defined as no more than 4 drinks on any single day and no more than 14 drinks per week.[94] The American Geriatrics Society recommends a limit of 1 drink daily for both men and women aged 65 years and older.[6]

Several examples from large randomized trials of other interventions demonstrate the problems of relying exclusively on intermediate or surrogate outcomes and on observational data to judge the causality of preventative interventions. In the field of cardiovascular prevention, postmenopausal estrogen therapy demonstrated potential benefits on cardiovascular risk factors and was associated with lower CVD risk in many observational studies, yet definitive randomized trials suggested, if anything, an increased rate of stroke.[95] This example and others suggest that results from epidemiological studies and trials using surrogate outcomes may not extend to prevention of clinical

events. If anything, the uncertainty related to the health effects of alcohol consumption is even larger, and hence confidence in applying its short-term effects to longer-term chronic disease outcomes is necessarily lower. Moreover, epidemiological studies have identified potential harms from even moderate drinking. These too have not been confirmed in randomized trials, yet patients, physicians, and public health professionals are all asked to use far-from-definitive data in making recommendations. Only a randomized trial can provide conclusive evidence as to whether or not daily alcohol consumption lowers risk of cardiovascular disease or diabetes, while also collecting information on other outcomes that will allow for a more thorough and unbiased understanding of all potential effects of moderate alcohol consumption. As such, a definitive randomized trial of moderate alcohol consumption compared with abstention can play a crucial role in the eventual establishment of the first fully evidence-based guidelines for the use or nonuse of alcohol.

The rationale for a randomized trial of moderate alcohol consumption is further underscored by the inherently inconclusive nature of epidemiological evidence. For example, with regard to alcohol consumption, differences in the associations of alcohol consumption with risk of cardiovascular disease have been noted in different geographic regions.[96,97] Some meta-analysts express concern about the possibility of inappropriate reference groups in many cohort studies and highlight the advantage of randomized trials with mortality endpoints.[98] In addition, observational studies using genetic variants as proxies or instruments for alcohol consumption have come to inconsistent conclusions.[99,100]

Given the inability to judge causality in epidemiological studies and the limited scope of previous randomized trials of moderate alcohol consumption, equipoise exists about the health effects of moderate drinking. In conjunction with the urgent need to provide an evidence base for drinking guidelines worldwide, this uncertainty provides the rationale for a long-term, randomized trial of moderate drinking compared with no or very low alcohol intake on cardiovascular disease, diabetes, and mortality.

1.3.2. RATIONALE FOR THE TRIAL INTERVENTION

The alcohol intervention to be studied is based upon epidemiological evidence for dose and beverage type, previous clinical trial evidence for feasibility, and U.S. and international guidelines for safety.

The doses of alcohol assigned in the two arms – ~0 and ~15 g daily – are designed to test the primary hypothesis regarding the effect of alcohol on CVD and mortality. Because of the steep descending limb of the alcohol-CVD relationship, even modest levels of intake above abstention in the control group may influence trial outcomes and reduce statistical power. At the same time, given the relatively flat portion of the alcohol-CVD relationship between 15 and 30 g daily, there is little evidence that doses above ~15 g would provide greater cardiovascular benefit. Therefore, participants are asked and counseled to consume no alcohol in the abstention arm and one standard (~15 g) serving – approximately 5 ounces (~150 ml) of wine, 12 ounces (~350 ml) of beer, or 1.5 ounces (~45 ml) of spirits – daily in the alcohol arm.

Although studies are not perfectly consistent in the relative effects of different alcoholic beverages, their similarities greatly outweigh their differences, both in direct effects on biomarkers and on risk of

chronic disease in epidemiological studies. Moreover, clinical practice and national guidelines do not differentiate among beverages in establishing safe limits to drinking. Because drinking preferences differ between individuals and even within individuals over time, maximal flexibility in beverage type increases the likelihood of adherence among individuals assigned to alcohol consumption. Therefore, participants are not restricted in the type of alcohol they choose to consume.

Previous trials provide specific evidence for these choices. No study of 3 months or longer has used doses beyond ~15 grams of alcohol daily, and this dose has been used for as long as 24 months (Section 1.2.5). Further, all successful longer-term trials have used commercially available beverages; the lone trial to use a grain alcohol-based test of pure ethanol demonstrated poor adherence in only six months.

Although maximal caps on drinking in national guidelines differ substantially, the NIAAA currently recommends limits of 14 drinks per week for men under 65, but only 7 drinks per week for women and for men aged 65 years and older. As a result, a dose of ~15 g daily (in the absence of contraindications) would be viewed as within recommended limits by both NIAAA and virtually all national bodies worldwide.

1.3.3. RATIONALE FOR TRIAL POPULATION

Although epidemiologic evidence generally suggests that alcohol consumption tends to be associated with lower risk of coronary heart disease across a wide variety of populations, ethical, practical, and clinical considerations suggest that this hypothesis is most efficiently studied in high-risk individuals. From a practical standpoint, a high-risk population with a high background rate of events requires a smaller potential sample size, minimizing the number of participants needed to recruit and follow. This population also tends to have more extensive contact with health care systems, improving recruitment, and may have a particularly vested interest in cardiovascular prevention strategies, which may enhance adherence. Ethically, a high-risk population minimizes the number of participants placed at risk in a randomized trial, and with declines in problem drinking behavior with older age, tends to reduce potential harms from alcohol while maximizing potential benefits. From a clinical and public health perspective, this population is also the most likely to benefit if the primary or secondary hypotheses of MACH15 are confirmed, for these high-risk individuals stand to benefit the most from any given decrease in relative risk and would therefore have the most favorable risk-benefit ratio for alcohol consumption. Concordantly, results in a global, diverse, high-risk population are apt to be generalizable to a wide variety of lower-risk populations in terms of relative risk reduction, even if any absolute risk reduction is necessarily smaller.

1.4   POTENTIAL RISKS AND BENEFITS

1.4.1   KNOWN POTENTIAL RISKS

Although alcohol consumption has not been tested in any long-term randomized trial, and short-term trials of its use within recommended limits have rarely demonstrated any clear signals of harm, it nonetheless may have potential risks based upon findings from studies reviewed above. Possible risks

of daily moderate alcohol consumption are presented with qualitative estimates of their likelihood below.[101]

More Common:
- Alcohol is an addictive substance, although the likelihood for any individual differs substantially based upon a host of environmental and personal characteristics. The likelihood of going on to problem drinking among middle-aged and older adults who currently drink within recommended limits is unknown.
- Alcohol is sedating, even with recommended limits, and may interfere with the ability to drive or operate dangerous or delicate machinery, including cars, boats, and other vehicles.
- Alcohol may impair sleep quality.
- Alcohol may acutely impair balance and lead to falls.
- In those with genetic differences in alcohol metabolism, alcohol can cause severe flushing. This can also occur if alcohol is taken with metronidazole.
- Alcohol can increase the sedative effects of any medication that causes drowsiness, including drugs for anxiety and depression.
- In people with chronic liver disease such as hepatitis B or C, moderate alcohol use can cause liver damage. This is not known to occur among people with otherwise normal liver function.

Less Common:
- Each alcoholic beverage contains 100-150 calories and may increase risk of weight gain; this appears to be more so among men than women.
- Alcohol consumption may increase or decrease blood pressure following its consumption.
- Alcohol consumption may trigger atrial arrhythmias.

Rare:
- In observational studies one drink per day has been associated with an increased risk of breast cancer of approximately 10% and has also been associated with higher risk of oropharyngeal and esophageal malignancies, particularly in smokers.

1.4.2 KNOWN POTENTIAL BENEFITS

There are no definitively recognized benefits of alcohol consumption on any specific health condition. It is widely used in social situations and considered an essential part of specific rites and rituals and has established biochemical effects that include increased HDL-C, lower fibrinogen, and increased adiponectin. The potential benefits of moderate alcohol consumption on risk of CVD and diabetes based upon findings from observational studies reviewed above will be tested in this trial.

2   OBJECTIVES AND PURPOSE

The primary objective of the MACH15 Trial is to determine the effects of one U.S. serving of alcohol (~15 g) daily compared to no alcohol intake on the risk of incident cardiovascular disease among adults at above-average cardiovascular risk over an average of 6 years of follow-up.

The secondary objective of this trial is to determine the effects of one serving of alcohol (~15 g) daily compared with no alcohol intake on the risk of incident diabetes among participants free of diabetes at baseline.

The primary trial outcome is time from baseline to a composite endpoint comprised of the first occurrence of a non-fatal myocardial infarction, non-fatal ischemic stroke, hospitalization for angina, coronary/carotid revascularization, or all-cause mortality.

The secondary trial outcome is progression among normoglycemic and pre-diabetic individuals to American Diabetes Association (ADA)-defined diabetes.

3 TRIAL DESIGN AND CLINICAL OUTCOME MEASURES

3.1 TRIAL DESIGN DESCRIPTION

The Moderate Alcohol and Cardiovascular Health Trial (MACH15) is an international, balanced-design randomized trial, comparing the effects of one standard serving (~15 grams) of alcohol intake daily to abstention.

The trial cohort will include approximately 7800 people aged ≥ 50 years in two high-risk groups:
- Patients with stable clinical cardiovascular disease (CVD)
- Individuals whose estimated 10-year risk of CVD events equals or exceeds 15%

The eligibility criteria are described in *Chapter 4: Participant Enrollment*.

Recruitment will occur in an initial vanguard phase at 7 clinical sites, followed by the addition of approximately 9 additional clinical sites. Participants will be recruited over a 3-year period and will be followed for approximately 4.5-7.5 years with a common close-out date. Recruitment procedures are described in *Chapter 4: Participant Enrollment* and follow-up procedures in *Chapter 6: Trial Procedures and Schedule*.

Participants will be stratified by clinical site and randomly assigned to either one standard serving (~15 g) of alcohol daily or abstention for an average of 6 years following a two-week wash-out period as described in *Chapter 5: Intervention*.

The sample size for MACH15 was established to provide 80% power to detect an 18% relative decrease in the rate of the composite primary outcome in participants randomized to the alcohol arm compared with the abstention arm. *Chapter 8: Statistical Considerations* reviews sample size calculations and related considerations.

3.2. PRIMARY HYPOTHESIS

Does one standard serving (~15 g) of alcohol consumption daily reduce the rate of CVD or mortality compared to abstention from alcohol?

This hypothesis will be tested using a primary outcome of time from baseline to a composite endpoint comprised of the first occurrence during follow-up of a non-fatal myocardial infarction, non-fatal ischemic stroke, hospitalization for angina, coronary/carotid revascularization, or all-cause mortality. The anticipated event rate for this outcome is 2.6%/year.

3.3 SUBGROUP HYPOTHESES

Are the effects of one standard serving (~15 g) of alcohol daily on the primary outcome compared with abstention from alcohol consistent across subgroups defined by age, HDL-C, sex, baseline CVD risk, geographic region, and prevalent diabetes at enrollment?

Subgroup analyses for secondary outcomes are described in *Chapter 8: Statistical Considerations*.

3.4   SECONDARY AND TERTIARY HYPOTHESES

MACH15 pre-specifies secondary and tertiary hypotheses. Secondary hypotheses address the secondary objective of the trial, the outcome of diabetes, and a restricted outcome designed to support and confirm the primary analysis. Tertiary hypotheses address the individual components of the primary trial endpoint and a second restricted outcome and the development of impaired fasting glucose among individuals with normal glucose status at baseline.

3.4.1. SECONDARY HYPOTHESES

- Among participants free of diabetes at enrollment, does one standard serving (~15 g) of alcohol daily reduce the rate of incident diabetes compared to abstention from alcohol?

This hypothesis will be tested using a secondary outcome of progression among normoglycemic and pre-diabetic individuals to American Diabetes Association (ADA)-defined diabetes. The anticipated event rate for this outcome is 1.7%/year.

- Does one standard serving (~15 g) of alcohol consumption daily reduce the rate of CVD or cardiovascular mortality compared to abstention from alcohol?

This hypothesis will be tested using a secondary outcome of time from baseline to a composite endpoint comprised of the first occurrence during follow-up of a non-fatal myocardial infarction, non-fatal ischemic stroke, hospitalization for angina, coronary/carotid revascularization, or cardiovascular mortality.

3.4.2. TERTIARY HYPOTHESES

- Among participants free of pre-diabetes or diabetes at enrollment, does one standard serving (~15 g) of alcohol daily reduce the rate of pre-diabetes compared to abstention from alcohol?

This hypothesis will be tested using a tertiary outcome of progression among normoglycemic individuals to ADA-defined prediabetes.

- Does one standard serving (~15 g) of alcohol consumption daily reduce the rate of hard CVD or cardiovascular mortality compared to abstention from alcohol?

This hypothesis will be tested using a tertiary outcome of time from baseline to a composite endpoint comprised of the first occurrence during follow-up of a non-fatal myocardial infarction, non-fatal ischemic stroke, or cardiovascular death.

- Does one standard serving (~15 g) of alcohol consumption daily reduce the rate of individual cardiovascular events or mortality compared to abstention from alcohol?

This hypothesis will be tested using tertiary outcomes of time from baseline to individual endpoints comprised of the first occurrences during follow-up of myocardial infarction, ischemic stroke, hospitalization for angina, coronary/carotid revascularization, all-cause mortality, and cardiovascular mortality.

3.5   CLINICAL OUTCOME MEASURES

In the MACH15 Trial, the clinical outcome events occurring during follow-up will be ascertained in both arms every three months during follow-up contacts with participants (either phone calls or in-person clinic visits), by masked or unmasked assessors using a structured interview to minimize ascertainment bias. Clinical outcome events will be initially identified through self-reports and laboratory measures. This will be followed by the collection of medical records (hospitalization admission and history, laboratory results, and/or electrocardiogram [ECG] imaging) by unmasked clinical site staff and then reviewed and adjudicated at the clinical site by a masked Medical Safety Officer (MSO). Adjudicators (MSOs) will use their clinical judgment based on the available evidence to classify each case and will be guided by pre-specified definitions and operational rules. In addition, a subset of outcome events will be validated with central adjudication.

MACH15 has based criteria, definitions for outcomes, and operational rules on those used by others studies, such as SPRINT and the LIFE Study and updated them based on scientific publications referenced in each section.

3.5.1 TRIAL OUTCOMES

The primary, secondary, and tertiary outcomes are as follows:

Primary:
Time from baseline to a composite endpoint comprised of the first occurrence of a non-fatal myocardial infarction, non-fatal ischemic stroke, hospitalization for angina, coronary/carotid revascularization, or all-cause mortality.

Secondary:
1.   Time from baseline to a composite endpoint comprised of the first occurrence of a non-fatal myocardial infarction, non-fatal ischemic stroke, hospitalization for angina, coronary/carotid revascularization, or cardiovascular death.
2.   Progression among normoglycemic and pre-diabetes individuals to American Diabetes Association (ADA)-defined diabetes.[1]

Tertiary:
1.   Time from baseline to a composite endpoint comprised of the first occurrence of a non-fatal myocardial infarction, non-fatal ischemic stroke, or cardiovascular death.
2.   Time from baseline to the first occurrence of each of the components of primary outcome (5 outcomes).
3.   Time from baseline to cardiovascular death.
4.   Progression among normoglycemic individuals to ADA-defined prediabetes.[1]

3.5.2 OUTCOMES DEFINITIONS

Myocardial Infarction (MI): Defined as the death of part of the myocardium due to an occlusion of a coronary artery from any cause, including spasm, embolus, thrombus or rupture of a plaque. MACH15 will use standard case definitions for both fatal and nonfatal MI based on the combination of symptoms, elevation in biomarkers, and/or ECG findings. The algorithm for classifying MI includes elements of the clinical presentation (signs and symptoms), results of cardiac biomarker determinations, and ECG readings, and is based on the 2003 American Heart Association Position Statement "Case Definitions for Acute Coronary Heart Disease in Epidemiology and Clinical Research Studies"[2] and consideration of the 2012 "Third Universal Definition of Myocardial Infarction".[3] MACH15 adjudicators will be guided by specific, pre-specified definitions and operational rules. Adjudicators will use their clinical interpretation of the ECGs and other available evidence for the event to classify the MI.[2]

Stroke: MACH15 will use standard case definitions for both fatal and nonfatal stroke. Stroke will be defined based on all available data, including symptoms and signs, imaging of the brain and large vessels, and cardiac testing, e.g., echocardiography. Based on "An Updated Definition of Stroke for the 21st Century" AHA/ASA Expert Consensus Document,[4] central nervous system (CNS) infarction will be defined as A) pathological, imaging, or other objective evidence of CNS injury in a defined vascular distribution; or B) clinical evidence of CNS injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded. Exclusionary conditions for stroke include major brain trauma, intracranial neoplasm, coma due to metabolic disorders or disorders of fluid or electrolyte balance, peripheral neuropathy, or central nervous system infections. In cases where there is enough documentation, stroke will be classified by subtype.

Hospitalization for angina (or non-MI acute coronary syndrome) is defined as overnight hospitalization for symptoms, such as chest pain, chest tightness, or shortness of breath, produced by myocardial ischemia that do not result in myocardial infarction, but are treated medically or surgically during an overnight stay. The symptoms generally last less than 20 minutes, and may have occurred prior to the admission. This definition also includes hospitalizations for the diagnosis of angina/symptomatic coronary artery disease from a physician based on history and a positive diagnostic test (angiography, exercise stress testing, perfusion scan or stress echocardiogram).

Coronary/carotid revascularization: Revascularization is confirmed when participants undergo urgent or elective coronary bypass grafting, angioplasty, endarterectomy, thrombectomy, or any similar procedure intended primarily to ameliorate coronary/carotid artery stenosies.

Death attributable to cardiovascular disease (CVD): death attributable to CVD events, defined as those that comprise the MACH15 primary outcome (specifically MI, ischemic stroke, hospitalized angina, and coronary/carotid revascularization), and based on temporal relationship considering event medical records (e.g., hospitalization for MI or stroke), or postmortem findings related to an acute CVD event.

Other: In addition to the above, MACH15 will assess additional diabetes related outcomes:
- Progression among normoglycemic and pre-diabetes individuals to ADA-defined diabetes;
- Progression among normoglycemic individuals to ADA-defined prediabetes.

Both these ADA-defined outcomes will be confirmed by two measurements of either HbA1c or fasting plasma glucose obtained at the annual clinic visits or based on documented use of medication treated diabetes starting between in-person clinic visits.

4   PARTICIPANT ENROLLMENT

4.1   INCLUSION/EXCLUSION OVERVIEW

The objective of identifying formal inclusion/exclusion criteria is to enroll a trial population that will ensure adequate event rates for statistical power, promote generalizability, and maximize safety. Inclusion/exclusion criteria have been made as simple as possible to ensure standard implementation across all clinical sites. Specifically, the eligibility criteria have been developed to facilitate the identification and inclusion of a trial population that will adhere to the trial protocol and are at above average risk for cardiovascular disease.

Implementation of these inclusion/exclusion criteria and related recruitment strategies will be accomplished to meet several goals with respect to the composition of the trial population. The overall goal for recruitment is approximately 7,800 participants to include ~50% women and demographic characteristics representative of the community surrounding each of the MACH15 clinical sites. In recruitment, there is an implicit hierarchy based on trial hypotheses and design considerations: first, attain the overall sample size for sufficient power to test the main hypothesis of trial; and second, ensure a sufficiently diverse trial population so that results are broadly applicable. Recruitment of a cohort of participants that are committed to helping answer the scientific question by adherence to their protocol assigned treatment is essential as non-adherent participants, drop-outs and suspected losses to follow-up will not be replaced with newly recruited participants.

These goals will be monitored on an ongoing basis and the Recruitment and Retention Subcommittee (R&R) and the Steering Committee will evaluate recruitment strategies and implement corrective actions as needed (see Manual of Procedures [MOP] for specific strategies and actions).

4.2   PARTICIPANT INCLUSION CRITERIA

To be eligible for the MACH15 Trial an individual must meet all of the following criteria:

1. Age ≥50 years at screening

2. Postmenopausal, defined as 12 consecutive months without menstruation

3. Not alcohol naïve, defined by having consumed at least one drink of alcohol in the past five years

4. High risk for the occurrence of a new cardiovascular disease event, defined as having any one of the following:
    a) American Heart Association (AHA)/American College of Cardiology (ACC) Risk Score ≥15% within the past 24 months (among those without clinical or subclinical cardiovascular disease [CVD])
    b) Clinical CVD (more than 6 months prior to randomization), defined by:
        1) Previous myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), carotid endarterectomy (CE), carotid stenting;
        2) Peripheral artery disease (PAD) with revascularization;

3) Acute coronary syndrome with or without resting electrocardiogram (ECG) change, ECG changes on a graded exercise test (GXT), or positive cardiac imaging study;
4) Prior stroke documented on brain imaging or with a persistent deficit.
c) Subclinical CVD, confirmed in available medical records:
1) At least a 50% diameter stenosis of a coronary, carotid, or lower extremity artery;
2) Coronary artery calcium score ≥400 Agatston units;
3) Ankle brachial index (ABI) ≤0.90;
4) Left ventricular hypertrophy (LVH) by ECG (based on computer reading), echocardiogram report, or other cardiac imaging procedure report;
5) Abdominal aortic aneurysm (AAA) ≥5 cm with or without repair.
d) Age ≥75 years

Note that eligible individuals residing in the same household can participate if they agree to be randomized as a unit to the same intervention at the same randomization time.

4.3   PARTICIPANT EXCLUSION CRITERIA

An individual who has any of the following criteria will be excluded from participation in MACH15 (see MOP for further detail regarding criteria and/or assessment tools):

1. High alcohol consumption, defined by any one of the following:
   a) Alcohol Use Disorders Identification Test (AUDIT) score >5 at screening
   b) Drinking, on average, >7 alcoholic beverages/week during the past 6 months
   c) Drinking 6 or more alcoholic beverages on one occasion during the past 6 months.

2. Yale-Brown Obsessive Compulsive Scale-heavy drinking (Y-BOCS-hd) total score of ≥6 on questions 7, 8, and 10

3. Within the 6 months prior to randomization, cardiovascular disease event (MI, revascularization procedure, or stroke)

4. AHA Class III-IV heart failure

5. History of alcohol or substance abuse (medical record confirmed or self-reported history)

6. Other intolerance or allergy to alcohol

7. Dual antiplatelet therapy

8. History of gastric bypass surgery

9. Any serious chronic liver disease (e.g., active hepatitis B and C infections) or liver tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT] and gamma-glutamyl transpeptidase [GGT]) >2 times the upper limit of the normal range using local standards

10. Personal history of any colon or liver cancer

11. Any other cancer with a life expectancy of less than 3 years

12. Diagnosed with breast cancer that required either surgery or removal of breast tissue or chemotherapy

13. Mother or sister ever diagnosed with breast cancer that required either surgery or removal of breast tissue or chemotherapy

14. Estimated glomerular filtration rate (eGFR) <30 ml/min /1.73m^2 or end-stage renal disease (ESRD)

15. Ongoing use of any medication for which alcohol consumption is contraindicated

16. A Patient Health Questionnaire (PHQ-9) ≥15 at screening or a positive response on question 9 dealing with suicide ideation

17. History of any organ transplant

18. Unintentional weight loss >10% in last 6 months

19. Currently participating in another clinical trial (intervention trial) with CVD outcomes. Note: Participant must wait until the completion of his/her activities or the completion of the other trial before being screened for MACH15. Local restrictions for entry by participants can be more conservative if mandated.

20. Not willing or able to provide a name and contact information for at least one additional contact person other than self

21. Diagnosis of dementia

22. Investigator discretion regarding appropriateness of participation or concern about intervention adherence, examples include: moderate – severe psychiatric illness, behavioral concerns regarding likelihood of low adherence to trial protocol, a medical condition likely to limit survival to less than 3 years, or an advanced chronic disease, such as cognitive impairment without a dementia diagnosis or any condition that requires 24-hour care.

23. Not willing or able to provide a signed and dated informed consent form

24. Unable to successfully complete the washout period

25. Not willing or able to comply with all trial procedures

4.4   STRATEGIES FOR RECRUITMENT

4.4.1   RECRUITMENT OVERVIEW

The recruitment goal of MACH15 is to enroll approximately 7,800 participants, approximately 500 at each of the 16-20 clinical sites around the globe, who have an above-average cardiovascular risk.

Participants will be recruited over a 3-year period and followed for an average of 6 years. Due to the international nature of the trial, clinic-specific minority enrollment targets will be determined.

All recruitment related activities will be overseen by the Recruitment & Retention (R&R) Subcommittee. To accommodate the variability across global regions in catchment area characteristics, media market outlets, and access to eligible participants, each clinical site will develop and submit to R&R a clinical site-specific recruitment plan. All recruitment materials will be reviewed and approved by the appropriate clinical site Institutional Review Board/Ethics Committee (IRB/EC) before being used.

The R&R Subcommittee will play a significant role in monitoring the progress of trial-wide recruitment and provide a forum for advising clinical sites on problem identification, goal-setting, strategy deployment and evaluation in their efforts to achieve site and trial-wide recruitment goals. In addition, the R&R Subcommittee will collate and evaluate recruitment strategies during the vanguard phase and advise all clinical sites on their effectiveness to maximize trial-wide recruitment.

4.4.2   RECRUITMENT ACTIVITIES

A multifaceted approach to screening and enrollment is essential to achieve the recruitment goal. For this global multicenter trial, recruitment strategies targeting both existing populations within the clinical practice of the clinical sites as well as individuals from outside these practice settings will be used to identify potentially eligible participants.

Recruitment for the trial will utilize specific community resources to promote recruitment of women and minority/under-served populations to ensure adequate representation of groups residing in the communities surrounding the clinical sites. Recruitment strategies that have worked well in other trials related to cardiovascular disease[1,2] will be employed. Sites may focus on:
1) Recruitment from within a general practice or other medical practice or health system–based setting; and/or
2) Community-based recruitment.

4.4.3   RECRUITMENT IN EXISTING POPULATIONS IN CLINICAL SITES EMBEDDED WITHIN MEDICAL PRACTICES/HEALTH SYSTEMS

Methods for identifying potentially eligible participants within the clinical practice or the research clinic settings may include: a targeted review of medical records or databases for those meeting the trial's inclusion criteria, referrals from providers/employees within the practice, and/or from practice participants themselves. Additional approaches may also include written materials developed centrally and/or locally such as direct mailing and/or availability of trial brochures and posters in the medical offices. Locally developed materials are encouraged in collaboration with the local IRB/EC and the Coordinating Centers (see MOP).

4.4.4   SCREENING

To minimize in-person screening visits by ineligible volunteers, persons demonstrating interest in the trial may complete a phone or on-line pre-screening as allowed by the local IRB/EC. Potential trial

participants may also attend a pre-screening visit for the same purpose. Potential participants must attend the Screening Visit to complete all necessary screening assessments (see *Chapter 6: Trial Procedures and Schedules*). According to local IRB/EC regulations, informed consent will be obtained for screening and possible trial participation as well as data sharing, potential genetic studies, and sample storage. No data will be collected prior to informed consent.

4.4.5 RE-SCREENING OF PARTICIPANTS PREVIOUSLY NOT MEETING INCLUSION/ EXCLUSION CRITERIA

Under certain circumstances participants that failed to meet certain eligibility criteria or met certain exclusion criteria initially (temporarily on dual antiplatelet therapy, CVD event less than 6 months, etc.) may be re-screened (see MOP for process).

4.4.6 RECRUITMENT EVALUATION PLAN

Using the recruitment database, each clinical site will track all relevant screening inclusion/exclusion data to enable the comparative evaluation of site-specific recruitment strategies, to monitor recruitment progress trial-wide, and to adapt strategies for recruitment where indicated. The primary measure of "success" will be the number of participants effectively enrolled at each clinical site.

4.5 PARTICIPANT WITHDRAWAL

Participants may withdraw informed consent at any time during the trial, personally or through their designated representative.

The clinical site Principal Investigator must document the reason for withdrawal of any participant from trial participation (see MOP for documentation tool).

4.6 PERMISSION TO EXTEND TRIAL FOLLOW-UP

As part of the initial informed consent, participants will be asked to consent for future contact according to national regulatory requirements.

5   INTERVENTION

5.1   INTERVENTION DESCRIPTION

The MACH15 Trial will include two intervention arms: one will assign participants to consume a moderate daily amount of alcohol defined as ~15 g (a standard U.S. serving) and the other will assign participants to abstain from alcohol. Because standard units of alcohol vary between countries, to ensure uniformity, clinical sites will convert ~15 g of alcohol to the standard unit for their localities. This comparison represents a clinical scenario in which a moderate amount of alcohol is 'recommended' by a clinician for potential health benefits. The intervention will average 6 years in duration, with a common participant close-out date. Although the beverage choice of participants will be actively and repeatedly monitored, participants in the alcohol arm can choose to consume beer, wine, or spirits. There is no clear evidence that any one beverage is preferable, and this approach both mimics usual drinking patterns and offers the greatest opportunity for long-term adherence.

The intensity of intervention will be similar in both arms of the trial, except for the assignment to consume or not consume alcoholic beverages. Promotion of adherence will be an important goal throughout the trial. Continuous feedback and discussions of challenges and solutions will take place between clinical site staff (e.g., health coach, dieticians), coordinators and participants. Adherence assessments will be performed during in-person visits, phone visits, and via individualized automated participant contacts (e.g., smart phone application, email, text messages) at varying frequencies throughout the trial (see Section 5.4.2). Participants in the alcohol arm will receive adherence counseling if they fall below 85% adherence (more than 4 non-adherent days per month) while those in the abstention arm will receive counseling if they fall below 100% adherence.

5.2   INTERVENTION DELIVERY PLAN

Due to the regulatory differences in alcohol sales between states, countries, and regions, clinical sites will have flexibility in terms of providing reimbursement for or distribution of alcohol. The clinical sites will propose various models for facilitating participants' receipt of a monthly (or other period) supply of alcohol and the degree of success for each model will be reported to and monitored by the Intervention Subcommittee. Alcohol dispensing to participants will be adjusted as needed to facilitate best adherence and, based on experience with successful models, shared among the clinical sites. The reimbursement for or distribution of alcohol will be directly tied to the participant's adherence to the protocol and responsiveness to regular contacts, which will provide additional protection from escalation in use. A more detailed description of the options for distribution of or reimbursement for alcohol will be provided in the Manual of Procedures (MOP).

Because most participants will incur increased costs if asked to drink daily, a compensation limit has been set equal to the monthly cost of the most commonly consumed alcoholic beverage in the region, depending upon prevailing policies and regulations at the clinical sites. The amount of the reimbursement will not be so large as to influence informed consent. Sites will have discretion regarding

whether to provide remuneration, reimbursement for or provision of nonalcoholic beverages for the abstention arm.

5.2.1 ALCOHOL ARM

Participants in the alcohol arm will consume one U.S. serving (~15 g) of wine, beer or spirits daily for approximately 6 years. They will be asked to consume alcohol only after activities that require dexterity and alertness are completed for the day (i.e., at night) and will be advised to consume alcohol as part of a healthy diet.

5.2.2 ABSTENTION ARM

Participants in the abstention arm will abstain from drinking alcohol for approximately 6 years. Complete abstention is recommended to ensure sharp contrast between the two trial arms; however, a modest degree of tolerance towards alcohol consumption in the abstention arm will be allowed. Participants may consume a limited number of alcoholic beverages at their discretion on special occasions. This will be monitored by site staff to ensure that adherence to the protocol is not compromised.

5.3 DIET AND LIFESTYLE FACTORS

Healthy dietary habits and lifestyle will be recommended to all participants for the duration of the trial, independently of the arm to which they are randomized. All participants will be given general advice and will be encouraged to follow a healthy diet, tailored to local recommendations.

5.4 INTERVENTION ADHERENCE

Adherence to the intervention regimens is necessary to the success of MACH15. All participants will be well-informed prior to entering the trial about the importance of adhering to their assigned intervention and that adherence will be routinely monitored.

5.4.1 RUN-IN (OPTIONAL)/WASHOUT PERIOD

Prior to randomization, individuals meeting all eligibility criteria will complete a two-week period during which they are to abstain from drinking alcohol. This will assist prospective participants with understanding their ability and willingness to comply with lifestyle changes regarding alcohol consumption. This also provides a brief washout period prior to baseline biospecimen collection.

Some clinical sites may choose to institute a run-in period prior to the washout during which prospective participants are to consume 1 drink (~15 g) of alcohol daily for 7 to 14 days.

Participants who successfully complete the two-week abstinence period (with or without an earlier optional run-in period of daily alcohol use) will be scheduled for their baseline randomization visit.

5.4.2 ADHERENCE MEASURES

Adherence to the intervention will be measured throughout the trial using a system of automated and in-person subjective and objective data collection tools. Participants will complete adherence assessments during each in-person visit at baseline, 3 months, 6 months, 12 months, and then annually until the trial ends. Collection of biological samples to monitor adherence will also occur during in-person clinic visits. Adherence assessments will also be completed during quarterly phone calls from clinical site staff.

In-person clinic visits will be supplemented by random, individualized automated participant contact via smart phone applications, email and/or text messages which will assess the number and types of drinks consumed in the prior 24 hours. Where automated, electronic contact is not feasible, brief phone calls from clinic staff to assess adherence will be performed. Participants will be periodically assessed for adherence via electronic means or phone calls at least 7 to 10 times every three months. Contact will be tailored to the participant's intervention arm and adherence profile, with greater intensity early in the trial, adjusting in frequency as needed based on individual compliance and responsiveness to contact.

5.4.2.1 OBJECTIVE BIOMARKERS OF ADHERENCE

Group adherence to the intervention will be assessed using High Density Lipoprotein Cholesterol (HDL-C) as an indirect biological marker. Additional more recently developed direct, objective biomarkers of adherence, especially urine biomarkers and hair samples may be used in all or a random sample of participants (see MOP for additional detail).

5.4.2.2 DATA COLLECTION INSTRUMENT

Contacts with clinical site staff may involve data collection on adherence to the intervention using the Timeline Followback (7 day) recall form and Yale-Brown Obsessive Compulsive Scale-heavy drinking (Y-BOCS-hd).

The Timeline Followback recall form asks participants to report the number of alcoholic drinks consumed each day in the previous 7-day period. The Y-BOCS-hd tracks changes in alcohol craving over time and will assist clinic staff in identifying participants at risk for developing problem drinking.

5.4.2.3 INDIVIDUALIZED AUTOMATED PARTICIPANT CONTACT

Beginning at the initiation of the pre-randomization washout period and continuing throughout follow-up, participants will receive brief electronic communications to assess and/or promote adherence. These automated contacts will occur at least 7 to 10 days each quarter and prompt participants to provide information on the amount and type of alcohol that was consumed in the prior 24 hours. Given the varied levels of familiarity and comfort with electronic communication, participants will choose their preferred method of communication (smart phone application, email or text message) and may change their communication format anytime during the trial. Clinical site staff will carefully monitor this system and, if the automated contact attempts are left unanswered or if adherence declines, they will initiate follow-up with an off-schedule phone call, as shown in Figure 5.1.

Methodology to detect non-adherent or unresponsive participants and subsequent steps.
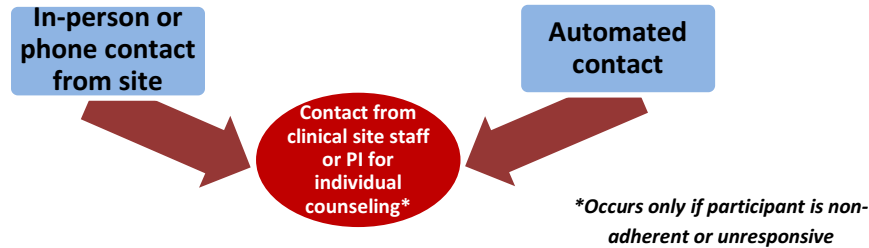
5.4.3 INDIVIDUAL ADHERENCE COUNSELING

Specific steps to improve adherence will be established and explained in the MOP. Adherence problems may be identified by the participant via: 1) self-report; 2) comments about lack of adherence; or 3) stating he/she does not want to continue in the trial.

Participants with less than 85% adherence in the alcohol arm or 100% adherence in the abstention arm or that drink excessively will receive adherence counseling by clinic staff using individualized motivational interviewing techniques (see Table 5.1). Such counseling will occur during each in-person clinic visit and phone visit and as needed based on responses to the adherence assessment measures. The participant will receive personalized advice directed to achieve ideal adherence to the protocol.

TABLE 5.1: TRIGGERS FOR ADHERENCE COUNSELING

Intervention Arm	Women	Men	Action
Daily Alcohol Low adherence (<85%)	No alcohol >1 day in 7 days of contact OR consumption of >1 alcoholic beverage >1 day in 7 days of contact	No alcohol >1 day in 7 days of contact OR consumption of >1 alcoholic beverage >1 day in 7 days of contact	Adherence counseling
Excessive alcohol consumption	>10 drinks in 7 days of contact	>14 drinks in 7 in days of contact	Intensive alcohol counseling
Abstention Low adherence (<100%)	Any alcohol consumption beyond or not in accordance with vouchers	Any alcohol consumption beyond or not in accordance with vouchers	Adherence counseling
Excessive alcohol consumption	>10 drinks in 7 days of contact	>14 drinks in 7 days of contact	Intensive alcohol counseling

The baseline visit will include formal counseling and motivational interviewing methods that have been used successfully in other clinical trials. They will be administered by a health coach, dietician, or similar

professional trained during trial start-up and periodically refreshed via training during the trial. At each subsequent in-person clinic visit and phone visit, key concepts in maintaining adherence to the assigned intervention arm will be reiterated.[1-5]

To maximize adherence, participants will be encouraged to bring spouses or significant others to clinic visits. This approach is explicitly recommended by www.clinicaltrials.gov and encourages spouses to act as trial partners, an approach that has been used in trials of other psychosocially-active interventions with some success.[6]

Additionally, clinical sites may provide health-related information and quarterly newsletters developed locally or centrally to reinforce the importance and value of each participant's role in the success of MACH15.

The Intervention & Adherence Subcommittee will collate and evaluate strategies to promote adherence to both study arms during the vanguard phase and will advise all clinical sites on their effectiveness to maximize trial-wide adherence during the subsequent study period.

6 TRIAL PROCEDURES AND SCHEDULE

6.1 TRIAL PROCEDURES/EVALUATIONS OVERVIEW

The data collection schedule for in-person clinic visits and phone visits in the MACH15 Trial is outlined in Table 6.1. Participant contacts include a prescreening phone call (optional) and an in-person screening visit aimed at determining eligibility for the trial. If eligible, participants will enter a run-in period (optional) and a 2-week washout period where they will be instructed to adhere to abstinence of alcohol. At the end of the washout period, participants will return to the clinic to complete the baseline trial assessments, randomization, and education regarding treatment assignment. Some clinical sites may choose to do the randomization and education on a separate day from the baseline assessments. In-person clinic visits will then occur at 3, 6, and 12 months, and every 12 months thereafter until close-out. Data may be collected over more than one day per participant preference. Phone calls for adherence counseling and ascertainment of safety and outcomes information will occur at 2 weeks, 4 weeks, 9 months, and every 3 months thereafter, except when the quarterly call falls at an annual in-person visit. Participants will have additional automated contacts (phone, email, text) related to adherence, described in *Chapter 5: Intervention*.

TABLE 6.1: MEASURES AND FREQUENCY

Contact Timeline:	Screening	Run-in (optional)/ Washout	Baseline/ Randomi-zation[1]	2 & 4 weeks	3 & 6 months	9 months	12 months & Q12mos after	15 months & Q3mos after[2]	90 months or Closeout
Contact Mode:	Visit	Call	Visit	Call	Visit	Call	Visit	Call	Visit
Measures									
Informed consent[3]	X		X						
Contact information	X				X		X		X
Seated blood pressure and pulse	X		X		X		X		X
Weight			X				X		X
Waist circumference			X				X		X
Height			X						
Concomitant medications	X		X				X		X
Medical history	X								
Sociodemographics			X				X		X
Serious Adverse Events and MACH15 AEs		X	X	X	X	X	X	X	X
CVD outcomes					X	X	X	X	X
Lab-phlebotomy and processing	X		X		X		X		X
Genomic material			X						

Fasting glucose/ hemoglobin A1c	X[4,5]		X[6]				X[6]		X[6]
AST/ALT/GGT	X		X		X		X		X
Creatinine	X								
HDL-C	X[4]		X		X		X		X
Total cholesterol	X[4]		X[7]						
Triglyceride/LDL-C			X						
Blood storage			X				X[8]		X[8]
Urine storage			X				X[8]		X[8]
Hair clippings			X[8]				X[8]		X[8]
Alcohol use questionnaires									
AUDIT	X								
Timeline Followback (7-day)	X			X	X	X	X[9]	X	X[9]
Y-BOCS-hd (3 items)	X				X		X		X
Other questionnaires									
Smoking History			X						
Fagerstrom Test of Nicotine Dependence			X				X		X
EQ-5D-5L			X				X		X
PHQ-9	X						X		X
Food Frequency Questionnaire			X[10]				X[10]		X[10]
Physical Activity Measure			X[10]				X[10]		X[10]
Verify eligibility			X						
Health Coaching									
Counseling on run-in (optional)/washout	X	X							
Behavioral assessment and counseling for intervention and adherence		X	X	X	X	X	X	X	

Abbreviations: mos = months; Q = every; CVD = cardiovascular disease; AST = aspartate aminotransferase; ALT = alanine transaminase; GGT = gamma-glutamyl transferase; HDL = high density lipoprotein; LDL = low density lipoprotein; AUDIT = Alcohol Use Disorders Identification Test; Y-BOCS-hd = Yale-Brown Obsessive Compulsive Scale-heavy drinking; PHQ-9 = Patient Health Questionnaire-9.

[1] Randomization and counseling for adherence may be done on same or different visit from Baseline Visit per site preference.

[2] Quarterly phone calls except when quarterly calls coincide with an annual in-person visit.

[3] Separate informed consents may be obtained for collection and storage of samples to be used for genomic analyses and to collect alternate contact information where required by local regulations.

[4] If the participant has had these labs within 24 months, historical values may be used.

[5] Either fasting glucose or HbA1c (non-fasting) may be used at screening to help determine prevalent diabetes for the purpose of cardiovascular risk score.

[6] To assess for incident diabetes, participants may have fasting glucose and/or HbA1c (fasting not required) drawn annually per clinic preference. If the value is above the ADA-defined cutoff for pre-diabetes, the participant will be asked to return to the clinic for a second blood draw to confirm the diagnosis. (Participants with known diabetes or that have been started on diabetes medication during the trial need not have a second blood draw.)

[7] Does not need to be repeated if completed at screening.

[8] Optional annual collection per clinical site preference.

[9] If participants report 100% adherence during the previous quarter, the Timeline Followback is not required at the annual visit.

[10] Optional on-line questionnaires.

6.1.1   TRIAL SPECIFIC PROCEDURES

Inclusion and exclusion criteria are described in *Chapter 4: Participant Enrollment*. Additional trial specific procedures are described below and in the Manual of Procedures (MOP).

6.1.1.1   ANTHROPOMETRIC MEASURES

Anthropometric measures will be assessed using standardized methods at the baseline visit. Weight and waist circumference will be measured at each annual visit thereafter.

6.1.1.2   ALCOHOL USE MEASURES

The *Alcohol Use Disorders Identification Test* (*AUDIT*) is a 10-item questionnaire developed by the World Health Organization to assess alcohol consumption, drinking behaviors, and alcohol-related problems. It will be administered at the screening visit to identify and exclude participants with hazardous and harmful drinking habits or who may be alcohol dependent. Individuals who score above 5 on the AUDIT will be excluded from participation in the trial; this is conservative, below the recommended thresholds of 7-8.

Questions from the *Yale-Brown Obsessive Compulsive Scale-heavy drinking* (*Y-BOCS-hd;* questions 7, 8, 10) will be administered at the screening visit, 3 month visit, 6 month visit, and annual visits thereafter to track changes in alcohol craving over time and to identify participants who may have developed problem drinking. Individuals who score is ≥6 at the screening visit, indicating moderate to severe cravings, will be excluded from participation in the trial.

6.1.1.3   BEHAVIORAL AND PSYCHOLOGICAL ASSESSMENTS

Current smoking status and history of smoking, including secondhand smoke exposure, will be assessed at the baseline visit. Nicotine dependence will be assessed at the baseline visit and each annual visit thereafter, using the *Fagerstrom Test of Nicotine Dependence*.

The *EQ-5D-5L*[TM] *(EuroQol-5 Dimensions-5 Levels)* is a self-administered, 5-item instrument applicable to a wide range of health conditions and treatments. It encompasses questions of mobility, self-care, usual activities, pain/discomfort and anxiety/depression and is designed to provide a single index value for health status. This commonly used measure of health utilities will convert quality of life and health status into quality adjusted life-years (QALYs) for cost-effectiveness analysis. The EQ-5D-5L[TM] will be administered to all participants at the baseline visit and annually thereafter.

The *Patient Health Questionnaire-9 (PHQ-9)* is a self-report measure of depression that has been recommended by the American Heart Association (AHA) Advisory Panel on Depression and Coronary Heart Disease, has a low response burden (9 items, 2-3 minutes to complete), excellent reliability, and good sensitivity and specificity for diagnosing depression. This assessment will be completed at the screening visit and all annual visits thereafter. At screening, participants will be excluded who score ≥15 (moderate-severe depression) or indicate a positive response on question 9 dealing with suicide ideation. Information regarding alerts for elevated scores during the trial will be included in the MOP.

The *Food Frequency Questionnaire* (FFQ) consists of a finite list of foods and beverages with response categories to indicate usual frequency of consumption over the time period queried. This is an optional on-line questionnaire that will be completed ants following their annual visits.

The *Physical Activity Measure* is a self-report of time spent per week engaged in nine types of physical activity. This is an optional on-line questionnaire that will be completed following their annual visits.

6.1.1.4 CLINICAL MEASURES

Seated blood pressure and pulse will be assessed in a standardized manner, after a 5-minute rest period using a standard automated device or, if necessary, a manual device. The preferred method is the automated device as it offers reduced potential for biases and decreased demand on staff in terms of training and effort in data collection. Three measures will be taken 1 minute apart and the average of the 3 measures will be obtained. Blood pressure and pulse will be collected at the screening visit, baseline visit, 3 month visit, 6 month visit, and all annual visits.

Concomitant medications are required to be recorded at screening, baseline and then reviewed and revised at annual follow-up visits. Prescription and non-prescription medication use will be collected and generic names will be recorded and entered in the database. Clinical sites may choose to collect information about medications more frequently. Participants will be asked to bring all medications to the screening, baseline, and annual visits. However, other appropriate sources for obtaining this information may also include current pharmacy action profiles, and/or verification of medications documented in the medical record.

Medical history is collected at screening to determine eligibility (see *Chapter 4: Participant Enrollment*). Data regarding presence of comorbidities are important for descriptive purposes, subgroup analyses and prognostic analyses. Clinical sites may supplement participant self-report with medical record information, if available.

Serious adverse events (SAEs) and selected adverse events (AEs), further referred to as MACH15 AEs, will be collected and reported during all participant visits (phone and in-person). Adverse event ascertainment and classification is described more fully in *Chapter 7: Assessment of Participant Safety*. Briefly, medical events and symptoms will be solicited at each visit, using a standard form that is administered by clinical site staff that may be unmasked to the intervention arm assignation. SAEs and MACH15 AEs will be reviewed at the clinical site by a masked clinician who will make the assessment as to relatedness.

Trial outcomes will be assessed in both randomized groups in the same way and on the same schedule. After randomization, participants will be assessed every 3 months for cardiovascular outcomes using a standard form that is administered by clinical site staff that may be unmasked to the intervention arm assignation. Copies of medical records will be collected for masked adjudication of MACH15 trial outcomes as described in *Chapter 3: Trial Design and Clinical Outcome Measures*. Clinical site staff will use available resources and contact information to assess vital status annually on participants that have not responded to contact, but have not withdrawn consent.

6.1.1.5 SUPPORTING MEASURES

Contact information for the participant and alternate contacts will be collected at screening and reviewed at each in-person clinic visit in order to assist clinic staff with retention. Information will be stored centrally only if permitted by the clinical site's Institutional Review Board/Ethics Committee (IRB/EC).

Sociodemographic information will be collected including age, race/ethnicity, occupation, education, marital status, and number and relationship of persons living with the participant (no identifying information about persons living with the participant will be collected). These data will be obtained during the baseline visit and will be used to characterize the final trial population. Some demographics, such as marital status, may be updated during the course of the trial.

6.1.1.6 ADHERENCE MONITORING

Details of the assessment and monitoring for adherence are described in *Chapter 5: Intervention*. Briefly:

The *Timeline Followback (7 day)* will be administered at the screening visit to ascertain current drinking habits. Following randomization, the Timeline Followback (7-day) will be administered at each visit and quarterly call throughout the duration of the trial as a measure of adherence to the assigned intervention arm. However, if a participant reports 100% adherence during the previous 3 months (automated contact/calls), the Timeline Followback is not required at the annual visit.

Measures of adherence: using a smart phone/tablet app, text messages, or phone calls (per participant preference), participants will report whether they have consumed alcohol in the past 24 hours, and if so, what type and how many servings. Participants will be queried randomly, at least 7 to 10 times per quarter.

Health Coaching for Adherence will occur both at in-person clinic visits and phone visits by trained staff. See *Chapter 5: Intervention* for details.

6.2   LABORATORY PROCEDURES/EVALUATIONS

6.2.1   CLINICAL LABORATORY EVALUATIONS

Blood collection will occur at the screening visit, baseline visit, 3 months, 6 months and each annual visit. Specific laboratory assessments (e.g., liver function tests, serum creatinine) are important for determining eligibility status. During follow-up, laboratory results will be used to assess safety and for trial-related outcomes and markers of compliance. The amount of blood collected at one visit will be approximately 60 ml or about 4 tablespoons; part will be used for local safety labs, and the remainder will be stored either centrally or locally (local IRB/EC approval required) for other future biomarker analyses (see 6.2.1.2). Local sites may also collect and store additional blood with approval from the Ancillary Studies Committee, the MACH15 Steering Committee, and their IRB/EC.

6.2.1.1   LOCAL LABORATORY ANALYSES

Laboratory analyses to be completed at the local laboratory include standard hematology and biochemistry tests: hemoglobin A1c, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), creatinine, fasting glucose, total cholesterol, HDL-C, triglyceride, LDL-C. All local laboratories will be certified or controlled as per local rules or regulations.

6.2.1.2   STORED SAMPLES

At baseline, blood, urine, and hair clippings (optional) will be stored for future measurements of other risk factors for CVD and diabetes, possible measures of ethanol exposure, and potential modifiers of the effects of alcohol (see Appendix B: MACH15 Potential Assays). All participants will be asked to provide written consent for future genetic studies including Genome Wide Association Studies (GWAS) as well as transfer to and storage of biological specimens at the central biorepository. Baseline laboratory samples will be stored locally and shipped on a set schedule to the central biorepository at the Brigham and Women's Hospital/Harvard Cohorts Biorepository. For participants that decline to have specimens stored centrally, only blood for local labs (see 6.2.1.1) will be collected and processed.

Clinical sites may also choose to collect and store samples at other visits with approval from the Ancillary Studies Committee, the MACH15 Steering Committee, and their IRB/EC.   These samples are marked with footnote 8 in Table 6.1: Measures and Frequency.

6.2.2   SPECIMEN PREPARATION, HANDLING AND STORAGE

Blood samples will be collected at the screening visit, baseline visit, 3 and 6 month visits, and each annual visit. Participants will be asked to be fasting for the baseline visit. Participants may be asked to be fasting at screening and annual visits to obtain a fasting glucose (prevalent or incident diabetes assessment) per site preference (clinical sites may choose to use HbA1C [non-fasting] instead of fasting glucose). Participants will not be asked to fast for the 3 month and 6 month visit. Specific procedures for blood and urine collection, standardized processing, and storage are explained in the MOP.

6.2.3 SPECIMEN SHIPMENT

On a pre-specified schedule, clinical sites will ship stored samples from the baseline visit to the central biorepository. Specific instructions, including information about the specimen tracking system, are explained in the MOP.

6.3 TRIAL VISIT SCHEDULE

6.3.1 PRE-SCREENING

Clinical sites may engage in prescreening activities by phone or other methods (such as health fairs, community engagements, etc.). The MACH15 protocol does not prescribe what needs to take place during pre-screening activity.

6.3.2 SCREENING

The in-person screening visit procedures include:
- Informed consent – Screening
- Contact information
- Medical history
- Concomitant medications
- Blood pressure and pulse
- AUDIT
- Y-BOCS-hd (3 items)
- Timeline Followback (7-day)
- PHQ-9
- Health Coaching (for adherence during washout)
- Blood draw for AST, ALT, GGT, and creatinine. Participants who have not had HDL, total cholesterol, and either fasting glucose or HbA1c in the prior 24 months will also need these at screening.

6.3.3 RUN-IN PERIOD (OPTIONAL)

Some clinical sites may opt to have participants complete a 7-14 day run-in period, asking participants to drink 1 drink of alcohol each day. This will be followed immediately by the 2-week washout period. See *Chapter 5: Intervention*, for details.

6.3.4 WASHOUT PERIOD

All participants will complete a 2-week washout period prior to enrollment. The washout period is described in *Chapter 5: Intervention*. At the end of the washout period, participants will be contacted by phone to assess the washout, continued eligibility, and confirm the baseline visit appointment, if appropriate. Participants must continue to maintain abstinence until the baseline visit, which will occur at least 14 days (and ideally within 21 days) of the start of the washout.

- Assessment for SAEs and MACH15 AEs
- Confirm baseline visit appointment if eligible (adherence to abstinence in the washout required)

6.3.5 BASELINE/RANDOMIZATION

The baseline visit will be the randomization visit and will include the following assessments/procedures:
- Informed Consent – Randomization
- Anthropometrics, blood pressure, and pulse
- Concomitant medications
- Sociodemographics
- Assessment of SAEs and MACH15 AEs
- Blood draw for AST, ALT, GGT, and lipid panel (total cholesterol, HDL-C, triglycerides, and either measured or calculated LDL). Fasting glucose and/or HbA1c will be drawn per clinic preference if not already obtained at screening. If the value is above the ADA-defined cutoff for pre-diabetes (see MOP for further detail), the participant will be asked to return to clinic for a second blood draw to confirm. (Participants with known diabetes need not have a second blood draw.)
- Collection of blood, urine and hair clippings (optional) for storage; genomic material will also be stored from this visit
- Smoking History
- Fagerstrom Test of Nicotine Dependence
- EQ-5D-5L^{TM}
- Confirmation of eligibility
- Behavioral assessment interview
- Randomization
- Coaching session on assigned intervention

Clinical sites may choose to do the baseline data collection and randomization over 2 visits. When the randomization is not done on the baseline visit day, the goal will be to do the randomization within 30 days. Continued eligibility will be confirmed on the day of randomization.

6.3.6 FOLLOW-UP

After the baseline/randomization visit, participants will be seen in clinic for subsequent visits at 3 months, 6 months, 12 months, and then annually until close-out. Follow-up phone calls will occur at 2 weeks, 4 weeks, and 9 months during the first year, and every 3 months thereafter (except for annual visits when participants are seen in clinic). See Table 6.1: Measures and Frequency for the sequence of events and special considerations (e.g., fasting visits) and the MOP regarding visit windows.

6.3.6.1 3 AND 6 MONTH IN-PERSON VISITS

- Contact information updated
- Blood pressure and pulse

- Blood draw for AST, ALT, GGT, HDL-C
- Timeline Followback (7-day)
- YBOCS-hd (3 items)
- Health Coaching (for adherence)
- Assessment for SAEs and MACH15 AEs
- Assessment for CVD outcomes

6.3.6.2 ANNUAL VISITS (12, 24, 36, 48 MONTHS, ETC.)

- Contact information updated
- Anthropometrics, blood pressure, and pulse
- Concomitant medications
- Sociodemographics updated
- Timeline Followback (7-day) (not required if participant reports 100% adherence during the previous 3 months)
- Y-BOCS-hd (3 items)
- EQ-5D-5L™
- PHQ-9
- Fagerstrom Test of Nicotine Dependence
- Health Coaching (for adherence)
- Assessment of SAEs and MACH15 AEs
- Assessment of CVD outcomes
- Blood draw for AST, ALT, GGT, and HDL-C. To assess for incident diabetes, participants may have fasting glucose and/or HbA1c drawn annually per clinic preference. If the value is above the cutoff for pre-diabetes (see MOP for further detail), the participant will be asked to return to clinic for a second blood draw to confirm. (Participants with known diabetes or that have been started on diabetes medication during the trial need not have a second blood draw.)
- Blood, urine and hair clipping collection for storage and future analyses per Appendix B as approved by the Ancillary Studies Committee, the MACH15 Steering Committee and local IRB/EC.

6.3.6.3 PHONE CALLS (2 AND 4 WEEKS)

- Timeline Followback (7-day)
- Health Coaching (for adherence)
- Assessment of SAEs and MACH15 AEs

6.3.6.4 PHONE CALLS (9 MONTHS AND EVERY 3 MONTHS THEREAFTER*)

- Timeline Followback (7-day)
- Health Coaching (for adherence)
- Assessment of SAEs and MACH15 AEs
- Assessment of CVD outcomes

Phone calls will occur at 9 months and every 3 months thereafter except when a quarterly call coincides with an annual visit.

6.3.7 EARLY TERMINATION VISIT

In the event a participant chooses to end participation in the trial before the scheduled end of trial visit, clinical sites will make every effort for the participant to come in for an early termination visit. At that visit, the close-out assessments (same as annual visit) will be administered if the last annual visit occurred >6 months ago. Outcomes, SAEs, and MACH15 AEs will be collected regardless of time since last annual visit. Any SAE, MACH15 AE, or pregnancy will be followed up until resolved or stable up until 30 days after the final clinical site visit.

6.4   AUTOMATED CONTACTS

Participants will be contacted to assess for and encourage adherence using a variety of technologies including smart phone applications, email, text messaging, and phone calls, per their preference.   See *Chapter 5: Intervention* for details.

7 ASSESSMENT OF PARTICIPANT SAFETY

7.1 SPECIFICATION OF SAFETY PARAMETERS

To maximize the safety of participants in this trial, MACH15 has adhered as closely as possible to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Recommended Council Guidelines on Ethyl Alcohol Administration in Human Experimentation.[1] As in studies conducted by the United States Department of Agriculture (USDA), participants will be asked to consume alcohol only after activities that require dexterity and alertness are completed for the day (i.e., at night). The level of alcohol consumption proposed throughout this trial (one ~15 g unit per day) is actually less than that used in USDA studies.[2]

Key safety-related eligibility criteria are exclusions for participation in the MACH15 Trial. These inclusion/exclusion criteria can be found in *Chapter 4: Participant Enrollment* and will be adhered to in order to maximize safety while ensuring the inclusion of appropriate participants in the trial. Once participants have agreed to participate and provided consent, all participants will be monitored for safety issues potentially related to the participation in the trial.

A Data and Safety Monitoring Board (DSMB) will be appointed to monitor participant safety (see Section 7.5.2). To protect participants further, adverse events will be monitored using a variety of methods including: structured solicitation of hospitalizations, approved questionnaires, and laboratory tests (e.g., liver functions tests) at all follow-up contacts by regular telephone and in-person visits. In addition, alcohol consumption will be monitored by self-report and biochemical testing. As a result, the risk for any escalation in alcohol use will be minimized.

Alcohol, the product of interest in this trial, does not concern a medicinal product but a food substance. The safety focus of the MACH15 Trial will be on collecting Serious Adverse Events (SAEs) (see section 7.1.2 and 7.4.2). Only non-serious Adverse Events (AEs) that are defined as events of special interest (referred to as MACH15 AEs, described in section 7.4.3) or AEs leading to trial discontinuation will be systematically collected. Pre-existing conditions and pre-planned procedures (surgeries or therapies) scheduled prior to signing the Informed Consent are not considered (S)AEs.

 MACH15 SAEs and AEs will be *documented* in source documentation at the clinical site, *collected* in the case report forms (CRFs) on the secure MACH15 website and *reported* to the DSMB, the NIH/NIAAA, and the Institutional Review Board/Ethics Committee as appropriate. It is important to note that all outcomes of the MACH15 Trial will also be monitored as safety events in addition to follow-up as a trial outcome event (see *Chapter 3, Section 3.5: Clinical Outcome Measures*).

7.1.1 DEFINITION OF ADVERSE EVENTS (AE)

The Office for Human Research Protections (OHRP) defines an Adverse Event (AE) as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an Investigational Product, whether or not related to that

Investigational Product or protocol-related procedures. For simplicity, an AE of special interest (Section 7.4.1) will be referred to as a MACH15 AE.

7.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

The OHRP defines Serious Adverse Events (SAE) as any AE that:
- • results in death;
- • is life-threatening (places the participant at immediate risk of death from the event as it occurred);
- • results in inpatient hospitalization or prolongation of existing hospitalization;
- • results in a persistent or significant disability/incapacity;
- • results in a congenital anomaly/birth defect; or
- • based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

7.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets all of the following criteria:
1) **unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents such as the IRB/EC-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2) **related or possibly related** to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3) suggests that the research places participants or others at a **greater risk of harm** (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2   CLASSIFICATION OF AN ADVERSE EVENT

7.2.1 RELATIONSHIP TO TRIAL INTERVENTION

The unmasked assessor at the clinical site will enter/collect all SAEs and MACH15 AEs in the CRFs using the documented source information. The masked clinician who examines and evaluates the participant report will document all safety information and determine the event's causality based on temporal relationship and clinical judgment.

The classification of potential relationship to the intervention is as follows:

- • DEFINITELY Related will be an AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation (e.g.: concomitant drug, concomitant

disease); and the relationship in time is very suggestive (e.g.: it is confirmed by dechallenge and rechallenge).

- POSSIBLY Related will be an AE that might be due to the alcohol; an alternative explanation (e.g.: concomitant drug, concomitant disease) is inconclusive; and the relationship in time is reasonable; therefore, the causal relationship cannot be excluded. Or an AE that does not have the minimum information for investigators to be able to assess the relatedness.
- NOT RELATED will be an AE that is not related to the use of alcohol and for which sufficient information exists to indicate that the cause is unrelated to the trial.

7.2.2 EXPECTEDNESS

In light of the duration of the trial and the trial population, many MACH15 (S)AEs reported by participants are likely to qualify as expected events, including cardio-metabolic events, cancer, and accidents. Expected events are occurrences that are listed in the informed consent form or those which are unrelated to alcohol, but are to be expected in the trial population. The determination of expectedness will be by a masked clinician.

7.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The documentation and collection of all SAEs and all MACH15 AEs will begin after Informed Consent is obtained and end after procedures for the final visit have been completed. Participants will be contacted and interviewed regarding possible SAEs and MACH15 AEs in a standardized fashion throughout the trial according to the Visit Schedule (Table 6.1: Measures and Frequency Table). If a participant has died or cannot be reached, their alternate contact will be interviewed if allowed by local legislation. SAEs and MACH15 AEs (Section 7.4) will be investigated through the collection of data during this interview process, the abstraction or acquisition of copies of medical records, emergency medical services reports, death certificates, coroner and/or autopsy reports, and/or the completion of attending physician questionnaires, as appropriate. In addition to fixed time points, events may be received spontaneously via the participant, proxy, or a member of the clinical site staff. All clinical sites will take appropriate action regarding the event and will be responsible for documenting, collecting, processing, classifying, and coding MACH15 AEs and SAEs within the online safety collection system within the secure MACH15 website.

The clinical site Principal Investigator (PI) will submit all safety updates and periodic reports to the Regulatory Authority(ies) and local IRB/EC, as required by applicable local regulatory requirement(s). Individual safety reports, if required, will be created by the clinical site PI. Central, trial-wide SAE listings and an annual safety report provided to the DSMB will be available to the individual clinical sites for their reporting needs.

7.4 REPORTING PROCEDURES

Due to the trial population, the burden of collecting and reporting on every possible AE in MACH15 is excessive. Therefore, clinical sites will report all SAEs and only MACH15 AEs centrally.

7.4.1 ADVERSE EVENT REPORTING PROCESS

After informed consent is signed, the unmasked assessor at the clinical site who examines and evaluates the participant will document all safety information in the source file at the clinical site. After awareness of an SAE or MACH15 AE, the unmasked assessor at the clinical site will collect and enter all SAEs and MACH15 AEs into the online safety collection system within the secure MACH15 website. The clinical site masked clinician will review the information and indicate whether the event was expected or not and the relationship of the SAE or MACH15 AE to trial intervention. All SAEs and MACH15 AEs (see 7.4.3) will be processed and evaluated in order to be reported to the DSMB, the NIH/NIAAA, and the local IRB/EC, as appropriate according to local legislation. If an event meets criteria for an unanticipated problem, additional, expedited reporting to NIH/NIAAA and regulatory bodies will occur. Unanticipated problems may reveal additional risks which may require changes to this protocol and informed consent.

7.4.2 SERIOUS ADVERSE EVENT REPORTING PROCESS

All deaths and immediately life-threatening events, whether related or unrelated, will be promptly documented, collected in the online safety collection system on the MACH15 website by the clinician and then will be centrally reported to the DSMB and the NIAAA/NIH on an expedited basis, per prevailing guidelines. Other SAEs, regardless of relationship, will be entered into the online safety collection system and they will be centrally reported to the DSMB and the NIAAA/NIH on a regular schedule.

Clinical sites will follow local reporting procedures for reporting SAEs to their IRB/EC. Where required by local legislation any SAE occurring within 30 days after the last clinical site visit will also be documented, collected and reported if appropriate. However, clinical site assessors do not need to actively monitor a participant for new SAEs after the final clinical site visit.

7.4.3 ADVERSE EVENTS OF SPECIAL INTEREST IN MACH15 (SAE AND MACH15 AE)

There is special interest in a number of AEs or SAEs due to their relationship to alcohol consumption.[3] Participants will be queried about these MACH15 events specifically at their regular contacts and visits. Please note that a MACH15 AE can also be a SAE. The MACH15 AEs include:

- Total and site-specific cancer excluding non-melanoma types of skin cancer
- Road or water accidents that require medical attention
- Major falls requiring medical attention in the hospital or emergency ward
- Fall-related fractures (i.e., only fractures resulting from a fall, not due to disease, illness or non-fall-related fractures)
- Atrial fibrillation requiring hospitalization
- Congestive heart failure (CHF) requiring hospitalization
- Hemorrhagic stroke requiring hospitalization

In addition, investigators will report the following:

- Increase in liver tests to >2 times the upper limit of normal (ULN)
- Alcohol use disorder
- Unexpected events for which the clinician believes that participation in MACH15 caused the event or contributed to the immediate cause of the event

7.4.4 REPORTING OF PREGNANCY

The use of alcohol is a known risk factor during pregnancy. One of the main inclusion criteria in the trial is postmenopausal status. Therefore, women included in the trial will have a postmenopausal status and pregnancies are not expected to occur. However, if a pregnancy does occur, participation will be discontinued on the intervention.

7.4.5 INCIDENT CONDITIONS THAT RESULT IN PERMANENT OR TEMPORARY STOPPING OF ALCOHOL BUT CONTINUED FOLLOW-UP FOR OUTCOMES

The use of alcohol may be harmful in the following conditions. For this reason, the intervention will be discontinued at least temporarily in the following incident conditions (this list is not intended to be exhaustive):

- Dementia
- Heart failure Class III or IV
- Breast cancer
- Gastric bypass surgery
- Serious chronic liver disease (e.g., active hepatitis B and C infections) or liver tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT] and gamma-glutamyl transpeptidase [GGT]) >2 times the upper limit of the normal range using local standards; GI bleeding.
- Estimated glomerular filtration rate (eGFR) drops to <30 ml/min /1.73m^2 or end-stage renal disease (ESRD)
- Ongoing use of any medication for which alcohol consumption is contraindicated
- A Patient Health Questionnaire (PHQ-9) score ≥15 or a positive response on question 9 dealing with suicide ideation
- Any organ transplant
- Pregnancy
- Development of alcohol use disorder

7.5   SAFETY OVERSIGHT

Assuring participant safety is an essential component of MACH15. Each participating PI has primary responsibility for the safety of the individual participants enrolled at his/her clinical site, while the DSMB will have primary responsibility for monitoring the accumulating trial data for signs of adverse trends in

the trial. The safety of the participant is always a major concern and, if warranted, the PI and/or central safety monitors can recommend discontinuation of the trial intervention for a particular participant.

7.5.1 SAFETY SUBCOMMITTEE

The Safety Subcommittee will review trial data related to the overall safety of trial participation, address IRB/EC issues (related to participant safety) that may arise, review clinical practice-related issues and oversee the clinical safety of all trial participants. The Safety Subcommittee is chaired by a Central Monitor (CM). The CM is a masked physician and will be responsible for the review of the SAEs that might meet the requirement for DSMB and NIH/NIAAA reporting.

The Safety Subcommittee will meet regularly with the aim to review any safety issues related to screening and participation in the trial. In addition, this committee will discuss adverse event reports, ensure consistency in SAE/MACH15 AE coding and reporting, and review any potential trends. The Safety Subcommittee provides early monitoring of adverse events and ensures standardization of clinical practice and safety issues across all clinical sites.

7.5.2 DATA AND SAFETY MONITORING BOARD (DSMB)

The DSMB appointed to monitor the safety of the MACH15 Trial is described in *Chapter 11: Trial Organization, Section 11.2.4* and the review and the evaluation of safety data is described in *Chapter 8: Statistical Considerations, Section 8.5.*

8 STATISTICAL CONSIDERATIONS

8.1 STATISTICAL ANALYSIS PLAN

The major statistical approaches and analyses that will be performed during the MACH15 Trial are described in this chapter.

8.1.1 PRIMARY AND SECONDARY OUTCOME ANALYSES

The primary analysis will assess the significance of any difference observed in the distribution of time from randomization until occurrence of the primary endpoint, an expanded cardiovascular disease (CVD) endpoint which includes death from any cause, using censored survival data analysis methods for clustered data. A detailed definition of the endpoint is given in *Chapter 3: Trial Design and Clinical Outcome Measures*. Kaplan-Meier estimates of survival will be obtained for participants randomized to each arm, taking into account household clustering,[1] and the log-rank test for clustered data,[2-5] stratified by clinical site, and will be used to assess the statistical significance of any differences observed. The primary comparisons of intervention groups will be performed according to the "intention to treat" principle: all randomized participants will be grouped according to their intervention assigned at randomization. Hazard ratios and 95% confidence intervals will be calculated using Cox regression model for clustered data,[6,7] adjusted for clinical site by a set of indicator variables. Estimates for the proportion of participants who remain event-free at pre-specified time points, and the associated confidence intervals, will be calculated similarly. Log-log plots of survival will be used to examine the assumption of proportional hazards, and effect modification by time since randomization will be assessed through the introduction of indicator variables for each 6-monthly or annual time period. If the proportional hazards assumption is not justified, in secondary analysis, we will report time-specific effect estimates and consider the use of accelerated failure time models which may provide a more parsimonious fit to the data. Should best practices for statistical analysis of trials with designs similar to MACH15 develop during the course this trial, the analysis plan will be revised accordingly. The analysis of the secondary endpoint, incidence of diabetes, will be conducted as described above.

There are numerous risk factors for CVD and diabetes, and these will be measured at baseline and at subsequent visits, including age, body mass index, hemoglobin, blood pressure, gender, race/ethnicity, healthy lifestyle, and other co-morbidities. Although randomization ensures that, on average, treatment groups will be balanced with respect to all of these factors, this may not be true in the given trial. Thus, we will assess the success of randomization by first comparing the baseline characteristics of participants in the treatment groups, and then re-assess treatment effects in secondary analysis after adjusting for the risk factors associated with the strongest imbalances. To adjust as finely as possible for confounding by measured risk factors, an additional secondary analysis will be conducted that adjusts for all measured risk factors.

Non-adherence to the assigned treatment is another potential challenge to power an unbiased treatment effect estimation that we will address in secondary sensitivity analysis by conducting *per protocol* and *as treated* analyses,[8] by using instrumental variables methods,[9,10] by potential outcomes

approaches,[11] by comparing the compliance estimates and by computing log rank tests weighted by time-varying probability of adherence.[12] *Per protocol* analysis excludes non-compliant participants from their respective arms. *As treated* analysis ignores treatment assignment but, rather, analyzes participants according to the amount of alcohol intake reported, regardless of what was assigned. The "contamination-adjusted intention-to-treat" uses instrumental variable analysis to address non-adherence in a two-stage approach. The potential outcomes approach is an estimation procedure for the intention-to-treat effect that maintains randomization-based properties under more plausible, non-ignorable noncompliance and non-ignorable missing-outcome conditions. The log rank tests weighted by time-varying probability of adherence involves modeling the probability of non-adherence given available covariate data, and then uses the inverse of these estimated probabilities, suitably stabilized, to reweight the log rank test statistic to mimic the study population that would have been observed, had there been no non-adherence

To assess adherence during the first year of the trial, the change in high density lipoprotein cholesterol (HDL-C) will be compared over an approximate 6-month period between the two groups. Based on a two sample t-test, the mean change in the intervention arm to the mean change in the abstention arm will be compared. Since this analysis is based upon individual level change scores, there is no need to control for clinical site or other time-invariant covariates.

8.1.2   SUBGROUP ANALYSES

Effect modification by pre-specified risk factors for CVD will be investigated by calculating stratum-specific point and interval hazard ratios and by assessing the statistical significance of any differences observed through a partial likelihood ratio test for clustered survival data. The pre-specified sub-groups are age, HDL-C, sex, baseline CVD risk, geographic region, and prevalent diabetes at enrollment. Age will be grouped as <70 and 70+ years of age, and HDL-C and baseline CVD risk will be grouped in tertiles. There are no *a priori* effect modifiers hypothesized, and MACH15 is not powered to detect any. Unless there is strong modification of the treatment effect, the power of this trial to detect any effect modification will be low.

8.1.3   INTERIM ANALYSIS

At the discretion of the Data and Safety Monitoring Board (DSMB), interim analyses will be performed periodically. Each meeting will include an administrative review to assess accrual, retention and the progress of the trial. In addition, there will be a review of efficacy, safety, and the occurrence of any adverse effects. For early stopping for efficacy, it will be suggested that the trial be stopped if the p-value for the log rank test for the primary endpoint and secondary endpoint are both < 0.001, following the Haybittle-Peto rule,[13,14] and if, in addition, the results for other endpoints, including fatal and non-fatal myocardial infarction (MI), fatal CVD, hospitalized angina, revascularization, ischemic stroke and all-cause mortality are consistent with the results for incident CVD and diabetes. Futility analysis will be done once per year for the duration of the trial up to the sixth year, where at each time, given the observed data up to that point, the probability of observing an effect of the hypothesized value or anything more extreme would be less than 5% for both the pre-specified primary and secondary

endpoint. Safety and adverse events will be carefully monitored, including total and clinical site-specific cancer, hospitalizations, motor vehicle collisions, falls, fall-related fractures, alcohol misuse, atrial fibrillation, hemorrhagic stroke and increase in liver function tests to >3X ULN, and unmasking and stopping for safety will be considered should rates in the intervention arm appear unacceptably elevated compared to the abstention arm, accounting for multiple comparisons and adequate follow-up.

An interim analysis of HDL-C is described in Section 8.3 below. Results of this analysis will also be brought to the DSMB, with a discussion of stopping if no difference in levels between study arms is observed.

8.2   SAMPLE SIZE CALCULATIONS

Sample size calculations involved extensive explorations over a range of primary endpoint definitions and baseline rates, baseline adherence rates and improvements to these due to household network effects, proportions of households with 1, 2 and 3 eligible members, intra-household correlation coefficients, and minimum expected effect sizes.

We originally assumed that our trial will be individually randomized trial, and that the primary combined expanded CVD incidence endpoint in the abstention arm will have a rate of 0.026/person-year, modestly higher than the 2.2% annual rate observed in SPRINT,[15] increased slightly because, unlike SPRINT, we are including diabetic individuals and total mortality as an outcome and excluding CHF alone. Participants will enroll during the first 3 years and then will be followed for an average of 6 years. We have assumed that there will be 1% annual loss to follow-up (LTF) in both groups, and 10% non-adherence at any point in time over follow-up for participants who are the sole person in their household to be randomized, leading, for these participants, to an effective hazard ratio of 0.838 under an assumed true hazard ratio of 0.82 as in Ronksley, et al.[16] Under these assumptions, to provide a minimum of 80% power at a two-sided 0.05 significance level for detecting a 18% relative decrease in the intervention group endpoint rate, for an individually randomized trial design with one participant per household, we will need 3,900 participants per arm,[17] for a total of 7,800.

Although we conservatively powered the trial for an expected relative risk (RR) of 0.82, there is substantial evidence suggesting that for CVD, an RR of 0.75 is likely to be observed. If so, we will have adequate power for baseline rates as low as approximately 0.0125/person-year, significantly lower than the observed rate in MESA.

Power for CVD (n=7,800, 1% annual LTF and 10% non-adherence in single households, 9% in multiple participant households, ICC=0.005, proportion of households with ≥2 members=70%, proportion of additional household members eligible=30%)			
	Relative Risk		
Annual Event Rate	**RR=0.82**	**RR=0.80**	**RR=0.75**
1.4%	55%	65%	84%
1.8%	65%	75%	92%
2.2%	74%	83%	96%
2.6%	80%	88%	98%
3.0%	85%	92%	99%
3.4%	89%	94%	99%

Figure 8.1 presents power for different values of relative risks (0.80, 0.82 and 0.84) as a function of a range of plausible annual events rates (from 0.014/year to 0.035/year).

FIGURE 8.1: POWER FOR PRIMARY ENDPOINT

Power for primary endpoint (n=7,800, 1% annual LTF and 10% non-adherence in single households, 9% in multiple participant households, ICC=0.005, proportion of households with ≥2 members=70%, proportion of additional household members eligible=30%)
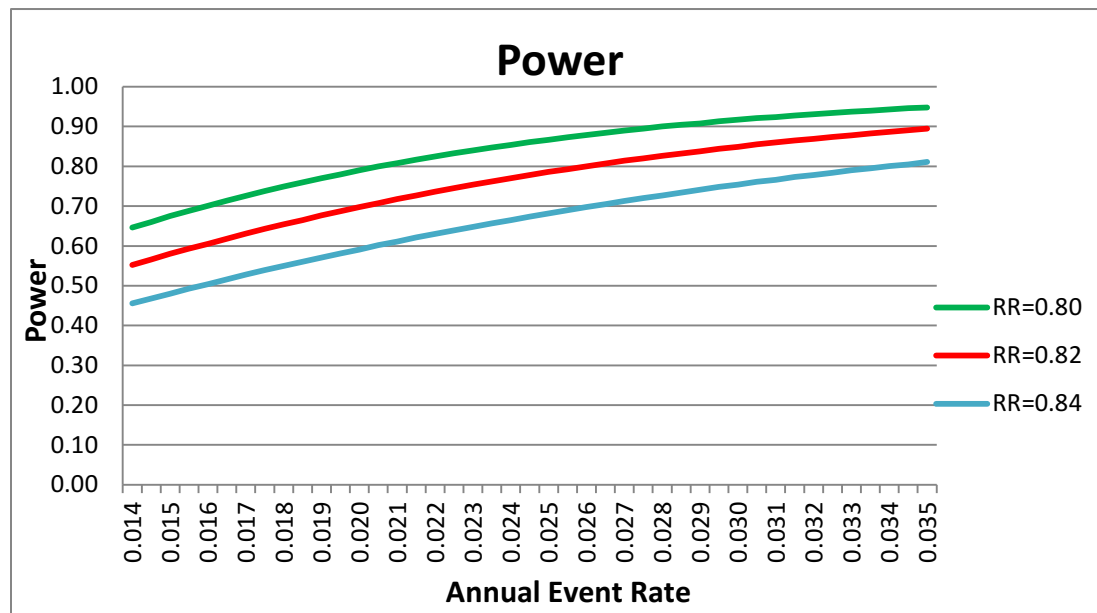
For the secondary diabetes outcome, with alpha=0.05 and assuming baseline prevalence of diabetes of 25% leading to an available sample size of 5,850, with an assumed diabetes incidence rate of 0.017/person-year in the abstention arm, as consistent with an 8.2% cumulative incidence in MESA over 5 years of follow-up among 45-84 year olds,[18] and with all assumptions as above concerning household clustering parameters, the table below displays the minimum power to detect RR for diabetes under even lower annual diabetes rates than has been assumed.

TABLE 8.2: MINIMUM POWER FOR DIABETES ANNUAL EVENT RATES

Minimum Power for Diabetes (n=5,850, 1% annual LTF and 10% non-adherence in single households, 9% in multiple participant households, ICC=0.005, proportion of households with ≥2 members=70%, proportion of additional household members eligible = 30%)			
	Relative Risk		
Annual Event Rate	**RR=0.80**	**RR=0.75**	**RR=0.70**
1.3%	50%	70%	85%
1.5%	55%	75%	90%
1.7%	60%	80%	93%

The trial will be adequately powered to detect relative risks of 0.75 and lower for diabetes over a plausible range of baseline event rates, assuming a baseline prevalence of 25%. The proportion of participants who have diabetes at baseline will not change the power to detect the primary outcome, but it will change the power to detect the effect of alcohol on risk of diabetes, the secondary study outcome. If the proportion of participants with diabetes at baseline is 30% rather than 25%, we will have power to detect a RR of 0.74 instead of 0.75 if the background incidence rate is 1.7%/person/year as expected, 0.73 instead of 0.74 if the background rate is 1.5%, and 0.71 instead of 0.72 if the background rate is as low as 1.3%. If the proportion of enrolled participants with prevalent diabetes exceeds expectation, potential limits to enrollment may be considered in conjunction with the DSMB to ensure adequate power for this outcome (see Section 8.5).

TABLE 8.3: MAXIMUM DETECTABLE RELATIVE RISK FOR DIABETES

Maximum Detectable Relative Risk for Diabetes (1% annual LTF and 10% non-adherence in single households, 9% in multiple participant households, ICC=0.005, proportion of households with ≥2 members=70%, proportion of additional household members eligible = 30%)		
	n=5,850 (25% baseline diabetes prevalence)	n=5,460 (30% baseline diabetes prevalence)
1.3%	0.72	0.71
1.5%	0.74	0.73
1.7%	0.75	0.74

During the vanguard phase, it will be essential to demonstrate that the minimum annual adherence rates are in place, to ensure adequate power. Hence, although HDL-C levels may or may not be part of the mechanism by which alcohol intake affects cardiovascular and diabetes risk, HDL-C is known to be an excellent marker of alcohol intake .[19] Therefore, to assess adherence during the vanguard phase, we will compare the change in HDL-C over an approximately 6 month period between the two trial arms. Based on a two sample t-test for comparing the difference between the changes in the intervention and abstention groups, the minimum detectable change in HDL that could be expected for 80% power, assuming that there is no change in the abstention group, is given. We consider an assessment of adherence after 1,000 participants have been enrolled in total at the 7 vanguard clinical sites that are followed for at least 3 months. Assuming that the range of the standard deviation of the change in the HDL will be from 5 mg/dl to 8.5 mg/dl, corresponding to a 50% range around the median value, 6.7 mg/dl, reported by the meta-analysis by Rimm et al.,[19] the minimum detectable difference between average changes in HDL cholesterol in the two groups in absolute values and in percents, for 80% power are given in the table above.

TABLE 8.3: CHANGE IN HIGH DENSITY LIPOPROTEIN-CHOLESTEROL

Standard deviation of the change in HDL-cholesterol	Minimum detectable change (n=1,000)	
	mg/dl	%
5	0.89	1.9
6.5	1.15	2.4
8	1.42	3.0
8.5	1.51	3.1

In the comprehensive meta-analysis of change in HDL-C in relation to alcohol intake based on 25 studies,[19] it was found that a 41 g/day alcohol over an average of 4 weeks was related to a 5.1 mg/dl increase in HDL-C. For a dose of approximately 15 g/day, we would expect a 1.5 mg/dl increase in HDL-C over 3 months of observation in the first year. Clearly, we will have adequate power to detect this difference, even if the standard deviation for the change in HDL-C is on the highest end of what might be reasonably expected.

8.3   RECRUITMENT RATE

The accrual period in MACH15 is 3 years and during this period the rate of accrual will be monitored on a monthly basis. We expect a recruitment rate on average of 11 new participants/clinical site/month. If the observed rate falls appreciably below the projected level, the reasons will be identified and remedial actions taken to protect the power of the trial and alleviate concerns about selective entry and other aspects of quality.

8.4   RANDOMIZATION METHOD

We propose permuted block randomization with random block lengths. Following the design of the Look AHEAD Trial,[20] we will randomize participants stratified by clinical site using a block randomization structure with randomly permutated block sizes of 4 and 8, to ensure balanced allocation and to avoid participant allocation being predictable,[21] as can occur with single-size block allocations. Alternative randomization methods exist (e.g., complete, simple, urn, and covariate adaptive); however, such schemes can lead to imbalance if, for example, inclusion criteria change midway through recruitment in response to new data from other trials or changes in guidelines. Use of additional, less important stratification factors is not generally recommended for trials the size of MACH15[22] and may delay randomization until data are entered and verified. In a trial of this size, doing so introduces additional operational complexities, with little expected gain in balance by these factors.

The randomization protocol and the randomization process will be prepared and executed by investigators from the Data Management Center (DMC) through the secure web-based data management system, so that eligibility is automatically confirmed. The trial statisticians will revise the randomization protocol to ensure that sufficient baseline and eligibility data are entered and validated before participants are randomized into the trial. In addition, the trial statisticians will closely monitor the intervention allocations by clinical site to ensure protocols are being adhered to and balance is being maintained.

8.5   DATA SAFETY MONITORING BOARD REPORTS

The progress of MACH15 and the trial's potential for attaining its goals will be regularly evaluated by the DSMB. The feasibility of the trial will be formally assessed by the DSMB early in the trial prior to initiation to ensure that the trial interventions are being safely delivered.

The DSMB will oversee the safety of participants and will provide oversight of the trial with respect to its primary aims. Following the protocol approval, the DSMB will periodically review and evaluate data on recruitment, quality control, compliance, adverse events, and outcomes. The DSMB may recommend corrective action, changes in the protocol, early stopping of the trial or parts of the trial. Each meeting will include an administrative review to assess accrual, retention, and the progress of the trial. In addition, there will be a review of efficacy, safety, and the occurrence of any SAEs or MACH15 AEs. The DSMB will also review and advise on proposed changes to the protocol. The Statistical Coordinating Core (SCC) will be the primary group interacting with the DSMB, preparing reports, and responding to queries.

The approach that developed to efficiently prepare DSMB reports includes a large number of statistical tables, flow-charts and plots. By maintaining a spreadsheet on a shared drive with tables and figures identified in the table of contents, statisticians indicate what has been completed and enter the location of the associated files. Any SCC member can review masked progress on the report at any time, and when it is complete, the program coordinator will run an application which quickly creates a draft document, including a table of contents. Other material can be added to the draft, and later changes to single tables or graphs can be incorporated individually. Once the technical material is ready (typically 2 weeks from the data freeze), a complete draft is assembled. In addition, we will use a website security model that can allow DSMB members restricted access to designated pseudonymised material.

Comprehensive data on all quality control activities will be included. Comparisons of measures of distribution of values over time, and among clinical sites or instruments will also be included. The SCC will develop and maintain standards to identify outliers, and to initiate and coordinate separate review of these for accuracy.

Reports to the DSMB are planned for every six months once recruitment is initiated. Hard copy open and closed reports will be generated for the DSMB and open reports for the Project Officer. Open reports will also be sent to the DMC and Clinical Coordinating Core leadership, and a subset of these will be continually updated on the trial website. These will allow for verification of completeness, timeliness, reliability, and accuracy of collection and coding of data.

9 DATA MANAGEMENT

9.1 TRIAL WEBSITE OVERVIEW

All MACH15 clinical sites will use the World Wide Web (WWW) to enter MACH15 data collected from participants. Each clinical site will have a password protected area on the MACH15 home page through which data will be entered. Documentation of the data entry system will be maintained at the Data Management Center (DMC). In addition, training materials for clinical site staff will be available in a downloadable format on the MACH15 website (www.mach15trial.org). Site-specific reports relating to aggregate participant demographics, recruitment goals, screening yield, among other reports, will be available on the website based on live data and available 24/7. All data are password protected, with individual passwords for each person with access to the clinical site. Access is limited on an individual basis depending on each person's associated clinical site and role in the trial.

Data security is paramount in the digital age in which we live and work; 2048 bit signatures and up to 256 encryption, and Instant SSL certificates offer the highest possible levels of security. This meets or exceeds security recommendations specified by the National Institute of Standards and Technology (NIST). All communication between the users and the MACH15 website are encrypted to prevent unauthorized viewing of any trial information. All servers are housed at a state-of-the- art data center a few miles from the DMC campus, with strong physical security controls to prevent unauthorized access to the servers and storage. A two-part disaster back-up program is employed, in which trial data is backed up nightly to institutional back-up resources, as well as an internal departmental back-up system which acts as a secondary recovery point. In the event that the primary back-up system is unavailable to restore critical data, data can be restored from the secondary point. The secondary back-up also provides back-up copies in an offsite location, kept in a locked, fire and waterproof storage cabinet away from the data center. Clinical sites will have local procedures in place for back-up and recovery of data following a disaster.

9.2 DATA COLLECTION

Each participating clinical site will maintain appropriate medical and research records for this trial, in compliance with International Conference on Harmonization (ICH) E6 and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH-funded trial, clinical records for the purposes of quality assurance reviews, audits, and evaluation of trial safety, progress, and data validity will be made available as required. Data collection is the responsibility of the clinical site staff under the supervision of the clinical site Principal Investigator (PI). The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data will be collected in multiple ways at all participant encounters, either by direct electronic Case Report Forms (eCRF) or hard copy CRFs that are later data entered into the eCRF. Data entry screens will mirror the hard copy CRFs for ease and accuracy of data entry. Clinical site staff will be expected to review hard copy CRFs for accuracy and completeness and resolve any data issues prior to data entry. Clinical data (including SAEs and MACH15 AEs, concomitant medications, clinical laboratory results data)

will be entered into the MACH15 website, a 21 CFR Part 11-compliant data capture system provided by the DMC. Copies of the eCRF will be provided for use as source documentation and maintained for recording data for each participant enrolled in the trial. Clinical sites will capture progress notes as needed and those will be maintained in the participant's official trial record.

9.2.1   DATA ENTRY

During data entry, a variety of programmed edit checks are performed for key variables, such as automatic range checks, identification of data that are inconsistent, incomplete, or inaccurate, etc. When the edit checks fail, data may be flagged for further review or prevented from becoming part of the trial database. Data queries will be based on live data and carried out on the computerized databases at the DMC to perform consistency checks on key variables and other data (See *Chapter 10: Quality Assurance and Quality Control, Section 6: Data Queries*).

9.2.2   RANDOMIZATION

MACH15 will use an internet-based, web browser randomization procedure. Clinical sites access the randomization application through the trial website. Access to this application is password protected and its communications are encrypted. Once security requirements are satisfied, the eligibility of the participant is verified and randomization will occur.

9.2.3   CLINICAL SITE TRACKING

The MACH15 website will maintain a Clinical Site Tracking System where all tools used to track, report, and monitor various aspects of the trial reside: recruitment, safety, adherence, outcomes, and regulatory activities. The system includes a fully integrated tracking and notification system that advises clinical site staff about participant follow-up windows and projects clinic and laboratory workload. Tracking a participant begins at screening and continues automatically throughout the trial by integrating participant follow-up data with a schedule of target dates for each of the participant encounters.

9.3   DATA MONITORING

All participant and site specific monitoring reports and queries reside on the MACH15 website and viewing is restricted depending on the user's associated clinic site and role in the trial. Additional reports will be generated for the various subcommittees, Clinical Coordinating Centers, and clinical sites. Possible reports to be provided include information on recruitment, loss to follow-up, adherence to the trial and the intervention, outcomes, SAEs and MACH15 adverse events, and data management. These reports will enable a user to click on a static link on the MACH15 website which will start a real-time report processed by SAS (statistical analysis system) and returned as output in the user's web browser. These reports access live data and run within seconds. Clinical sites will have access to live data showing exactly where their clinic stands in relation to their goals and those of the other clinical sites, as well as projections of activity needed to meet their goals.

9.3.1 MONITORING REPORTS

Clinical site monitoring reports will be generated and available via the trial website to the clinical sites, Clinical Coordinating Centers, and various subcommittees based on live data in order to identify issues as soon as possible. These reports will be utilized to identify and notify clinical sites not meeting trial standards. Data monitoring and cleaning will occur continuously throughout the trial. When problems are identified, they will be acted on quickly and the resolution will be tracked. Additional information on monitoring reports can be found in *Chapter 10: Quality Assurance and Quality Control*.

9.3.2 DATA SETS FOR TRIAL OVERSIGHT

All data collected on the MACH15 Trial website will reside at the DMC at Wake Forest University Health Sciences (WFUHS). All data analyses for trial oversight will be conducted at the Statistical Coordinating Center (SCC) at Harvard School of Public Health (HSPH). Analyses are described in *Chapter 8: Statistical Considerations* and all data to be used in the analyses for trial oversight conducted by the DSMB and NIAAA/NIH will be frozen, at appropriate intervals, in order that these data can be securely transferred, in a timely manner, from WFUHS to HSPH for analyses.

9.4 SECURITY AND DATA PROTECTION

The confidentiality of all participant information (including but not limited to any genetic analysis) will be protected at the clinical sites and the DMC. Paper records and computer files will be appropriately safeguarded from unauthorized access.

9.4.1 DATA SECURITY AT THE CLINICAL SITES

Paper and/or electronic records for trial participants will be stored at the clinical sites. Copies of records identified only by participant identification (PID) number pertaining to MACH15 AEs, SAEs, and outcomes, including necessary medical records, will be stored at the DMC via the secure and encrypted website. All records will receive the same care as would ordinary medical records. Only MACH15 trial personnel who have completed MACH15 training in data handling will have access to trial CRFs.

Similar care will be used in the handling of the electronic and paper records of trial data stored at each clinical site. Access to the data in any local MACH15 database will be controlled by a system of user identification names and passwords to ensure only authorized staff can enter. Each clinical site staff member must complete the MACH15 data handling training program before being given an ID and password to use the data system on the MACH15 website.

9.4.2 DATA SECURITY AT THE DMC

All data collected identified by PID number including necessary medical records, will be stored at the DMC via the secure and encrypted website. Access to the website, privileges to various areas of the website, and to the data on the website is managed by the DMC Project Manager. Access and privileges allowed to each individual will be specified by the DMC Project Manager. All passwords stored within the web data system will be encrypted using secure socket layer (SSL) encryption.

Confidentiality of information within the DMC will be protected through a variety of procedures and facilities:

1. The confidential nature of the data collected, processed, and stored at the DMC is explained to all new personnel.
2. All access to DMC office space containing data is controlled through a single door, which is locked and only accessible by key or security badge.
3. All participant data sent to the DMC is encrypted as described above.
4. All participant data stored on the Wake Forest University's mainframe computers are likewise encrypted. In addition, all such databases are protected by passwords that must be supplied before the data can be accessed. Passwords are released only to DMC staff with a need to use the particular file, and are changed on a regular schedule.
5. All printouts, plots, and reports containing individually identifiable data are produced on printers and plotters within the DMC's secure office space. All reports will be available using only participant ID rather than participant name.
6. The DMC will obtain a Certificate of Confidentiality for MACH15, which prevents researchers from being forced to disclose identifying information by certain legal proceedings.

Protected Health Information (PHI) such as participant name, addresses, contact information and other identifiers of concern, if collected and data entered, will be securely stored separately from the main clinical data on eCRFs. PHI will only be centrally stored at the DMC when allowed by local regulations, and otherwise will stay at the local clinical site.

9.5   RECORDS RETENTION

Documents pertaining to the trial should be retained for a minimum of 2 years after the formal discontinuation of MACH15 Trial. These documents should be retained for a longer period, however, if required by local regulations. It is the responsibility of trial leadership to inform the PI when these documents no longer need to be retained.

9.6   PUBLICATION AND DATA SHARING POLICY

MACH15 will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

MACH15 will be registered in an international trial registry, www.clinicaltrials.gov, after approval of the protocol by the DSMB.

# 10   QUALITY ASSURANCE AND QUALITY CONTROL

10.1   QUALITY ASSURANCE AND QUALITY CONTROL OVERVIEW

Data integrity and quality are among the highest priorities in clinical trials. There are two primary purposes for quality control: to document the level of quality and to provide feedback to the clinical and laboratory centers in order to maintain and improve the quality of the data over the course of the trial. This chapter outlines the quality assurance and quality control activities that will be conducted in the MACH15 Trial. Two phrases are used: 1) quality assurance is the collection of manuals and procedures that will be in place to assure the integrity of the data; and 2) quality control which describes the monitoring and analytic activities that assess performance during data collection and its processing.

The Measurement Procedures and Quality Control (MPQC) subcommittee establishes guidelines for quality assurance and quality controls which are detailed in the Manual of Procedures and oversees quality control and quality assurance activities for the trial overall, integrating input from other subcommittees. Reports will be presented to MPQC on a regular basis and any areas of concern will be presented to the Steering Committee for consideration.

The Clinical Coordinating Centers (CCCs) at Wake Forest University Health Sciences (WFUHS) and Julius Clinical (JC) will have the primary responsibility for operational aspects of quality control monitoring, working directly with clinical sites on their performance. The MACH15 website provides necessary reports for CCCs, subcommittees and clinical sites to ensure that all aspects of the trial are being carried out in accordance with the protocol.

FIGURE 1: MACH15 ORGANIZATIONAL MONITORING STRUCTURE
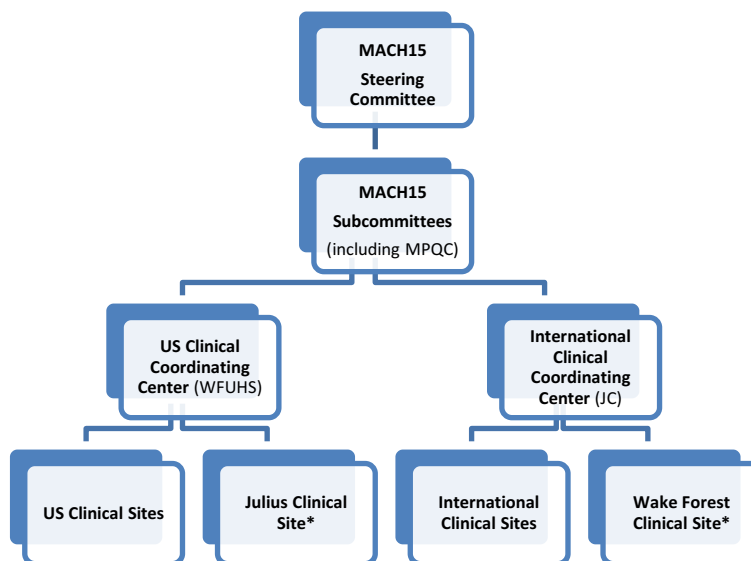
*Note that Julius Clinical and Wake Forest Clinical Coordinating Centers will monitor each other's clinical sites.

10.2 MANUAL OF PROCEDURES

In MACH15, as with any multicenter clinical trial, standardization of trial procedures is essential. The Manual of Procedures (MOP) includes the detailed descriptions of all trial procedures. This MOP is used for training purposes and as a reference throughout the duration of the trial for all clinical site investigators and staff. The MOP will be updated as necessary throughout the duration of the trial and updates will be communicated to clinical sites via the MACH15 website.

Essential trial procedures will be standardized and a written description provided in the MOP. This will include procedures such as administration of standard forms and questionnaires, appropriate process for measuring vital signs, biospecimen collection and storage, and other data collection procedures. Furthermore, standard event definitions and event validation procedures will be used.

10.3 CLINICAL SITE STAFF TRAINING

Training for clinical site investigators and staff is crucial to standardizing procedures and assuring high data quality. MACH15 will use several different training models that have been proven to be effective in previous clinical trials: central training for clinical site staff, web-based training, on-site training by CCC personnel, and a train-the-trainer approach. Phone calls and web-based platforms may be used for periodic refresher trainings.

Some trial procedures and forms will require certification prior to clinical staff conducting clinic visits. Certifications will be tracked centrally and staff will be periodically recertified.

10.4 CLINICAL SITE INITIATION

Clinical site initiation to screen and randomize participants is dependent upon completion of a series of preliminary tasks. These include tasks such as completion of appropriate regulatory approvals (Institutional Review Board [IRB] or Ethics Committee [EC]) and documents; letters of agreement; clinical site staff training and certifications where necessary; receipt of all trial supplies; and the development of a site specific recruitment plan. CCCs will provide the appropriate assistance toward these ends as needed.

10.4.1 REGULATORY APPROVAL

Clinical sites must have IRB/EC approval prior to site initiation and participant enrollment. The CCCs will work closely with the clinical sites to facilitate this approval and provide all documentation needed for submission. An informed consent form template will be developed by the Coordinating Centers which will then be adapted for use at local clinical sites. The Data Management Center (DMC) will track initial IRB/EC approvals and annual continuing reviews throughout the trial.

10.5   CLINICAL SITE MONITORING

Clinical site monitoring is an important aspect of quality control and standardization of protocol procedures and will be conducted by personnel from the CCCs or other trial leadership as necessary. Monitoring will take place remotely by the CCCs and through in-person site visits.

10.5.1 REMOTE MONITORING THROUGH QUALITY CONTROL REPORTS

MPQC, with input from other MACH15 subcommittees and the CCCs, will develop key performance indicators, both to document data quality and to provide feedback to individual clinical sites on their performance, which will be tracked in routine quality control reports. All reports will be generated by the DMC and available on the secure MACH15 website. The CCCs will be responsible for reviewing reports on trial progress and site-level quality metrics as requested by MPQC and/or the Steering Committee, as well as providing feedback to clinical sites on individual trial performance.

10.5.2 IN-PERSON MONITORING VISITS

Clinical site monitoring visits are important to maintain quality control and standardization of protocol procedures. These visits will be conducted by personnel from the CCCs. Monitor(s) will visit clinical sites periodically for the purpose of assuring that the trial is being conducted in accordance with the protocol. It is expected that the clinical site principal investigator (PI) be present or available for consultation during such scheduled monitoring visits. Site monitor(s) must be given access to all data pertaining to a participant's participation in this clinical trial, provided that participant confidentiality is maintained in accordance with local requirements. The scope of these visits is broad and can include, but is not limited to, review of all: regulatory documents, trial communications, site initiation, site staffing, Informed Consent Forms, inclusion/exclusion criteria, (source) data verification, and general site performance.

Site visits may also be conducted to evaluate performance deficits in one or more critical area, such as consistent departures from the protocol or MOP. Site visits will also be an opportunity for refresher training and/or training of new staff.

The CCC staff will prepare a written overview of the site visit and submit it to the MACH15 Principal Investigator, who will forward it to NIAAA. A summary of the site visit, an overview of action items, and listing of any protocol deviations will be prepared and sent to the clinical site PI.

Site visit summaries and follow-up letters may be reviewed by the MPQC subcommittee or other MACH15 subcommittees with recommendations for follow-up actions or reporting changes as needed.

10.6   DATA QUERIES

Quality assurance concepts will be employed during the development of Case Report Forms (CRFs). Web-based data entry screens will be developed from the CRFs, and enable the incorporation of range and logical checks at the time of data entry. These features will contribute to quality assurance. Clinical site staff will review each set of completed CRFs for accuracy and completeness.

The DMC will be responsible for data checking, which will include checks for missing data, unrealistic values, and crosschecks for inconsistencies. Data will be checked on CRF submission and any additional data queries will be presented to the data entry clinical staff for immediate resolution, if possible. The DMC will produce data query reports on the website that summarize the number and types of queries by clinic. Clinical site staff will be responsible for reviewing and resolving the data queries in a timely manner.

CRF data may also be reviewed by CCC monitors as noted above in 10.4. Source data verification will be performed per the monitoring plan. Once data are concluded to be complete and accurate, the CRFs will be locked, meaning that the forms will become read-only. It is expected that clinical site PIs maintain adequate supervision and oversight such that they can attest to the quality of data collection at their clinical site.

10.7   DEVIATIONS FROM TRIAL PROTOCOL

Adherence to the trial protocol is crucial to collection of high quality data and to the internal validity of the trial. Clinical sites will report protocol deviations to their IRB/EC, if required as per local reporting requirements. All serious protocol deviations will be reported to the trial Principal Investigator the CCC and funding agency (NIAAA). Major protocol deviations will be addressed with clinical sites and reviewed as part of the site visits.

11 TRIAL ORGANIZATION AND ADMINISTRATION

11.1 OVERVIEW

The trial organization for MACH15 is similar to that of other large multicenter clinical trials sponsored by government or industry. The National Institute for Alcohol Abuse and Alcoholism (NIAAA) initiated this trial and is the funding institute.

The overall organizational structure consists of one core and three coordinating centers that will work together to successfully design and conduct the trial: the Administrative Core at Beth Israel Deaconess Medical Center (BIDMC), the Biospecimen Repository and Statistical Coordinating Center at Harvard School of Public Health (HSPH), the Data Management Center and U.S. Clinical Coordinating Center at Wake Forest University Health Sciences (WFUHS), the International Clinical Coordinating Center at Julius Clinical (JC). Scientific leadership is provided by the Steering Committee, with external oversight provided by Institutional Review Boards/Ethics Committees (IRB/EC) and a Data and Safety Monitoring Board (DSMB), appointed by NIAAA. Vanguard and additional clinical sites with a strong track record for success were and will be chosen in the U.S. and internationally to conduct the trial.

11.1.1 ADMINISTRATIVE CORE

The Administrative Core at BIDMC serves as a key component of the MACH15 organizational structure, as outlined in **Figure 1**.

The Administrative Core will have ultimate responsibility for the conduct of the trial, will be the primary liaison with NIAAA, and have responsibility for all required reporting and fiscal accountability.

11.1.2 DATA MANAGEMENT CENTER AND U.S. CLINICAL COORDINATING CENTER

The Data Management Center (DMC) and the Clinical Coordinating Center (CCC) at Wake Forest University Health Sciences comprise two specific areas: data systems, IT and analytic support, and U.S. clinical operations oversight.

Working closely with the Administrative Core and Julius Clinical, the DMC and WFUHS CCC will develop and maintain trial databases and related internal and public websites; develop and distribute forms and the Manual of Procedures (MOP); train trial personnel in standardized protocol implementation and data collection; develop and support a web-based adjudication of clinical events and endpoints; monitor and ensure high performance throughout the trial; facilitate communication among and between the various Coordinating Center entities and the U.S. clinical sites to ensure that the trial is being conducted per protocol.

MACH15 Organizational Structure
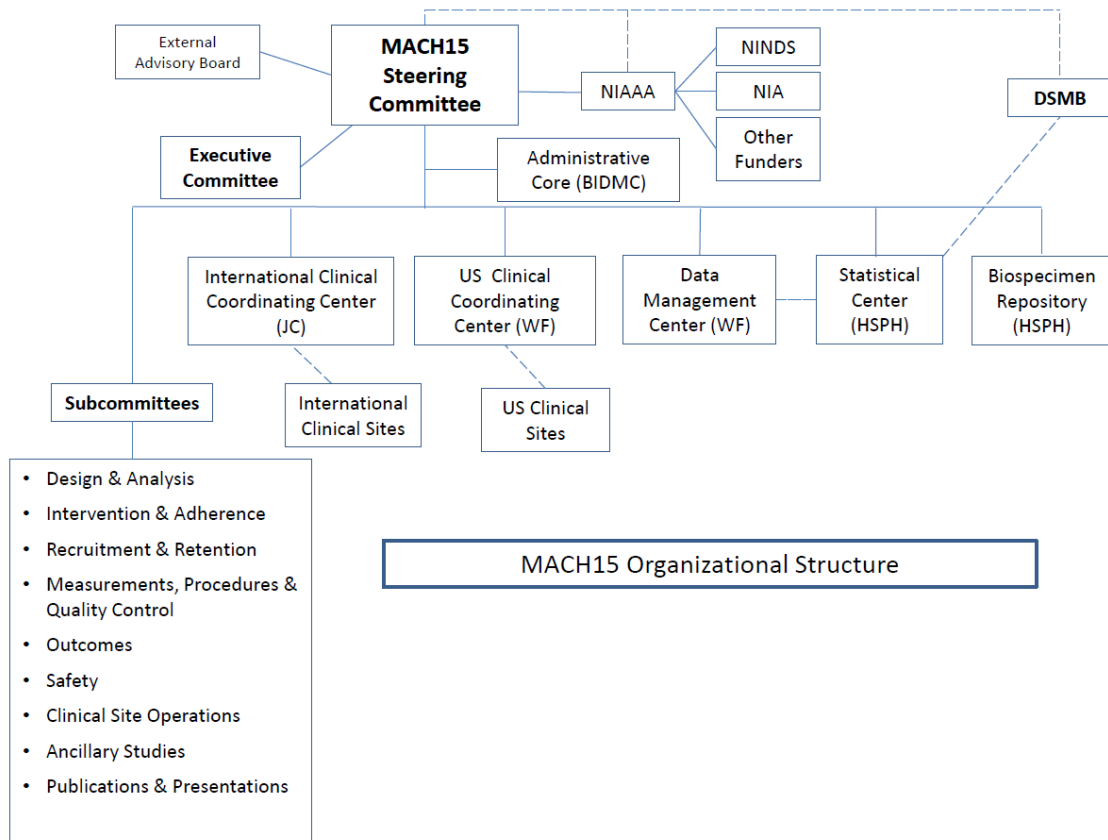
11.1.3 INTERNATIONAL CLINICAL COORDINATING CENTER

Julius Clinical is affiliated with the University Medical Center Utrecht and the Julius Center for Health Sciences and Primary Care in the Netherlands. Working closely with the Administrative Core and Wake Forest University Health Sciences, they participate in all aspects of the MACH15 trial development and implementation, will monitor and provide oversight for all international clinical sites, train trial personnel in standardized protocol implementation and data collection, and facilitate communication between the various Coordinating Center entities and the international clinical sites to ensure that the trial is being conducted per protocol.

11.1.4 BIOSPECIMEN CENTRAL REPOSITORY AND STATISTICAL COORDINATING CENTER

The Harvard Biospecimen Repository and Statistical Coordinating Center of MACH15 is an essential and vital core that will serve as a central repository for collected specimens of blood (sera, plasma) and urine for distribution as well as storage of these samples.

The Statistical Coordinating Center will also be responsible to conduct primary data analyses and secondary analysis and support in preparation of all manuscripts and presentations.

11.2 COMMITTEE STRUCTURE

The following committee structure will establish policy and ensure that MACH15 is conducted with the highest level of scientific integrity. As the trial evolves, the committee structure will be reviewed and revised to address additional needs.

11.2.1 STEERING COMMITTEE

The central decision-making body for MACH15 will be its **Steering Committee**, which will provide overall leadership for the trial and establish scientific and administrative policy.

The Steering Committee is composed of the following voting members: the MACH15 Principal Investigator from the Administrative Core, who serves as the Steering Committee chair; the Principal Investigator from each of the Coordinating Centers; each clinical site Principal Investigator (PI); and the NIAAA Project Officer. If a PI cannot attend a meeting at which a vote is taken, then the Co-Principal Investigator may vote (with the understanding that the Co-PI is fully informed about the issue). Additional investigators and staff may be invited to attend meetings but will not be voting members of the Steering Committee.

The Steering Committee oversees the overall conduct of the trial throughout all phases, develops the trial design, prepares the final protocol, and approves the trial forms and Manual of Procedures. During the data collection phases of the trial, this committee will oversee data collection practices and procedures to identify and correct deficiencies. The Steering Committee will consider and adopt changes in the protocol or procedures as necessary during the course of the trial.

The Steering Committee will work closely with NIAAA to interface with the DSMB, which will be formally structured by NIAAA. In turn, the DSMB will receive reports from the Statistical Coordinating Center at HSPH, which will prepare analyses in advance of and, based upon DSMB requests, following DSMB meetings.

For purposes of flexibility and rapid response, an **Executive Committee**, will be comprised of 5-6 select members of the Steering Committee (including the MACH15 PI and the NIAAA Program Officer). This committee will be charged with making decisions needed in real time when a full Steering Committee meeting is not feasible. Members of the Executive Committee will also be charged with resolving disputes or disagreements among investigators should they occur during this trial, seeking input from the Steering Committee when necessary.

11.2.2 EXTERNAL ADVISORY BOARD

The **External Advisory Board** (EAB) will be comprised of clinicians and scientists external to the clinical sites with knowledge and interest in the field, nominated by NIH officers and trial investigators and charged with providing ongoing suggestions and feedback on progress, new scientific questions of interest, potential collaborators, etc. In contrast to the DSMB, which formally monitors and is responsible for trial conduct, the EAB will not have a decision-making role on trial closure or

11.2.3 SUBCOMMITTEES

An important focus over the course of MACH15 is support of standing subcommittees. The following subcommittees will report directly to the Steering Committee:

1. **Design & Analysis** will have primary responsibility for the design of the trial and changes to that design after trial initiation.
2. **Intervention & Adherence** will develop strategies for providing the 'intervention' and promoting adherence.
3. **Recruitment & Retention** will develop strategies and identify best practices for recruitment and retention of participants and review clinical site success in this regard.
4. **Measurements, Procedures and Quality Control** will work closely with the Coordinating Centers to ensure that all aspects of the protocol are appropriately documented, consistently standardized, and performed to the highest quality.
5. **Outcomes** will have primary responsibility for definitions of all components of the primary, secondary, and tertiary outcomes and for adjudication of events.
6. **Safety** will have primary responsibility for definitions of safety outcomes and review of trends in their reports.
7. **Clinical Site Operations** will review the operational day-to-day functions of each clinical site and address concerns of clinical staff.
8. **Ancillary Studies** will solicit and review proposals to add trial-wide or site-specific ancillary studies, judging their scientific merit, cost and budget, specimen/participant burden, funders, and feasibility.
9. **Publications & Presentations** will create policies, procedures, and forms for proposed abstracts and papers and will review proposed projects for overlap with existing proposals, feasibility, appropriate inclusion of relevant co-authors, and consistency with the protocol.

11.2.4 DATA AND SAFETY MONITORING BOARD

An independent **Data and Safety Monitoring Board** (DSMB) will be established to monitor data and oversee participant safety. Members will be appointed by NIAAA to provide oversight of the trial and its ancillary studies. The MACH15 DSMB will include experts in cardiovascular medicine, diabetes, clinical trials, geriatrics, biostatistics, bioethics, quality of life, cost effectiveness, cognitive function and other areas as needed.

The DSMB normally meets twice a year to monitor safety, to advise NIAAA about trial progress and to make recommendations regarding trial continuation and protocol changes. In addition, the Administrative Core and/or Statistical Coordinating Center may provide data to the DSMB Chair to ensure early identification of any major adverse outcomes of the intervention. The DSMB has the responsibility to recommend to NIAAA whether the trial should continue, whether the protocol should be modified, or whether there should be early termination. The DSMB will provide reports to NIAAA

through the Executive Secretary, who will be appointed by NIAAA. Recommendations by the DSMB must be approved by NIAAA prior to implementation.

11.3   ROLE OF PRIVATE FUNDERS

Private funders will have no role in any aspect of the conduct of the MACH15 Trial. This includes any contributions to the design of the trial, the acquisition, analysis, or interpretation of data, the drafting of any articles or revision of their contents, and approval of their submission, presentation, or publication. All private funds will be received by the Foundation for the National Institutes of Health and disbursed within established guidelines to the NIH.

11.4   TRIAL TIMELINE

The projected timeline for MACH15 is shown in Figure 11.2. A development phase is proposed in which the Administrative Core and Coordinating Centers will create all necessary trial documents, forms and infrastructure, and vanguard clinical sites will hire and train necessary staff. The crucial step of Institutional Review Board/Ethics Committee approval will also occur in this phase.

Vanguard clinical sites will begin participant enrollment, with 9-12 months of formal vanguard activity expected. New clinical sites will be solicited, vetted and brought online at the conclusion of the vanguard phase. At that point, it is anticipated that all design changes will be implemented and full-scale enrollment will ensue.

Following approximately 3 years of open enrollment, the trial will enter the active 4.5 year follow-up phase, in which all participants continue to be followed in their respective intervention arm for a total mean follow-up of 6 years (range 4.5-7.5 years, depending on when originally enrolled). A final year of data cleaning and analysis will complete the 10-year project. It is anticipated that submission of a competing application to renew the trial for a second 5-year grant period will be submitted during the full recruitment period, contingent upon DSMB and NIH approval.

FIGURE 11.2: MACH15 PROPOSED 10-YEAR TIMELINE

Trial Start: 9/30/2016				
Infrastructure Development; Protocol, Manual of Procedures, and Forms Development; Clinical Sites IRB/EC Approval and Start-up	Vanguard Phase: Enrollment Begins	Additional Clinical Sites Added; Full Recruitment Continues	Follow-Up/ Competing Renewal	Analysis
9-12 mos	9-12 mos	3 years	4.5 years	1 year

11.5   ANCILLARY STUDIES

<mark>The MACH15 Trial encourages investigators to develop ancillary studies in conjunction with the trial and to involve other investigators, within and outside of the MACH15 Trial, in this process. An ancillary study may involve data collection from one or more MACH15 clinical sites for one or more cohorts, and use MACH15 participants, blood or urine samples, or other collected data, and may involve acquisition of additional data that are not compiled as part of the MACH15 data set.</mark> An ancillary study's objectives are not duplicative of and do not interfere with the main MACH15 Trial objectives. Ancillary studies enhance the value and productivity of MACH15 and help ensure the continued interest of the diverse group of investigators who are critical to the success of the trial as a whole. These studies provide an exceptional opportunity for investigators, either within or outside of MACH15, to conduct additional projects at relatively low cost. In general, ancillary studies will require additional funding from the NIH or other sources; note that funding from any source that might raise questions about conflicts of interest will not be permitted.

11.5.1 ANCILLARY STUDY REVIEW PROCESS

The Steering Committee must approve all ancillary studies to ensure that they do not impose an undue burden to clinical site staff or participants or conflict with the aims of the MACH15 Trial. Data collection may not proceed without the approval of the Steering Committee, after review by and on the advice of the Ancillary Studies Committee, and the local ethical committees.

The Ancillary Studies Committee (ASC) will conduct the preliminary review and provide recommendations to the Steering Committee for approval of ancillary studies. Submission will be in two parts, an initial letter of intent that will be evaluated, and if preliminary approval is given, a more detailed proposal will then be evaluated. Proposals will be assessed to evaluate whether they would interfere with other parts of the MACH15 protocol, would hamper continued recruitment or participation in MACH15, or would be inconsistent with the MACH15 aim of facilitating a broad range of research. The ASC will have regular calls to discuss proposals, and may, at its discretion, seek advice from outside experts to assist in its review. After review by the ASC, its recommendations will be forwarded to the Steering Committee for approval or disapproval. The DSMB may also be asked to judge the demands the proposed study places on participants and the priority in relation to MACH15 objectives.

Each ancillary study must include a MACH15 Principal Investigator or Co-investigator on the proposal. The Principal Investigator of the ancillary study is responsible for submitting the study proposal to the ASC, monitoring the study to ensure continuing compatibility with MACH15, and serving as a liaison to the MACH15 Steering Committee.

Investigators proposing ancillary studies must seek funding from unconflicted outside sources to conduct their research. Studies will be given a reasonable but limited time to secure funding, after which they will be deemed withdrawn. All ancillary study investigators will be required to budget adequately for all necessary resources for their studies. This includes, but may not be limited to, costs for data

collection, sample collection, sample shipping, sample extraction, sample analysis, data entry, website development, data analysis, data set preparation, data storage and publication of results. In assessing the acceptability of an ancillary study proposal, the Steering Committee will be concerned with both the explicit and the hidden costs to MACH15 entailed by the proposal. This will include costs to the Data Management Center and the Clinical Coordinating Centers for coordinating the additional data collection, the costs to clinical sites for notification of alert values and finally costs to the Biorepository and Statistical Coordinating Center for biomarker aliquoting (if necessary) and data analysis. The ancillary study's Principal Investigator should provide evidence that adequate support for carrying out these functions is available at his/her institution; if not, the MACH15 Coordinating Centers will conduct the activities required using resources that must be included in the ancillary study budget. Ancillary study results must be submitted to the MACH15 Publications and Presentations committee for review and approval prior to submission to a journal.

During the review process, highest priority will be given to studies which:
- have the highest scientific merit,
- do not interfere with or duplicate the main MACH15 Trial objectives or previously approved ancillary studies,
- produce the least burden on MACH15 participants,
- produce the least demand on MACH15 resources such as blood samples,
- require the unique characteristics of the MACH15 cohort, and
- contribute to the aim of examining a broad range of research questions.

Additional detail on the review process and criteria for judging proposals can be found in the Manual of Procedures.

11.6   PUBLICATIONS AND PRESENTATIONS

The Publications and Presentations Subcommittee (P&P) will create policies, procedures, and forms for proposed abstracts and papers (based on the existing Cardiovascular Health Study model: https://chs-nhlbi.org/Publications.htm). P&P will review proposed projects for overlap with existing proposals, feasibility, appropriate inclusion of relevant co-authors, and consistency with the trial protocol.

The P&P subcommittee will also review penultimate drafts of manuscripts for accuracy and consistency, appropriate NIH acknowledgements, and for planned submission to PubMed Central. Although primary results will not be expected until the end of the trial, the P&P subcommittee will promote early publications, including design paper(s), baseline papers, and papers with certain outcomes (e.g. lipids, compliance measures, etc.) that are not principal outcomes and that do not interfere with the primary objectives of the trial.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 ETHICAL STANDARD

The MACH15 Trial will be conducted in full compliance with the principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the participant. The trial must adhere to the basic principles of the International Conference on Harmonization-Good Clinical Practice (ICH GCP E6) or with local law if it affords greater protection to the participant. Recruitment of participants will start at each clinical site after approval is obtained from applicable Institutional Review Boards/Ethical Committees (IRB/EC). Participant safety will be carefully monitored in MACH15 as described in more detail in *Chapter 7: Assessment of Participant Safety*. Ethical issues arising at local levels will be monitored by the clinical site Principal Investigator, who has primary responsibility for the safety of the individual participants at his/her clinical site.

12.2 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE AND REGULATORY AUTHORITY

The protocol, informed consent forms, recruitment materials, and other required documentation will be submitted for review and approval to the IRB/EC and Regulatory Authority (RA). Approval must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC and RA, if applicable, before the changes are implemented to the trial. Protocol and/or consent form modifications or changes will not be initiated without prior written approval of the IRB/EC or RA, if applicable, except when necessary to eliminate immediate hazards to the participants or when the change(s) involve(s) only logistical or administrative aspects of the trial. A written verification that the amendment was submitted and subsequently approved will be obtained. All changes to the consent form, recruitment, and other participant materials will be IRB/EC approved and a determination will be made regarding whether previously consented participants will need to be re-consented.

All Serious Adverse Events (SAEs) will be reported according to clinical site specific regulations to the relevant IRB/EC/RA and centrally to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the Data and Safety Monitoring Board (DSMB). (See *Chapter 7: Assessment of Participant Safety*.)

A summary of the trial outcome will be sent to the IRB/EC/RA and NIAAA/NIH at the end of the trial.

12.3 INFORMED CONSENT PROCESS

12.3.1 INFORMED CONSENT/ASSENT AND OTHER INFORMATION DOCUMENTS PROVIDED TO PARTICIPANTS

Informed consent forms describing in detail the trial procedures, risks, and the participant's rights are provided to the participant and written documentation of informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization, if applicable, is required prior to enrollment in MACH15. A template informed consent document will be drafted which will then be adapted for use at

local clinical sites. The MACH15 Clinical Coordinating Centers will review all informed consent documents before submission to the local IRB/EC for approval.

12.3.2 INFORMED CONSENT PROCEDURES AND DOCUMENTATION

Informed consent will be obtained in compliance with the principles of the Declaration of Helsinki and ICH GCP E6, local regulations, and ethical standards of the applicable IRB/EC of the MACH15 clinical sites. The IRB/EC will review and approve all informed consent documents before they are presented to the participants.

a. All participants must be informed both written and orally.
b. All participants must give their informed consent BEFORE screening and randomization.
c. Informed consent is obtained from the participant by the clinical site investigator and/or by the designated research staff. The MACH15 research staff will fully inform the participant of all pertinent aspects of the MACH15 trial including the objectives, inclusion, intervention, trial procedures, significance, risks, and implications of the trial. All participants will be informed to the fullest extent possible, in language and terms they are able to understand. Participants will be given ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in MACH15. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time.
d. Prior to a participant's involvement in the trial, the written Informed Consent Form (ICF) will be signed, name filled in and personally dated by the participant and by the person who conducted the informed consent discussion. A copy of the signed and dated written ICF will be provided to the participant. The original signed ICF will be stored in the participant's individual file, held by the investigator. By signing the ICF, the participant agrees to allow the investigator and research staff to recontact the participant for the purpose of obtaining informed consent for additional safety evaluations if needed, or to obtain information about his or her vital status. The participant also accepts that the trial will obtain access to specified relevant medical information in respect of national regulations. The participant will be asked to provide a contact person(s) to act on the participant's behalf in case of mental or physical disability or death. If required by local legislation, the contact person that is named will be asked if they are willing to provide their contact information to be contacted if necessary. If they are willing, a separate informed consent will be obtained from the contact.
e. The form used for obtaining the participant's informed consent must be the current version that has been reviewed and approved by the appropriate IRB or Ethics Committee.

12.4 PARTICIPANT AND DATA CONFIDENTIALITY

The confidentiality of all participant information (including but not limited to any genetic analysis) will be protected in accordance with national and international data protection laws. The investigator will assure that participants' anonymity will be maintained and that their identities are protected from unauthorized parties. The investigator will maintain documents (i.e. participant signed ICF, medical records, etc.) in strict confidence.

Participants will be assigned a participant identification number (PID). On the MACH15 website, case report forms (CRF), other documents and specimens, participants will be identified by this PID. The investigator will securely keep a participant identification log documenting the PID, names and addresses at the clinical site. Only when allowed by national regulations, protected health information (PHI) may be stored at the Data Management Center (DMC). This step will ensure maximum protection of PHI when samples are sent to defined analytical sites and data are transferred to the DMC. Sample storage will be conducted according to procedures described in section 12.4.1 and 12.6 for samples designated for protocol defined analysis or long-term storage, respectively.

All data collected in this trial are confidential and every effort will be made to affirm and uphold the principle of the participant's right to protection against invasion of privacy. No personal data will be discussed at any group meetings in connection with MACH15. The data are entered in the MACH15 website by using participant ID-codes or barcoded forms.

MACH15 trial data may also be transmitted to researchers of future ancillary studies to conduct data analyses after approval by IRB/EC and other relevant authorities as well as the MACH15 Steering Committee. Permission to transmit trial data for ancillary studies will be included in the informed consent.

12.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

The confidentiality of all participant information must be protected at the clinical sites and the DMC. The procedures to ensure confidentiality of participant information are described in *Chapter 9 Security and Data Protection*.

During the trial, blood samples will be drawn for shorter term storage until the pre-defined analyses have been performed. Additional material will be discarded unless it is pre-destined for longer-term storage in a biorepository (see section 12.6). This procedure ensures that the minimal amount of samples is collected from each participant. Any stored data or material will be used only for purposes defined in the applications for ethical approval. Samples designated for protocol defined analysis will be provided with a code, which links samples to the PHI (e.g. a combination of PID and visit number). This ensures that investigators can associate results relevant for safety with the personal information of the participants. All blood samples are stored at the clinical site at -80° C or lower until they are either analyzed locally or sent to a pre-approved laboratory for storage and/or analysis (determined locally), where the material is also stored at -80° C or lower. All data collected on the MACH15 website will reside at the DMC. As determined by local regulations, contact information for each participant will be stored either at the DMC or on servers within the geographic region of collection. All data analyses for trial oversight will be conducted at Harvard School of Public Health (HSPH).

12.4.2 MEDICAL RECORDS

Each MACH15 clinical site will consult their local IRB/EC regarding approval requirements to access medical records for MACH15 participants. Depending upon the institution, prior approvals for data transfer agreements may be needed to obtain participant information. Pursuant to such agreements

investigators may be required to sign a privacy agreement to protect the participant's PHI as well as comply with other policies and procedures as defined by the institution's or country's designated privacy, security, and compliance services.

MACH15 clinical sites will work with and comply to the respective regulations for data protection and privacy, when participant's medical records are accessed. Medical records requested for central adjudication related to safety or outcomes will be de-identified by the clinical site prior to uploading these documents to the MACH15 website for review by the central adjudicators.

12.4.3 PARTICIPANTS' RIGHTS TO THEIR OWN RESULTS

The participants may eventually get personal feedback on the results, such as blood pressure, cholesterol levels, diabetic status and body composition. More scientific data (i.e. data where trial level information may be meaningful, but personal data cannot be interpreted in a reliable way) may be given as average results, in a seminar-type session or in writing (through newsletters, homepage etc.). In general, participants are entitled to receive information on their personal results at the end of the trial. If any disease progression or serious side-effects are noted during the trial, the participant will be advised to seek medical care. A MACH15 AE or SAE will be issued and information on SAE's will be passed to the appropriate IRB/EC and to NIH/NIAAA, as described in more detail in *Chapter 7: Assessment of Participant Safety* and the Manual of Procedures (MOP).

12.5 INSURANCE AND REIMBURSEMENT

Participants will be insured against injury caused by their participation in the trial according to local legal requirements in the countries where MACH15 takes place.

Likewise, reimbursement to the participants is dependent upon prevailing policies and regulations at the clinical sites. The amount of the reimbursement must not be so large as to influence informed consent, i.e., choice to participate.

12.6 FUTURE USE OF STORED SPECIMENS

With the participant's approval and as approved the IRB/EC or other relevant authorities, extra, pseudonymized biological samples will be stored at local and/or central biorepositories. These samples could be used for future ancillary research studies, as approved by Ancillary Study Committee and the MACH15 Steering Committee, to investigate future related broad exploratory biomarkers and intermediate outcomes, such as, in the context of predicting risk of cardiovascular disease, mortality and type 2 diabetes in individuals drinking one glass of alcohol daily or abstaining from alcohol. Examples of exploratory biomarkers to be studied include, but are not limited to, metabolomics analysis, coagulation, lipids, fatty acids, genetic association, urine electrolytes, and heavy metals (*See Appendix B: MACH15 Potential Assays*).

These samples may be transferred to other laboratories for these specific purposes following data handler agreements as required by the local, national, and international rules and regulations that

apply. Any ancillary study not previously approved by the IRB/ECs and MACH15 Steering Committee will be required to apply for re-approval at both the steering committee and local Ethical Committees (EC) before commencing with data- or sample analyses. The biorepositories will also be provided with a code-link that will allow linking the biological specimen with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

In order to protect participant rights, samples for long-term storage will be stored with pseudonymized labelling using a sample identification code. The link between sample identification codes and PID will only be available at the DMC and the Statistical Coordinating Center (SCC). This will ensure that any studies performed to assess group level effects will only be provided with the minimally required information and only at the time when data have been fully deposited.

The biorepositories will be pre-approved by the appropriate Data Protection Agencies or other RA according to the local, national, and international rules and regulations that apply. During the conduct of the trial, an individual participant can choose to withdraw consent to have subsequent biological specimens stored for future research.

13   CONFLICT OF INTEREST POLICY

The MACH15 investigators have established a policy regarding Conflict of Interest, which is presented in the Manual of Procedures (MOP). The independence of this trial from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The trial leadership in conjunction with the NIAAA has established policies and procedures for all members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

CHAPTER 1. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

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APPENDIX A: LIST OF ABBREVIATIONS

A1c	Glycated Hemoglobin
AAA	Abdominal Aortic Aneurysm
ABI	Ankle Brachial Index
ACC	American College of Cardiology
ADL	Activities of Daily Living
AEs	Adverse Events
AHA	American Heart Association
ALT	Alanine Aminotransferase
ASC	Ancillary Studies Committee
AST	Aspartate Aminotransferase
AUDIT	Alcohol Use Disorders Identification Test
BIDMC	Beth Israel Deaconess Medical Center
CABG	Coronary Artery Bypass Grafting
CCCs	Clinical Coordinating Centers
CE	Carotid Endarterectomy
CFR 21	Code of Federal Regulations Part 21
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CRFs	Case Report Forms
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular Disease
DMC	Data Management Center
DSMB	Data and Safety Monitoring Board
EAB	External Advisory Board
EC	Ethics Committees
ECG	Electrocardiogram
eCRFs	Electronic Case Report Forms
eGFR	Estimated Glomerular Filtration Rate
EQ-5D-5L	Euro-Qol Five Dimensions Questionnaire
ESRD	End-Stage Renal Disease
FFQ	Food Frequency Questionnaire
GGT	Gamma-Glutamyl Transferase
GWAS	Genome Wide Association Studies
GXT	Graded Exercise Test
HDL	High Density Lipoprotein
HDL-C	High Density Lipoprotein Cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HSPH	Harvard School of Public Health

ICC	Interclass Correlation
ICF	Informed Consent Form
ICH E6	International Conference on Harmonization Section E6
ICH-GCP	International Conference on Harmonization-Good Clinical Practice
IRB	Institutional Review Board
JC	Julius Clinical
LDL	Low Density Lipoprotein
LDL-C	Low Density Lipoprotein Cholesterol
LIFE	Lifestyle Interventions and Independence For Elders Study
LTF	Loss To Follow-Up
LVH	Left Ventricular Hypertrophy
MACH15	Moderate Alcohol and Cardiovascular Health Trial
MESA	Multi-Ethnic Study of Atherosclerosis
MI	Myocardial Infarction
MOP	Manual of Procedures
MPQC	Measurement Procedures and Quality Control
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIH	National Institute of Health
NIST	National Institute of Standards and Technology
OHRP	Office for Human Research Protections
P&P	Publications and Presentations Subcommittee
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PHI	Protected Health Information
PHQ-9	Patient Health Questionnaire-9
PI	Principal Investigator
PID	Participant Identification
QALYs	Quality Adjusted Life-Years
R&R	Recruitment and Retention Subcommittee
RA	Regulatory Authority
RR	Relative Risk
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SCC	Statistical Coordinating Center
SPRINT	Systolic Blood Pressure Intervention Trial
SSL	Secure Socket Layer
ULN	Upper Limit of Normal
UP	Unanticipated Problems
USDA	United States Department of Agriculture
WF CCC	Wake Forest Clinical Coordinating Center

WFUHS	Wake Forest University Health Sciences
WHO	World Health Organization
Y-BOCS-hd	Yale-Brown Obsessive Compulsive Scale- Heavy Drinking

Classes and Selected Examples of Potential Assays for Possible Analysis at Central Biorepository	
Plasma	• Metabolites and Metabolomics (e.g., Trimethylamine-N-oxide, amino acids) • Proteins and Proteomics (e.g., protein hormones, immunological proteins) • Markers of Coagulation, Fibrinolysis, and Thrombosis (e.g., clotting factors, platelet count, circulating adhesion molecules) • Lipids and Lipidomics (e.g., apolipoprotein species) • Endocrine Factors (e.g., adipokines, sex steroid hormones, glycemic hormones) • Nutritional Factors (e.g., choline, betaine, thiamine) • Markers of Alcoholic Beverages (e.g., ethylglucuronide, phosphotidylethanol, tartrate) • Markers of Organ Dysfunction (e.g., cystatin, creatinine, N-terminal pro-B-type natriuretic protein, electrolytes)
Red Blood Cells	• Membrane Fatty acids
White Blood Cells	• Telomere length • DNA adducts • Genotyping (e.g., single-nucleotide polymorphisms (SNPs), candidate and genome-wide chips)
Urine	• Metabolites and Metabolomics • Proteins and Proteomics • Markers of Metabolism (e.g., nitrogen) • Electrolytes (e.g., sodium, potassium) • Markers of Alcoholic Beverages • Gut microbial co-metabolites (e.g., indoxyl sulphate, hippurate, aromatic amino acid degradation products)
Hair clipping	• Heavy Metals (e.g., selenium, mercury) • Markers of Alcoholic Beverages