Examination of Zinc, S-adenosylmethionine, and Combination Therapy vs. Placebo in Otherwise Healthy Alcoholic Patients and its Effect on the Alcoholic Lung Phenotype

(ExZACTO Study)

Protocol Version 2.3

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1. Introduction: Clinical Background

Alcohol abuse places a tremendous burden on society. According to the 2008 National Survey on Drug Use and Health, more than 50 percent of the adult population in the United States consumes alcohol, which would roughly translate into more than 125 million people. In this same survey, almost 7 percent reported heavy drinking.[1] Data from the 2001 National Epidemiologic Survey on Alcohol and Related Conditions reported that the lifetime prevalence of alcohol abuse was about 18 percent, making alcohol the most widely used and abused among all drugs.[2] While average alcohol intake has decreased over time, more recent data suggest that the incidence of alcohol use disorders has not changed.[3] Importantly, studies attribute more than 100,000 fatalities annually to alcohol consumption.[4] Even among otherwise "healthy" individuals, alcohol abuse causes significant morbidity and dysfunction of many organ systems including the heart, liver, and skeletal muscle.[5-8] In the past decade experimental evidence has emerged that elucidates the profound effects of chronic alcohol ingestion on the lung and how it creates a previously unrecognized 'alcoholic lung' phenotype that renders the individual susceptible to pulmonary infection and injury.

Alcohol exerts a significant suppressive effect on the immune system, which leads to a vulnerability to a wide array of infections, especially pneumonia. Studies in various organ systems have consistently demonstrated that alcohol abuse impairs the clearance of infectious organisms[9] resulting in 1) an increased risk for community-acquired and nosocomial pneumonia, 2) higher hospitalization-associated charges, 3) higher intensive care unit use and longer inpatient stays[10], and 4) higher mortality rates.[11] Alcohol abuse has a longstanding link with pulmonary infections, and in a recent study of patients admitted to a general hospital with pneumonia, 25-50% of such individuals were found to have a concomitant diagnosis of alcoholism.[12, 13] Moreover, these alcoholic patients were more likely to be infected with serious Gram-negative bacteria such as Klebsiella pneumoniae.[14] Despite this longstanding awareness, a detailed understanding of the mechanisms responsible for predisposing alcoholics to lung infections is lacking and may be the key to uncovering new intervention strategies that could reduce morbidity and mortality in these vulnerable subjects.

The alveolar macrophage plays a key role in protecting the individual from developing pneumonia. The increased risk of pneumonia in the alcoholic host involves at least three important factors: 1) colonization of the oropharynx with pathogenic bacteria, which occurs in approximately one-third of alcoholics; 2) increased frequency of aspiration as a result of depressed level of consciousness and diminished gag and cough reflexes; and 3) impaired integrity of the host immune system.[15] A crucial element of host defense in the lung is the alveolar macrophage. The lung is constantly exposed to the outside world, and the first cellular line of defense in protecting the alveolar space from invading pathogens is the resident macrophage. It is the primary phagocyte on the gas exchange surface of the lung and normally has the capacity to efficiently ingest and destroy inhaled pathogens. However, clinical and laboratory studies have identified that alveolar macrophages are impaired by chronic alcohol

ingestion. For example, we determined that alveolar macrophages isolated from rats on a chronic alcohol diet have significantly impaired immune function and are poorly equipped to phagocytose bacteria.[16] Therefore, alveolar macrophage immune dysfunction is clearly implicated in the link between chronic alcohol consumption and the increased risk of pulmonary infections.

Oxidative stress is a fundamental feature of the alcoholic lung phenotype and interferes with the function of numerous cell types including the alveolar macrophage. Our research group has identified in clinical and animal studies that chronic alcohol ingestion depletes the alveolar lining fluid levels of glutathione (GSH), a critical antioxidant, by ~80% and oxidizes the redox potential by 35-50 mV.[17-19] Further investigations determined that alcohol-induced oxidant stress impaired alveolar macrophage terminal differentiation and plasma membrane expression of the receptors necessary to drive phagocytosis and the respiratory burst.[16, 19-21] More importantly, oral GSH precursors attenuated the alcohol-induced oxidant stress and improved AM immune functions in animal models.[19, 22] These findings suggest that dietary supplements that restore GSH availability within the alveolar space could improve alveolar macrophage immune function in alcoholics, although the potential benefit of this therapeutic modality has yet to be tested in clinical studies.

The essential micronutrient zinc is crucial for normal immune function, and it is deficient in alcoholics. A key participant in normal host immune response is zinc, a trace element that is critical for normal protein metabolism, the function of more than 300 zinc metalloenzymes, and for membrane integrity.[23-25] Alcoholics are prone to numerous nutritional deficiencies as the result of poor dietary intake, and zinc deficiency has long been recognized in this context. Zinc deficiency in the healthy, non-alcoholic population is uncommon in the United States, but contributes to a significant burden of disease in other parts of the world such as sub-Saharan Africa and Southeast Asia where dietary intake is severely limited[26] and where children in particular are at high risk of pneumonia.[27] Consistent with this association, there is evolving evidence that zinc is critical to airway health.[23, 25, 28, 29] Importantly, even though there has been considerable attention to examining how alcohol-related zinc deficiency affects the liver, the important role of zinc deficiency in mediating the alcoholic lung phenotype has only been recently recognized in our animal studies.[30, 31] Furthermore, we have preliminary data showing that human alcoholics show evidence of zinc deficiency in the alveolar space, and the next logical step would be to explore the potential role of zinc therapy in these patients.

Despite the overwhelming evidence for zinc deficiency and oxidative stress in the alcoholic population, there are no trials evaluating the lung health effects of either dietary zinc or antioxidant supplementation in humans who abuse alcohol. If either of these strategies is able to reverse the immune dysfunction seen in the setting of chronic alcohol consumption, it offers a potentially simple therapeutic option for this high risk population.

2. Objectives

2.1 Primary Aim

ExZACTO is a four-arm (1:1:1:1), factorial design, placebo-controlled, double-blind randomized clinical trial. The study is a clinical intervention trial that will determine the impact of both dietary zinc supplementation and dietary S-adenosylmethionine (SAMe) supplementation, individually and in combination, on alveolar macrophage immune function, intracellular zinc levels in the alveolar macrophage, and overall redox potential of the epithelial lining fluid in the lung.

The primary null hypothesis is that there will be no difference in alveolar macrophage immune function with zinc treatment, SAMe treatment, or combination treatment when compared to placebo in patients with an alcohol use disorder. This will be tested against the alternative hypothesis of a non-zero difference between zinc treatment, SAMe treatment, and combination treatment versus placebo. The testing will be done at $\alpha < 0.05$, two-sided, and 80% power to detect a 30% difference between treatment and placebo. Based on our calculations, a total of 100 patients will need to be enrolled (25 in each of the four arms) to ensure adequate statistical power to detect this difference.

2.2 Secondary Aims

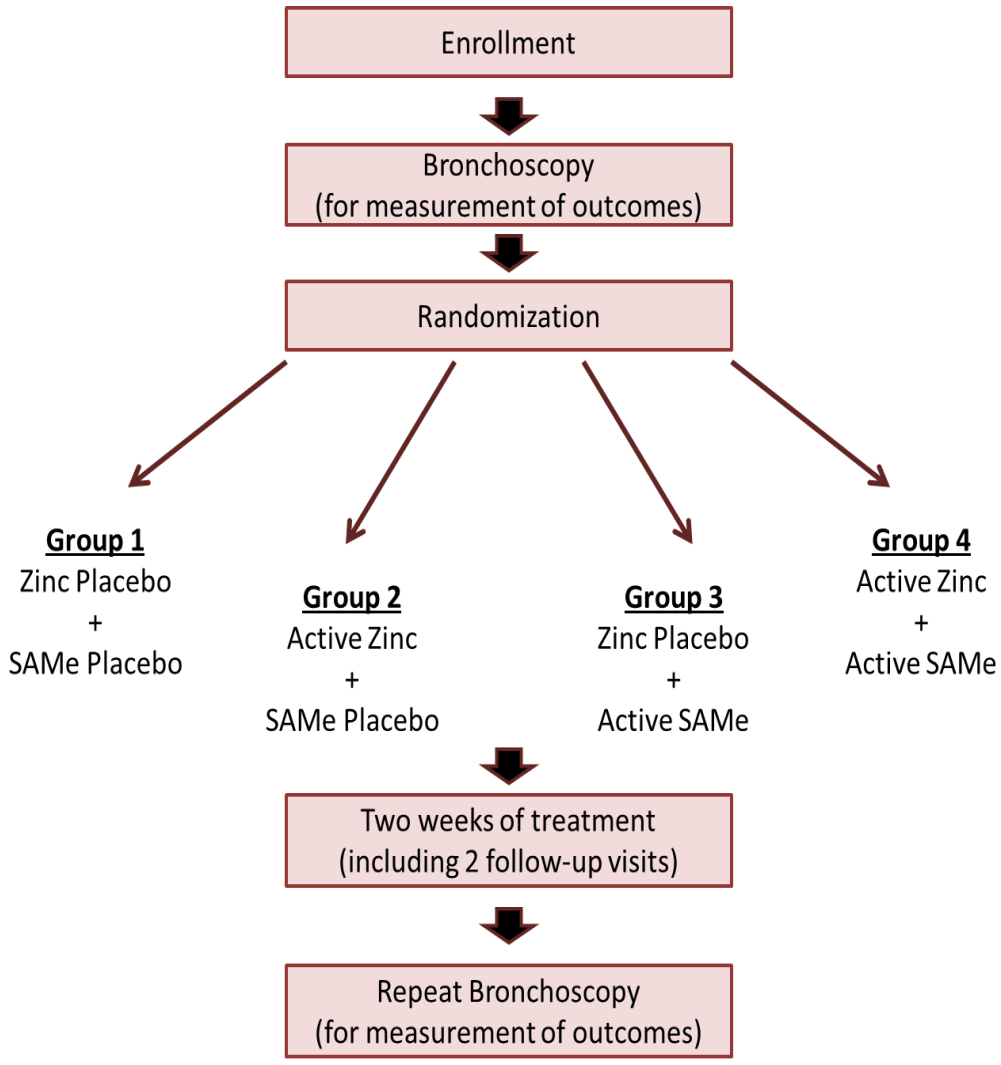
The primary aim is to determine if there improvement in phagocytic index with zinc treatment, SAMe treatment, and combination treatment. An improvement in immune function would signify a decrease in vulnerability to infection. There are other markers of the alcoholic lung phenotype, and these will be used as secondary aims. Specifically, we will examine the effect of zinc, SAMe, and combination treatment on alveolar macrophage intracellular zinc levels, redox potential, and GM-CSF receptor expression. The null hypothesis in each of these aims is that zinc, SAMe, and combination treatment will have no effect on the above outcomes, with the alternative hypotheses being that treatment will improve intracellular zinc levels, redox potential in the lung, and GM-CSF receptor expression in the alveolar macrophage.

3. Trial Design

3.1 Basic Design

ExZACTO is a single center, double-blind, placebo-controlled, randomized clinical trial to determine the effect of zinc supplementation and SAMe supplementation (both alone and in combination) on alveolar macrophage immune function, redox stress, alveolar macrophage GM-CSF reception expression, and intracellular zinc status in outpatient

alcoholic subjects. We will recruit a cohort of otherwise healthy patients with an alcohol use disorder from the Substance Abuse Treatment Program at the Atlanta VA Medical Center and randomize them to one of four treatment groups: 1) usual treatment plus placebo for two weeks; 2) usual treatment plus dietary zinc supplementation for two weeks; 3) usual treatment plus dietary SAMe supplementation for two weeks; and 4) usual treatment plus dietary zinc and SAMe supplementation for two weeks. The treatment allocation of these studies will be blinded to the patients and investigators. In all, each participant will receive a total of two different pills: 1) zinc placebo and SAMe placebo; 2) active zinc and SAMe placebo; 3) active SAMe and zinc placebo; or 4) active zinc and active SAMe. The placebo pills will appear identical to their active drug counterpart. A simple schematic of the study design is depicted below. While the goal of this study to evaluate the effect of two weeks of treatment, in certain instances subjects may receive treatment for longer than two weeks depending scheduling availability for the repeat bronchoscopy. All subjects will remain on treatment from the time of enrollment to the time of repeat bronchoscopy.



3.1.1 Power and sample size calculations

The primary outcome for this clinical trial will be the phagocytic index of the alveolar macrophage before and after at least 14-days of treatment. Phagocytic index is the most relevant primary outcome as it is a well-established marker of immune function and its improvement with either zinc treatment or SAMe treatment would indicate reversal of the alcoholic lung phenotype. Secondary outcomes will include change in GM-CSF receptor expression in the alveolar macrophage, change in alveolar macrophage zinc levels (signifying improvement of alveolar zinc deficiency), and change in redox potential [as measured by ratios of the redox couples glutathione/glutathione disulfide (GSH/GSSG) and cysteine/cysteine (Cys/Cyss) in the BAL and EBC fluid].

For the power calculations, we used data from previous animal studies, in which the estimated standard deviation for change in phagocytic capacity is between 0.2 (20%) and 0.40 (40%) depending on baseline values versus follow-up values, respectively. We assume a correlation coefficient of 0.85 between baseline and 14-day follow-up values within a treatment group. Given inherent variability in human data compared to animal data, our assumption will be that the separation of groups will not be as robust. Therefore, we took these predictions, as well as our some of our preliminary data in human subjects, into consideration when calculating sample size requirements. Assuming that we will detect on average a 30% increase in treated (zinc and/or SAMe supplemented) subjects and on average no change in the untreated subjects, a sample size of 19 alcoholics in each group will ensure statistical power exceeding 80% to detect a treatment difference of 30% at the 2-sided 5% significance level if the true difference between groups is 30%. However, in order to account for limitations including dropout and inadequacy of sampling, we will use a sample size of 25 subjects in each group (dietary zinc, dietary SAMe, and placebo) for a total of 100 subjects randomized for the entire study. This additional recruitment will ensure adequate statistical power is maintained at the completion of the study.

3.1.2 Interim analyses

There are no interim analyses planned as there would be no grounds for stopping the study early for therapeutic benefit. The DSMB will continually monitor the study for any adverse events and will make any determinations for early termination in the unlikely occurrence of harm.

3.1.3 Test statistic for the primary null hypothesis

The primary null hypothesis will be tested in an intent-to-treat analysis using ANOVA to compare in phagocytic function across the four treatment groups.

3.2 Study Population

3.2.1 Inclusion criteria

1. Age 18-60 years
2. Active alcohol use disorder (with last alcoholic drink within 8 days of randomization)

3.2.2 Exclusion criteria

1. Any active and uncontrolled medical problem(s)
2. Known zinc deficiency
3. Primary substance of abuse something other than alcohol
4. Current abnormal chest x-ray
5. HIV-positive
6. Any disorder of blood coagulation
7. Currently on medical treatment with anti-coagulants (including warfarin, heparin, direct thrombin inhibitors, or anti-platelet agents)
8. Daily use of vitamins or other nutritional supplements (Clarification: patients who are prescribed vitamins as part of their treatment for alcohol abuse will not be excluded and will be allowed to continue their prescribed vitamins throughout the study. Only patients on daily vitamin supplements prior to screening will be excluded.)
9. Renal impairment (GFR < 60)
10. Active bipolar disorder
11. Active Parkinson's disease
12. Current pregnancy
13. Contraindication to treatment with zinc or S-adenosylmethionine
14. Inability to give informed consent (i.e., limited cognitive capacity)
15. Non-English speaking

3.3 Randomization

A statistician who is otherwise uninvolved with this study will provide a randomization list, which will be prepared using a computer-based pseudo-random number generator. Our scheme will be permuted-block randomization with a block size of 8 and an allocation ratio of2:2:2:2. Based on pilot information, we expect a minority (10-15%) of participants to be non-smokers. To ensure equivalent representation of smoking and non-smoking subjects in each group, we will stratify randomization on current smoking status. After the patient is

enrolled in the study, but prior to randomization, he/she will undergo an initial bronchoscopy procedure. The randomization will occur only after this initial bronchoscopy procedure. The patient will be assigned to one of four treatment groups based on the randomization list.

3.4 Blinding

Treatment assignment will be masked to investigator, analyzing statistician, study staff, and subject. Only the dispensing pharmacist and the statistician who provides the randomization list will be aware of the treatment assignment.

4. Drugs and Dosages

4.1 Study Medications

There are a total of four treatment groups, and each randomized patient receives two types of pills. The first medication is either a tablet containing 50 mg of elemental zinc (zinc sulfate), or an identical appearing placebo tablet. The second medication is either 400 mg S-adenosylmethionine (SAMe), or an identical appearing placebo tablet. Patients assigned to the combination treatment arm will receive both active medications (i.e., zinc and SAM), and those assigned to the placebo arm will receive placebo tablets only. The remaining two groups will receive one placebo and one active medication (i.e., either zinc or SAMe).

4.2 Medication Administration

4.2.1 Zinc sulfate

A zinc sulfate tablet (containing 50 mg elemental zinc) or identically appearing placebo will be taken once daily for a total of two weeks. This medication can be taken at the same time as the other study medication below (i.e., SAMe). After randomization, subjects will receive 14+ tablets of active zinc or placebo, which is enough to complete the minimum 14-day course of therapy until the repeat bronchoscopy procedure can be performed.

4.2.2 S-Adenosylmethionine

A 400 mg tablet of s-adenosylmethionine (SAMe) or identically appearing placebo will be taken twice daily for a total of two weeks. This medication can be taken at the same time as the other study medication. After randomization, subjects will receive 28+ tablets of active SAMe or placebo, which is enough to complete the minimum 14-day course of therapy until the repeat bronchoscopy procedure can be performed.

4.3 Storage and Handling of Medications

The trial medications will be stored in a locked area with limited access. The investigational drug services at the VA will be responsible for maintaining an inventory of study medication. The study coordinator and investigators will distribute the medications after the pharmacist dispenses it. In the event of any emergency, the investigational drug services at the VA (including the dispensing pharmacist) will be able to break the blind. The study medication will not be used for any purpose other than this study.

4.4 Concomitant Medications

In general, the supplements used in this study are safe, but there may be a potential for some drug interactions. First, zinc salts may alter the absorption of some antibiotics, and this caution will be communicated with the participants. A full review of patient medication will be done prior to the study. The subjects in this study will be otherwise healthy, so we expect there to be minimal use of other medications. We will also advise patients not to take any other nutritional supplements during the time that they are in this trial as not to complicate the study. Second, SAMe is also a safe, readily available nutritional supplement, but can cause problems for patients with bipolar disorder and Parkinson's disease. Such subjects will be excluded from the study.

5. Trial Procedures

5.1 Recruitment and Pre-Screening

Study recruitment will primarily occur at the Atlanta VA Substance Abuse Treatment Program (SATP) clinic. IRB-approved recruitment posters will be displayed, and study brochures will be utilized. Interested patients will be pre-screened either by telephone evaluation or face-to-face during clinic visit with SATP provider. The purpose of the pre-screening is to identify patient who meet inclusion criteria and do not have any exclusions (listed in section 3.2). IRB-approved patient recruitment letters may also be utilized.

Recruitment will also occur in other parts of the VA hospital. Study brochures will be placed in VA clinics and other patient care areas. Interested patients may self-refer for the study by calling the study staff directly.

5.2 Baseline Visit

At (or prior to) the baseline visit, the study investigators in conjunction with the study coordinator will:

- Recheck to ensure that the patient meets all inclusion criteria and none of the exclusion criteria for the study (listed in section 3.2).

- **Obtain informed consent**:
    - Written informed consent will be obtained from each patient prior to performing any baseline evaluations. In certain instances the coordinator may ask screening questions to determine eligibility for the study, but no actual evaluation will take place prior to obtaining informed consent. A copy of the signed informed consent is given to the patient, and the study coordinator retains the original and has it sent to medical records for scanning. The informed consent document will be reviewed and approved by the Institutional Review Board as well as the Atlanta VA Medical Center Research and Development Committee prior to the initiation of the trial.

- Collect baseline demographic information and medical history.
- Obtain AUDIT and SMAST questionnaires on participants to grade alcohol consumption (see appendix 2 and 3).
- Obtain Drinking History Questionnaire, Alcohol Dependence Scale (ADS), Food Frequency Questionnaire (FFQ), and Timeline Followback Form-90 to better understand the drinking pattern. (see appendix 4-8; appendix 7 is provided to participants to define "standard drinks")
- Perform a physical examination.
- Order a chest x-ray (if one is not available from the past one year prior to enrollment).
- Collect urine for pregnancy testing (in women of childbearing age).
- Compensate the subject for the baseline visit with cash.

In certain instances, the patient will also undergo the bronchoscopy procedure described below on the same day as the baseline visit, but this would need to be scheduled in advance as the patient is required to not eat or drink anything for a minimum of 6 hours prior to the procedure. The actual randomization into treatment group will occur only after the initial bronchoscopy is done since the treatment follows the initial procedure. A schematic of the schedule of assessments is shown in appendix 1.

5.3 Bronchoscopy Procedure

5.3.1 Technical Procedure

- Study participants must not eat or drink anything for a minimum of 6 hours prior to the procedure. Prior to each bronchoscopy, blood will be collected for serum zinc, blood alcohol, biomarker testing, and measurement of redox stress. Urine will be collected for the presence of recreational drugs and ethyl glucuronide. Exhaled breath condensate will also be collected (described in section 5.4).

    Patients will undergo a flexible fiberoptic bronchoscopy with standardized bronchoalveolar lavage (BAL) technique (180 ml of isotonic saline in a sub-segment

of the right middle lobe or lingula) using standard conscious sedation techniques. Lidocaine will be used for topical anesthesia. To ensure safety, participants will be closely monitored during the procedure per the routine protocol in the hospital bronchoscopy suite. Bronchoscopy is a common procedure performed at the Atlanta VA Medical Center for clinical and research purposes with a published complication rate of less than 0.5% and 0% mortality rate.[33] The bronchoscopy will be supervised by one of the study investigators or an attending physician with credentials to perform the procedure. Subjects will be monitored for up to 4 hours after completion of the procedure per standard conscious sedation recovery protocol until fully recovered. An optional "no sedation" bronchoscopy will be considered when requested by the patient. The usual post-procedure recovery period would not be required for cases done without sedation.
For the initial bronchoscopy, subjects will be randomized after the procedure and given the study medication prior to discharge. Study volunteers will be compensated with $25 cash for each study visit and either a check or direct deposit after each bronchoscopy procedure. In addition, the study team will offer a $5 VA canteen voucher to the volunteer's driver (the friend or family member who must accompany the volunteer to the procedure).

5.3.2 Measurements

BAL fluid will be processed and a standard cell count and leukocyte differential will be determined. BAL fluid will be separated into cell component (i.e., alveolar macrophage isolation) for assays of zinc, GM-CSF receptor expression, and function (phagocytic index). The supernatant will be aliquoted and frozen at -70C for assays of Glutathione (GSH/GSSG), Cysteine (Cys/CySS). All experiments performed are common research protocols within our Alcohol research group. The excess cells and BAL fluid, if any, will be frozen for future analysis. After all enrollment and analyses are completed and all record-keeping requirements expire, all collected samples will be discarded.

5.4 Exhaled Breath Condensate Collection

5.4.1 Technical procedure

After the participant has abstained from food and beverages for at least one hour, they will rinse their mouth with distilled or de-ionized water. Participants will be seated upright, and breathe normally in and out through the mouthpiece. The mouthpiece is connected to an exhaled breath condensate (EBC) collection tube, called the R-tube, which consists of a plastic tube placed inside a chilled cooling sleeve. The total collection period, with the patient breathing normally through the

mouthpiece, is approximately 10–15 minutes. After the collection session, an evacuation plunger is utilized to collect the sample and a pipette is used to aliquot samples into 1 ml tubes. The samples are stored at –70° C until analyzed.

5.4.2 Measurements

The EBC samples will be analyzed for oxidative stress through the measurement of redox pairs of Glutathione (GSH/GSSG) and Cysteine (Cys/CySS). These particular measurements are feasible and have previously been done in similar studies of alcoholic patients.[32]

5.5 Follow-up Visits

Patients will have up to two follow-up visits during the two weeks that they are randomized to receive a study medication. These follow-up visits will occur prior to the second bronchoscopy procedure. In general, the first follow-up visit will occur sometime during the first week of therapy, and the second follow-up visit will occur sometime during the second week of therapy. At the discretion of the PI, the second follow-up visit may be performed on the day of the second bronchoscopy procedure. During the follow-up visit(s), the study coordinator will:

- Review the subject's compliance with study medication and assess alcohol use.
- Review the subject's alcohol intake and use of any other over-the-counter dietary or nutritional supplements.
- Review any adverse events or side effects from using study medications.
- Collect blood for alcohol level testing and biomarker testing (Follow-up Visit #1 only).
- Collect exhaled breath condensate using the procedure described above (Follow-up Visit #1 only).
- Compensate the subject for the visit with cash.

5.6 Second Bronchoscopy Procedure

- After at least two weeks of therapy with study medication (or placebo), the participants will undergo a repeat bronchoscopy procedure using the same method as described in section 5.3.1. Prior to the bronchoscopy, blood will be collected for serum zinc, blood alcohol, biomarker testing, and measurement of redox stress. Urine will be collected for ethyl glucuronide. Exhaled breath condensate will also be collected (described in section 5.4).

Subjects will again be compensated for undergoing the procedure, and the volunteer's driver will be offered a $5 VA canteen voucher. No further clinical follow-up will be

performed after the second procedure, but the patient will receive a phone call within the next week to ensure no issues arise after completion of the study requirements.

6. Adverse Events and Serious Adverse Events

6.1 Definition of Adverse Event

An adverse event (AE) is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function, as indicated by physical signs, symptoms, or laboratory changes occurring in any phase of the clinical trial, whether associated with study medications or placebo, and whether or not considered related to the study medications.

Adverse events include, but are not limited to:

1. Worsening (change in nature, severity, or frequency) of conditions present at the start of the trial.
2. Acute illness occurring during the trial.
3. Drug reactions.
4. Experiences related or possibly related to concomitant medications.
5. Clinically significant abnormalities in physical examination, vital signs, or laboratory values (examination of laboratory values will not be done on a routine basis during study visits, but may be performed if any concern for adverse event arises).

6.2 Serious Adverse Events

In general, serious adverse events are not expected with the use of these over the counter dietary supplements. However, if a serious adverse event does occur, the Principal Investigator report all serious adverse events (SAEs) that are unexpected (not listed in the most up-to-date Physician's Desk Reference) and potentially related to the study medication to the DSMB within two to three business days after becoming aware of the event. The study investigators will also conform to the AE and SAE reporting requirements of the IRB and the Research and Development Committee of the Atlanta VA.

6.3 Describing Adverse Events and Serious Adverse Events

The Principal Investigator will make a determination on reporting the relationship of the adverse event to study medication as one of the following:

- **None**: Unrelated to study medication
- **Possible**: Possible association with study medication is known
- **Probable**: Study medication has a known association with this type of event, and the event in question is probably due to the medication
- **Definite**: Study medication has a known association with this type of event, and the event in question is definitely due to the medication

The Principal Investigator will also make a determination of the severity of the adverse event as one of the following:

- **Mild**: No limitation of usual activities
- **Moderate**: Some limitation of usual activities
- **Severe**: Effects ranging from inability to carry out usual activities to life-threatening.

7. Trial Termination

7.1 Trial Termination

Termination of the trial may be recommended by Data and Safety Monitoring Board during one of their bi-annual meetings if there are concerns regarding safety or if the trial has failed to reach its declared goals.

7.2 Withdrawal of Consent

Participants who withdraw their consent during the course of the trial will discontinue their study medications and follow-up visits, but they will receive phone-call follow to monitor for adverse events and ensure appropriate safety surveillance.

The primary investigator will retain the right to withdraw a subject for any clinical/safety concerns or non-adherence to study protocol.

8. Data Collection and Statistical Considerations

Demographic data will be collected from patients undergoing initial screening for the study. During the study, we will collect data from enrolled subjects from blood samples, exhaled breath condensate and BAL fluid that are collected. The information collected for this trial will be recorded on Case Report Forms (CRFs) and entered in a web-based database called REDCAP. REDCAP is a secure, HIPAA-compliant, data management software website that requires appropriate VA credentials for access. All data entered in the REDCAP database will reside on VA servers.

For data analysis, the VINCI (VA Informatics and Computing Infrastructure) Workspace will be utilized. The VINCI Workspace will allow the team access to SAS (Statistical Analysis Software) while keeping all data on the VA's secured servers, thereby ensuring Veterans' privacy and data security.

9. Trial Administration

9.1 Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be appointed and charged with oversight responsibility for the performance and safety of the trial. The board will be comprised of three members (including a statistician) with clinical trial experience. An independent, experienced physician with no involvement in the study will serve as the chairman of the board. They will meet formally prior to the study to approve the protocol and thereafter convene about every six months or more frequently as needed. In general, the DSMB will receive reports comprised of: (1) the number of subjects that have signed consent, (2) number of screen fails, (3) number of drop-outs, (4) number of completers, (5) listing of reasons for drop-out, (6) a tabulated list of all adverse events, their frequency and severity, that occur during the study, (7) complete description on an IRB template of all serious adverse events that occur during the study, and (8) a written description of any known breaches of confidentiality of study subjects.

After each meeting, the DSMB will make formal recommendations regarding trial continuation. As there are no interim analyses, there will be no grounds for stopping the trial early for efficacy. However, the trial may be stopped early for any safety or performance issues. A special responsibility of the DSMB is to review serious adverse events (SAEs) as defined in this protocol. SAEs considered reportable per the Reportable Events policy will be reported to the chairman of the DSMB or designee within 48–72 hours for review. This initial review will determine whether there is a recommendation for a change in the protocol (or halt the study) until the matter can be considered by a quorum of the DSMB. All SAEs (reportable and non-reportable) SAEs will be available for review at the semi-annual DSMB meetings.

9.2 Institutional Review Board Approval

The Principal Investigator is responsible for obtaining and maintaining IRB approval throughout the entire course of this study.

9.3 VA Research and Development Committee Approval

In addition to IRB approval, the Principal Investigator will ensure that the Research and Development Committee at the Atlanta VA Medical Center approves the study and receives notification of IRB approval along with letters of approval for all amendments to the study per VA guidelines.

9.4 ClinicalTrials.gov Registration

This application includes a trial which requires registration in ClinicalTrials.gov. This registration will occur prior to study initiation.

9.5 Trial Documentation

All worksheets, supporting source documents and administrative records will be retained by the Principal Investigator for a minimum of two years following the last notification of approval by an appropriate regulatory authority. The consent forms and other research documents are scanned permanently into the medical record for veteran participants of the study per usual VA protocol.

9.6 Confidentiality

9.6.1 Patient Anonymity/Protected Health Information (PHI)

All PHI collected and processed for the purposes of this study will be managed by the investigators and study staff. The anonymity of participating patients will be strictly maintained. All subjects are identified by an assigned unique patient ID number on all worksheets, CRFs, and other documents. Documents that identify the patient and contain PHI (e.g., the signed informed consent form) will be maintained in strict confidence by the study investigators and study coordinator, except to the extent necessary to allow auditing by the appropriate regulatory authority. All electronic documents containing patient information will be stored electronically on VA-encrypted drives. All data collected as a hard copy will be kept in a locked file cabinet in a locked office. Only the investigators and study staff will have access to this information.

Auditors and other authorized agents as well as that of any other applicable government agencies will be granted direct access to the study subjects' original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subjects, to the extent permitted by law and regulations. Any presentations of results from this study will only exhibit de-identified data.

9.6.2 Website and Database Security

Access to the web-based database is provided by password protected individual account only. There are no group or generic accounts. Permission for each account is granted on the basis of its user's role in the trial, and the web site itself is accessed via a secure connection. No personal identifiers (names, addresses, medical record numbers, etc.) are ever transmitted to the web-based database, and all participant data is accompanied only by the unique study ID.

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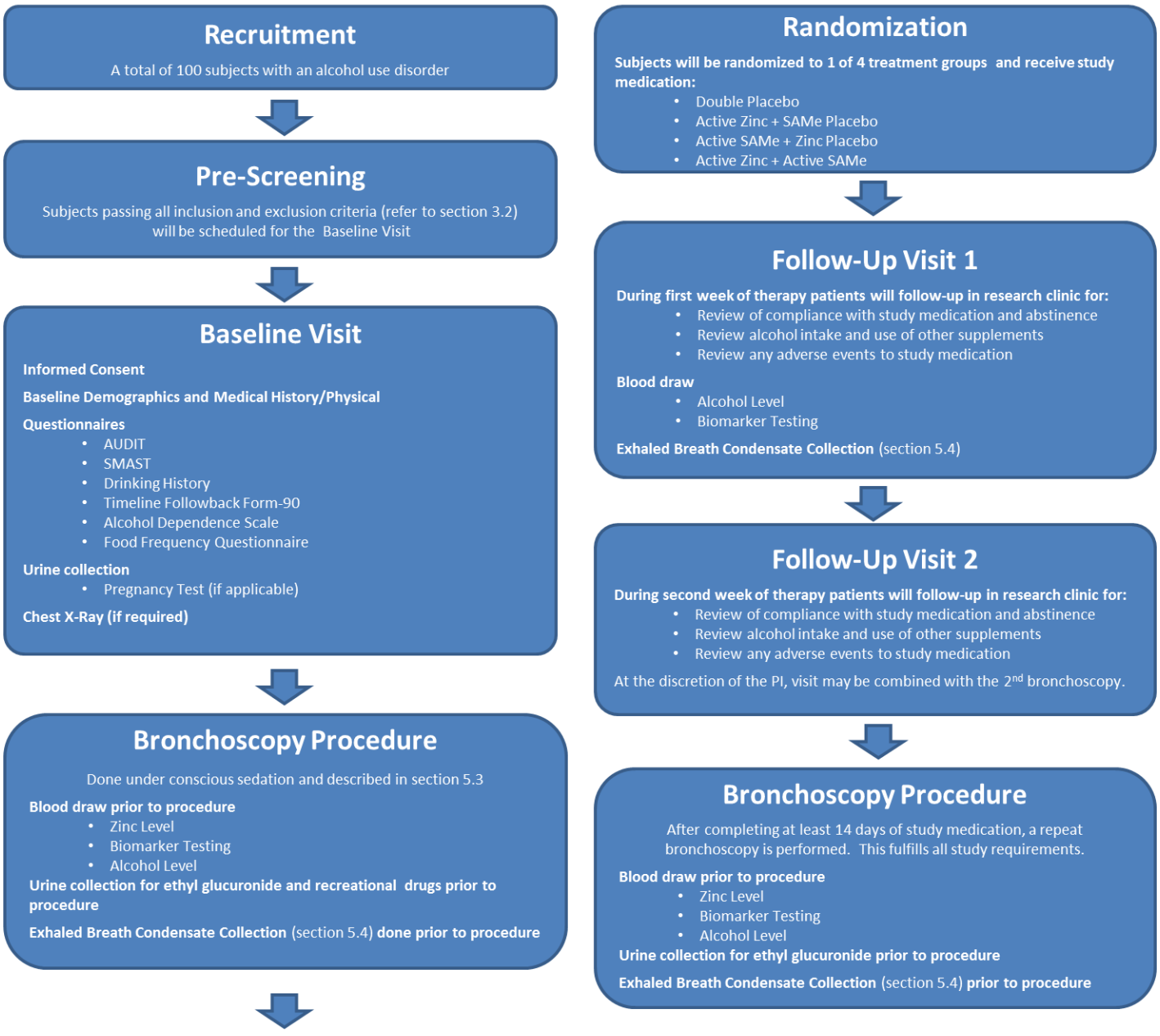
Appendix 1 – Schedule of Assessments



Appendix 2 – AUDIT Questionnaire

The Alcohol Use Disorders Identification Test: Interview Version

Read questions as written. Record answers carefully. Begin the AUDIT by saying "Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by "alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of "standard drinks". Place the correct answer number in the box at the right.

1. How often do you have a drink containing alcohol?

(0) Never [Skip to Qs 9-10]
(1) Monthly or less
(2) 2 to 4 times a month
(3) 2 to 3 times a week
(4) 4 or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

(0) 1 or 2
(1) 3 or 4
(2) 5 or 6
(3) 7, 8, or 9
(4) 10 or more

3. How often do you have six or more drinks on one occasion?

(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0

4. How often during the last year have you found that you were not able to stop drinking once you had started?

(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

5. How often during the last year have you failed to do what was normally expected from you because of drinking?

(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

7. How often during the last year have you had a feeling of guilt or remorse after drinking?

(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

9. Have you or someone else been injured as a result of your drinking?

(0) No
(2) Yes, but not in the last year
(4) Yes, during the last year

10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?

(0) No
(2) Yes, but not in the last year
(4) Yes, during the last year

Record total of specific items here

If total is greater than recommended cut-off, consult User's Manual.

Appendix 3 – SMAST Questionnaire

SHORT MICHIGAN ALCOHOL SCREENING TEST (SMAST)

NAME: _____ Date:_____

The following questions concern information about your involvement with alcohol during the past 12 months. Carefully read each countyment and decide if your answer is "YES" or "NO". Then, check the appropriate box beside the question.

Please answer every question. If you have difficulty with a countyment, then choose the respons that is mostly right.

These questions refer to the past 12 months only.	**YES**	**NO**
1. Do you feel that you are a normal drinker? (by normal we mean do you drink less than or as much as most other people.).....		
2. Does your wife, husband, a parent, or other near relative ever worry or complain about your drinking?.....		
3. Do you ever feel guilty about your drinking?.....		
4. Do friends or relatives think you are a normal drinker?.....		
5. Are you able to stop drinking when you want to?.....		
6. Have you ever attended a meeting of Alcoholics Anonymous (AA)?.....		
7. Has your drinking ever created problems between you and your wife, husband, a parent or other near relative?.....		
8. Have you ever gotten into trouble at work because of your drinking?.....		
9. Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking?.....		
10. Have you ever gone to anyone for help about your drinking?.....		
11. Have you ever been in a hospital because of drinking?.....		
12. Have you ever been arrested for drunken driving, driving while intoxicated, or driving under the influence of alcoholic beverages?.....		
13. Have you ever been arrested, even for a few hours, because of other drunken behaviors?.....		
*** SMAST Score**.....		

** See scoring instructions for correct scoring procedures.*

Appendix 4 – Drinking History Questionnaire

CURRENT DRINKING

1. How many alcohol beverages do you consume per day on average?

2. How long have you used at this rate (in years)? _____

3. If Male: In the past 12 months, how many times have you had 5 or more drinks in a day? _____

4. If Female: In the past 12 months, how many times have you had 4 or more drinks in a day? _____

5. In the past 12 months, what is the largest amount of alcohol that you have had in one day?
    a. Amount (in standard drinks, refer to chart):_____
    b. Over what time period (in hours):_____
    c. Type of beverage: _____
    d. Brand:_____

6. Beverage preferences

✓	Beverage List	Preferred Manner of Drinking	Method of Preparation	Brand(s)
	Beer or ale			
	Brandy			
	Gin			
	Hard Cider			
	Liqueurs (Cordials)			
	Malt Liquor			
	Rum			
	Sake			
	Sparkling Wine			
	Special Fortified Wine			
	Tequila			
	Vodka			
	Whiskey			
	Red, Dry Wine			
	Red, Sweet Wine			
	Rose Wine			
	White, Dry Wine			
	White, Sweet Wine			
	Wine Coolers			
	Other (specify):			
	Other (specify):			

PAST DRINKING

1. At what age did you first have 1 or more drinks of alcohol?_____

2. How old were you when you first became intoxicated:_____ ☐ Never intoxicated

3. If applicable: At what age did drinking begin to have an effect on your life, which you did not approve of? When did drinking first become a problem for you?

   Age when first problem:_____ ☐ Never a problem

4. Have you ever willingly quit drinking for a period longer than a few days? ☐ No ☐ Yes

5. How many past quit attempts have you had?_____ ☐ Not applicable, never attempted to quit

6. Have you ever been through alcohol treatment? ☐ No ☐ Yes

   If Yes, provide details:
   - ☐ Inpatient: _____year(s) of treatment
   - ☐ Outpatient: _____ year(s) of treatment
   - ☐ Alcoholics Anonymous (AA): _____ year(s) of treatment

Appendix 5 – Timeline Followback Form-90

Instructions:

- Think back over the past 90 days.
- Write down how many drinks you consumed each day on the calendar.
- Record the drinks you consumed **in terms of standard drinks**. This is important because different types of beverages contain different concentrations of alcohol. Refer to the *Standard Drink Chart* as necessary.
- Record a "0" for days when you did not drink any alcohol.
- Before you begin, please look at the SAMPLE CALENDAR on the next page.

Your Best Estimate:

We know it isn't easy to recall things with 100% accuracy. If you are not sure if you had 3 or 4 drinks on a given day, give it your best guess! Our goal is to get a sense of how frequently you drink alcohol, how much you drink, and your patterns of drinking.

Holidays such as Thanksgiving and Christmas are marked on the calendar to help you recall your drinking. Also, think about how much you consumed on personal holidays and events such as birthdays, vacations, or parties.

Sample calendar

July 2012						
S	M	T	W	T	F	S
1 2	2 1	3 0	4 Independence Day 2	5 2	6 4	7 2
8 2	9 2	10 2	11 2	12 2	13 2	14 2
15 2	16 1	17 1	18 0	19 0	20 3	21 3
22 2	23 0	24 0	25 1	26 3	27 2	28 0
29 2	30 0	31 2				

Appendix 6 – Alcohol Dependence Scale (ADS)

Instructions: Carefully read each question and the possible answers provided. Answer each question by circling the ONE choice that is most true of you. The word drinking in a question refers to "drinking alcoholic beverages." These questions refer to the past 12 months.

1. How much did you drink the last time you drank?
   a. Enough to get high or less
   b. Enough to get drunk
   c. Enough to pass out

2. Do you often have hangovers on Sunday or Monday mornings?
   a. No
   b. Yes

3. Have you had the shakes when sobering up (hands tremble, shake inside)?
   a. No
   b. Sometimes
   c. Often

4. Do you get physically sick (vomit, stomach cramps) as a result of drinking?
   a. No
   b. Sometimes
   c. Almost every time I drink

5. Have you had the "DTs" (delirium tremens) that is, seen, felt or heard things not really there; felt very anxious, restless, and over excited?
   a. No
   b. Sometimes
   c. Several times

6. When you drink, do you stumble about, stagger, and weave?
   a. No
   b. Sometimes
   c. Often

7. As a result of drinking, have you felt overly hot and sweaty (feverish)?
   a. No
   b. Once
   c. Several times

8. As a result of drinking, have you seen things that were not really there?
   a. No
   b. Once
   c. Several times

9. Do you panic because you fear you may not have a drink when you need it?
   a. No
   b. Yes

10. Have you had blackouts (loss of memory without passing out) as a result of drinking?
    a. No, never
    b. Sometimes
    c. Often
    d. Almost every time I drink

11. Do you carry a bottle with you or keep one close at hand?
    a. No
    b. Some of the time
    c. Most of the time

Alcohol Dependence Scale continued…

12. After a period of abstinence (not drinking), do you end up drinking heavily again?
    a. No
    b. Sometimes
    c. Almost every time I drink

13. In the past 12 months, have you passed out as a result of drinking?
    a. No
    b. Once
    c. More than once

14. Have you had a convulsion (fit) following a period of drinking?
    a. No
    b. Yes
    c. Several times

15. Do you drink throughout the day?
    a. No
    b. Yes

16. After drinking heavily, has your thinking been fuzzy or unclear?
    a. No
    b. Yes, but only for a few hours
    c. Yes, for one or two days
    d. Yes, for many days

17. As a result of drinking, have you felt your heart beating rapidly?
    a. No
    b. Yes
    c. Several times

18. Do you almost constantly think about drinking and alcohol?
    a. No
    b. Yes

19. As a result of drinking, have you heard "things" that were not really there?
    a. No
    b. Yes
    c. Several times

20. Have you had weird and frightening sensations when drinking?
    a. No
    b. Once or twice
    c. Often

21. As a result of drinking have you "felt things" crawling on you that were not really there (bugs, spiders, etc.)?
    a. No
    b. Yes
    c. Several times

22. With respect to blackouts (loss of memory):
    a. Have never had a blackout
    b. Have had blackouts that last less than an hour
    c. Have had blackouts that last for several hours
    d. Have had blackouts that last a day or more

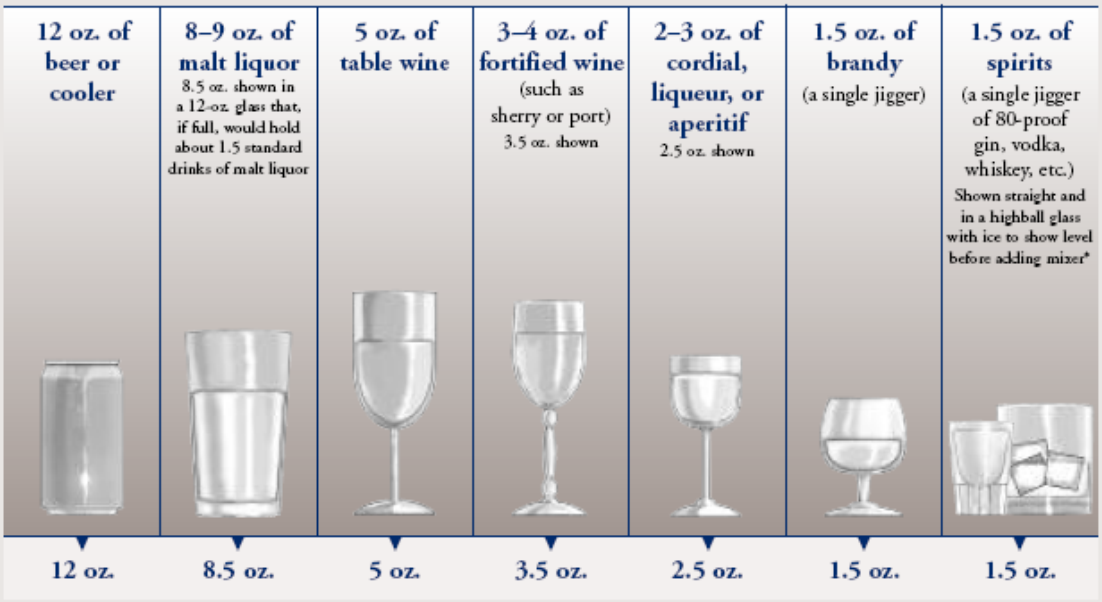
23. Have you tried to cut down on your drinking and failed?
    a. No
    b. Once or twice
    c. Often

24. Do you gulp drinks (drink quickly)?
    a. No
    b. Yes

25. After taking 1 or 2 drinks, can you usually stop?
    a. No
    b. Yes

Appendix 7 – Standard Drink Chart

A standard drink is any drink that contains about 14 grams of pure alcohol (about 0.6 fluid ounces or 1.2 tablespoons). Below are standard drink equivalents. These are approximate, as different brands and types of beverages vary in their actual alcohol content.



Many people do not know what counts as a standard drink, and thus are unaware of how many standard drinks are held in the containers in which these drinks are often sold. Some examples:

- For **beer**, the approximate number of standard drinks in
  - 12 oz. = 1
  - 16 oz. = 1.3
  - 22 oz. = 2
  - 40 oz. = 3.3
- For **malt liquor**, the approximate number of standard drinks in
  - 12 oz. = 1.5
  - 16 oz. = 2
  - 22 oz. = 2.5
  - 40 oz. = 4.5
- For **table wine**, the approximate number of standard drinks in
  - a standard 750 mL (25 oz.) bottle = 5
- For **80-proof spirits**, or "hard liquor," the approximate number of standard drinks in
  - a mixed drink = 1 or more*
  - a pint (16 oz.) = 11
  - a fifth (25 oz.) = 17
  - 1.75 L (59 oz.) = 39

**Note:* It can be difficult to estimate the number of standard drinks served in a single mixed drink made with hard liquor. Depending on factors such as the type of spirits and the recipe, one mixed drink can contain from one to three or more standard drinks.

Appendix 8 – Food Frequency Questionnaire

Food Questionnaire

This form asks about your usual food intake during _____.

Please use **pencil.**

Answer by filling in the correct oval.

● Yes ○ No

Do not make any other marks on the form. Please use a separate piece of paper to make comments.

SEX
○ Male
○ Female

TODAY'S DATE

MO	DAY	YEAR

GNA

PLEASE DO NOT WRITE IN THIS AREA

Part I: Usual Food Choices

These questions are about the types of foods you ate during _____.

1. Did you eat chicken or turkey?

○ Yes → **When you ate chicken or turkey, how often did you eat the skin?**
○ No
- ○ Almost always
- ○ Often
- ○ Sometimes
- ○ Rarely
- ○ Never

2. Did you eat beef, pork, ham or lamb?

○ Yes → **When you ate beef, pork, ham or lamb, how often did you eat the fat?**
○ No
- ○ Almost always
- ○ Often
- ○ Sometimes
- ○ Rarely
- ○ Never

3. Did you eat hamburger or other ground meat?

○ Yes → **When you ate hamburger or other ground meat, was it usually...** *Mark one or two.*
○ No
- ○ Regular
- ○ Lean
- ○ Extra lean
- ○ Ground chicken or turkey
- ○ Don't know

4. Did you drink orange, grapefruit or other fruit juices?

○ Yes → **Were any of these vitamins or minerals added (specially fortified) to the juices you drank?** *Mark all that apply.*
○ No
- ○ Extra Vitamin C
- ○ Vitamin E
- ○ Calcium
- ○ None
- ○ Don't know

5. Did you eat cold cereals?

○ Yes → **When you ate cold cereal, what type did you usually eat?** *Mark one or two.*
○ No
- ○ Highly fortified cereals (100% of Daily Values) such as Total®, Smart Start® and Product 19®
- ○ High fiber or bran cereals such as Raisin Bran® and All Bran®
- ○ Sweetened cereals such as Frosted Flakes® and Froot Loops®
- ○ All other cereals such as Cheerios®, Corn Flakes® and granola

6. Did you put milk (all types), cream or creamer on cereal?

○ Yes → **When you put milk, cream or creamer on cereal, what type did you usually use?** *Mark one or two.*
○ No
- ○ Cream or half and half
- ○ Whole milk
- ○ 2% milk
- ○ 1% milk or buttermilk
- ○ Nonfat or skim milk
- ○ Soy milk
- ○ Non-dairy creamer
- ○ Don't know

Part II: Usual Food Use

These questions are about foods you ate during _____.

14. Mark the column to show how often, on average, you ate the following foods. Mark your usual serving size as small, medium or large.

- A small serving is about one-half (½) the medium serving size or less.
- A large serving is about one-and-a-half (1½) times the medium serving size or more.

EXAMPLE: This person ate spaghetti with meat sauce every Saturday. They usually ate about 1½ cups.

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Spaghetti, lasagna, and other pasta with tomato and meat sauce	○	○	○	●	○	○	○	○	○	1 cup	○	○	●

CEREALS, BREADS, SNACKS

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Cold cereals	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Cooked cereals and grits	○	○	○	○	○	○	○	○	○	1cup	○	○	○
Milk on cereals	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Pancakes, French toast and waffles	○	○	○	○	○	○	○	○	○	2 pieces	○	○	○
Muffins, scones, croissants and biscuits	○	○	○	○	○	○	○	○	○	1 medium	○	○	○
White breads, including bagels, rolls and English muffins	○	○	○	○	○	○	○	○	○	2 slices or 1 medium	○	○	○
Whole grain breads and rolls	○	○	○	○	○	○	○	○	○	2 slices or 1 medium	○	○	○
Plain tortillas as a side dish (include flour and corn)	○	○	○	○	○	○	○	○	○	2 small or 1 medium	○	○	○
Cornbread and corn muffins	○	○	○	○	○	○	○	○	○	2 slices or 1 medium	○	○	○
Butter or margarine on breads, cereals, pancakes, etc.	○	○	○	○	○	○	○	○	○	2 pats or 2 teaspoons	○	○	○
Jam, jelly, honey, syrup and sugar (including in coffee, tea and cereal)	○	○	○	○	○	○	○	○	○	2 Tbsp.	○	○	○
Granola bars and cereal bars such as Nutri-Grain Bars®	○	○	○	○	○	○	○	○	○	1 bar	○	○	○
Sports or meal replacement bars such as Power Bars® and Clif Bars®	○	○	○	○	○	○	○	○	○	1 bar	○	○	○

SAUCES and CONDIMENTS

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Cheese sauce and cream sauce	○	○	○	○	○	○	○	○	○	¼ cup	○	○	○
Meat gravies	○	○	○	○	○	○	○	○	○	¼ cup	○	○	○
Ketchup	○	○	○	○	○	○	○	○	○	2 Tbsp.	○	○	○
Salsa (as dip or on foods)	○	○	○	○	○	○	○	○	○	¼ cup	○	○	○
Mayonnaise and mayonnaise-type spreads	○	○	○	○	○	○	○	○	○	2 Tbsp.	○	○	○

FRUITS

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Apples, applesauce and pears	○	○	○	○	○	○	○	○	○	1 medium or ½ cup	○	○	○
Bananas	○	○	○	○	○	○	○	○	○	1 medium	○	○	○
Peaches, nectarines and plums	○	○	○	○	○	○	○	○	○	1 medium or ½ cup	○	○	○
Apricots (fresh, canned or dried)	○	○	○	○	○	○	○	○	○	2 medium or 4 halves	○	○	○
Dried fruit (other than apricots) such as raisins and prunes	○	○	○	○	○	○	○	○	○	¼ cup	○	○	○
Oranges, grapefruit and tangerines (not juice)	○	○	○	○	○	○	○	○	○	1 orange or ½ grapefruit	○	○	○
Berries such as strawberries and blueberries	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Cantaloupe, orange melon and mango	○	○	○	○	○	○	○	○	○	¼ melon or ½ mango	○	○	○
Watermelon and red melon	○	○	○	○	○	○	○	○	○	1 medium slice	○	○	○
Any other fruit such as grapes, fruit cocktail, pineapple and cherries	○	○	○	○	○	○	○	○	○	½ cup	○	○	○

VEGETABLES and GRAINS (continued)

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Mark all vegetables you ate, including in salads, mixed dishes, sandwiches and stir-fries.													
Broccoli	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Cauliflower, cabbage and Brussels sprouts	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Green or string beans	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Green peas	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Corn and hominy	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Summer squash and zucchini	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Winter squash such as acorn, butternut and pumpkin	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Yams and sweet potatoes	○	○	○	○	○	○	○	○	○	1 medium	○	○	○
Cooked greens such as spinach, mustard greens and collards	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Onions and leeks	○	○	○	○	○	○	○	○	○	¼ cup	○	○	○
Fresh garlic, including in cooking	○	○	○	○	○	○	○	○	○	1 clove	○	○	○
Avocado and guacamole	○	○	○	○	○	○	○	○	○	¼ medium or ¼ cup	○	○	○
French fries, fried potatoes and hash browns	○	○	○	○	○	○	○	○	○	¾ cup	○	○	○
Potatoes (boiled, baked or mashed)	○	○	○	○	○	○	○	○	○	1 medium or ¾ cup	○	○	○
Refried beans	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
All other beans (baked, lima or chili without meat)	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Coleslaw	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Potato, macaroni and pasta salads made with mayonnaise or oil	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Brown rice, whole wheat pasta and other whole grains (as a side dish)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
White rice, noodles and other grains (as a side dish)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Butter, margarine, sour cream and other fat added to vegetables, potatoes and rice	○	○	○	○	○	○	○	○	○	1 pat or 1 teaspoon	○	○	○

PLEASE DO NOT WRITE IN THIS AREA

CEREALS, BREADS, SNACKS (continued)

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Low or nonfat potato chips, tortilla chips, corn chips and pretzels	○	○	○	○	○	○	○	○	○	2 handfuls or 1 sm. bag	○	○	○
Regular potato chips, tortilla chips, corn chips and puffs	○	○	○	○	○	○	○	○	○	2 handfuls or 1 sm. bag	○	○	○
Plain popcorn (no butter) or lowfat microwave popcorn	○	○	○	○	○	○	○	○	○	4 handfuls	○	○	○
Buttered or regular microwave popcorn	○	○	○	○	○	○	○	○	○	4 handfuls	○	○	○
Low or nonfat crackers such as saltines	○	○	○	○	○	○	○	○	○	6 medium	○	○	○
Whole grain crackers such as Triscuits® and rye crispbread	○	○	○	○	○	○	○	○	○	6 medium	○	○	○
Regular crackers such as Ritz® and club crackers	○	○	○	○	○	○	○	○	○	6 medium	○	○	○
Peanut butter, peanuts and other nuts and seeds	○	○	○	○	○	○	○	○	○	2 Tbsp. (spreads) or ¼ cup (nuts)	○	○	○

MEAT, FISH, EGGS

	HOW OFTEN DID YOU EAT THESE FOODS?									→	AMOUNT?		
	NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	Medium serving size	S	M	L
Eggs (egg substitute, mark "NEVER")	○	○	○	○	○	○	○	○	○	2 eggs	○	○	○
Bacon and breakfast sausage	○	○	○	○	○	○	○	○	○	3 strips or 2 links	○	○	○
Low or reduced fat hot dogs and sausage	○	○	○	○	○	○	○	○	○	1 hot dog or 2 ounces	○	○	○
Regular hot dogs and sausage such as bratwurst and chorizo	○	○	○	○	○	○	○	○	○	1 hot dog or 2 ounces	○	○	○
Lunch meats such as ham, turkey and lowfat bologna	○	○	○	○	○	○	○	○	○	2 slices	○	○	○
All other lunch meat such as bologna, salami and Spam®	○	○	○	○	○	○	○	○	○	2 slices	○	○	○
Canned tuna, tuna salad and tuna casserole	○	○	○	○	○	○	○	○	○	½ can tuna or 1 cup casserole	○	○	○
Beef, pork, ham and lamb	○	○	○	○	○	○	○	○	○	4 ounces	○	○	○
Ground meat, including hamburgers and meatloaf	○	○	○	○	○	○	○	○	○	1 medium patty or 3 ounces	○	○	○
Liver, chicken liver and organ meats	○	○	○	○	○	○	○	○	○	4 ounces	○	○	○
Fried chicken, including nuggets and tenders	○	○	○	○	○	○	○	○	○	1 large piece or 6 nuggets	○	○	○

PLEASE DO NOT WRITE IN THIS AREA

MEAT, FISH, EGGS (continued)

	HOW OFTEN DID YOU EAT THESE FOODS? NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	→ Medium serving size	AMOUNT? S	M	L
Chicken and turkey (roasted, stewed, grilled or broiled)	○	○	○	○	○	○	○	○	○	1 large or 2 small pieces	○	○	○
Fried fish, fish sandwich and fried shellfish (shrimp and oysters)	○	○	○	○	○	○	○	○	○	3 ounces or 1 sandwich	○	○	○
Shellfish, not fried (shrimp, lobster, crab and oysters)	○	○	○	○	○	○	○	○	○	3 ounces or ½ cup	○	○	○
White fish (broiled or baked) such as sole, halibut, snapper and cod	○	○	○	○	○	○	○	○	○	4 ounces	○	○	○
Dark fish (broiled or baked) such as salmon, mackerel and bluefish	○	○	○	○	○	○	○	○	○	4 ounces	○	○	○

SPAGHETTI, MIXED DISHES, SOUPS

	HOW OFTEN DID YOU EAT THESE FOODS? NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	→ Medium serving size	AMOUNT? S	M	L
Stew, pot pie, curries and casseroles with meat or chicken	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Chili with meat and beans	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Spaghetti, lasagna and other pasta with tomato and meat sauce	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Spaghetti and other pasta with tomato sauce (no meat)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Pasta with oil, cheese, or cream sauce, including macaroni and cheese	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Asian-style (stir-fried) noodles and rice such as chow mein, fried rice and Pad Thai	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Pizza	○	○	○	○	○	○	○	○	○	2 slices	○	○	○
Tofu, tempeh and products such as tofu hot dogs, soy burgers and tofu cheese	○	○	○	○	○	○	○	○	○	3 ounces, 1 hot dog or 1 burger	○	○	○
Burritos, tacos, tostadas and quesadillas	○	○	○	○	○	○	○	○	○	1 medium	○	○	○
Enchiladas and tamales	○	○	○	○	○	○	○	○	○	1 medium	○	○	○
Vegetable, minestrone and tomato soup	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Cream soups such as chowders, potato and cheese	○	○	○	○	○	○	○	○	○	1 cup	○	○	○

SWEETS

	HOW OFTEN DID YOU EAT THESE FOODS? NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	→ Medium serving size	AMOUNT? S	M	L
Low or nonfat frozen desserts such as lowfat ice cream, frozen yogurt and sherbet	○	○	○	○	○	○	○	○	○	1 scoop	○	○	○
Ice cream and milkshakes	○	○	○	○	○	○	○	○	○	1 scoop or 1 shake	○	○	○
Pudding, custard and flan	○	○	○	○	○	○	○	○	○	¾ cup	○	○	○
Doughnuts, pies and pastries	○	○	○	○	○	○	○	○	○	1 medium piece or slice	○	○	○
Cookies and cakes	○	○	○	○	○	○	○	○	○	2 med. cookies or 1 piece of cake	○	○	○
Chocolate, candy bars and toffee	○	○	○	○	○	○	○	○	○	1 regular bar or 2 pieces	○	○	○
Other candy such as Lifesavers®, licorice and jelly beans	○	○	○	○	○	○	○	○	○	4 pieces or 12 jellybeans	○	○	○

PLEASE ANSWER THESE THREE IMPORTANT QUESTIONS!

	NEVER or less than once per week	1-2 per week	3-4 per week	5-6 per week	1 per day	2 per day	3 per day	4 per day	5+ per day
Note that the frequency headings are different.									
How often did you eat foods that were cooked in fat (pan-fried, sautéed, or deep-fried)? *Count all fat such as margarine, butter, oil or lard.*	○	○	○	○	○	○	○	○	○
How often did you eat a serving of vegetables? *Do not count potatoes, salad or beans.*	○	○	○	○	○	○	○	○	○
How often did you eat a serving of fruit? *Do not count juices.*	○	○	○	○	○	○	○	○	○

SPAGHETTI, MIXED DISHES, SOUPS (continued)

	HOW OFTEN DID YOU EAT THESE FOODS? NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	→ Medium serving size	AMOUNT? S	M	L
Bean soups such as pea, lentil and black bean	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Miso soup	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Ramen noodle soup	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Other soups such as chicken noodle	○	○	○	○	○	○	○	○	○	1 cup	○	○	○

DAIRY PRODUCTS

	HOW OFTEN DID YOU EAT THESE FOODS? NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	→ Medium serving size	AMOUNT? S	M	L
Cottage cheese and ricotta cheese	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Low or reduced fat cheese, including cheese used in cooking	○	○	○	○	○	○	○	○	○	1 slice or ¼ cup shredded	○	○	○
All other cheese (American, cheddar or cream), including cheese used in cooking	○	○	○	○	○	○	○	○	○	1 slice, ¼ cup shredded or 2 Tbsp. cream	○	○	○
Yogurt, all types except frozen	○	○	○	○	○	○	○	○	○	6 ounces	○	○	○

VEGETABLES and GRAINS

	HOW OFTEN DID YOU EAT THESE FOODS? NEVER or less than once per month	1 per month	2-3 per month	1 per week	2 per week	3-4 per week	5-6 per week	1 per day	2+ per day	→ Medium serving size	AMOUNT? S	M	L
Mark all vegetables you ate, including in salads, mixed dishes, sandwiches and stir-fries.													
Green salad (lettuce or spinach)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Salad dressing (all types)	○	○	○	○	○	○	○	○	○	2 Tbsp.	○	○	○
Fresh tomatoes	○	○	○	○	○	○	○	○	○	1 medium or 4 slices	○	○	○
Carrots	○	○	○	○	○	○	○	○	○	½ cup	○	○	○
Green peppers and green chilies	○	○	○	○	○	○	○	○	○	¼ cup	○	○	○
Red peppers and red chilies	○	○	○	○	○	○	○	○	○	¼ cup	○	○	○

BEVERAGES and ALCOHOL

	HOW OFTEN DID YOU DRINK THESE BEVERAGES? NEVER or less than once per month	1-3 per month	1 per week	2-4 per week	5-6 per week	1 per day	2-3 per day	4-5 per day	6+ per day	→ Medium serving size	AMOUNT? S	M	L
Note that the frequency headings are different.													
Milk (all types) as a beverage	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Latte, cappuccino, mocha or hot chocolate	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Coffee (not lattes or mochas)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Tea, unsweetened or diet	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Tea, presweetened, bottled or instant	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Milk, cream or creamer added to tea and coffee	○	○	○	○	○	○	○	○	○	1 Tbsp.	○	○	○
Tomato juice, V-8® and other vegetable juices	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Orange juice and grapefruit juice	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Other 100% fruit juice such as apple, grape and cranberry	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Fruit drinks fortified with Vitamin C such as Hi-C®, and Kool-Aid®	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Meal replacement drinks and shakes such as Slim-Fast® and Ensure®	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Diet soft drinks (include energy drinks)	○	○	○	○	○	○	○	○	○	12 ounces or 1 can	○	○	○
Regular soft drinks (include energy drinks)	○	○	○	○	○	○	○	○	○	12 ounces or 1 can	○	○	○
Water (tap, bottled or sparkling)	○	○	○	○	○	○	○	○	○	1 cup	○	○	○
Beer (all types)	○	○	○	○	○	○	○	○	○	12 ounce can or bottle	○	○	○
Red wine	○	○	○	○	○	○	○	○	○	1 medium glass (6 oz)	○	○	○
White or rosé wine	○	○	○	○	○	○	○	○	○	1 medium glass (6 oz)	○	○	○
Liquor and mixed drinks	○	○	○	○	○	○	○	○	○	1 shot (1½ oz) or 1 mixed drink	○	○	○

THANK YOU!

Please take a moment to fill in any questions you may have skipped.