# Michigan Alcohol Improvement Network- Alcohol Reduction and Treatment (MAIN-ART) Trial

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# Michigan Alcohol Improvement Network- Alcohol Reduction and Treatment (MAIN-ART) Trial

## National Clinical Trial Number: (*TBD)*

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## Supported by:

National Institute of Alcohol Abuse and Alcoholism: K23026333

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## Amendments

| Date | Version | Section(s) | Changes |
|---|---|---|---|
| 4-2-2019 | 2 | 3.5, 5.1 | Subjects will be recruited in person and over the phone. Subjects who are recruited via phone will complete all assessments online/via phone.<br><br>Subjects will receive a $30.00 gift card for completing baseline and 3 months follow up and $40.00 for completing the 6 months follow up. |
| 6-10-2020 | 3 | 2,3,4 | Change primary outcome to feasibility and acceptability. Moved alcohol treatment engagement to a secondary outcome. Added criteria for feasibility, based on recruitment and retention, and acceptability, based on survey questions. |
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**PROTOCOL SUMMARY**

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|---|---|
| **Title:** | *Michigan Alcohol Improvement Network- Alcohol Reduction and Treatment Tool (MAIN-ART) study* |
| **Study Description:** | *This study aims to perform a randomized pilot test of an online web application designed to increase engagement in alcohol use disorder (AUD) treatment for alcohol-associated liver disease (ALD) patients. This study builds on existing research indicating that ALD patients are motivated by their liver health to stop drinking but frequently struggle to do so and have low rates of AUD treatment engagement. This study will enhance our knowledge of how correction of AUD misconceptions and a tailored, preference-sensitive AUD treatment matching approach may increase treatment engagement and potentially improve alcohol cessation.* |
| **Outcomes:** | *The primary goal of this trial is to examine the initial feasibility and acceptability of the behavioral intervention compared to treatment-as-usual. The primary outcome is feasibility and acceptibility and the secondary outcomes are alcohol treatment engagemtn and alcohol reduction. Our exploratory outcomes are to determine if misconception correction improved willingness for AUD treatment and to determine if tailoring treatment to patient preferences influenced the decision to engage in treatment. This trial is under-powered to detect statistically significant differences in outcomes.*<br><br>*Hypothesis: The MAIN-ART behavioral intervention will be both feasible and acceptable to patients.* |
| **Intervention Information:** | *The MAIN-ART behavioral intervention is an online web application with two modules: misconception correction and tailored, preference-sensitive AUD treatment matching. The intervention will be administered on a laptop or tablet to recruited outpatients with ALD. The intervention takes approximately 10-15 minutes. Recruited subjects will be followed up at 3- and 6-month intervals to assess for AUD treatment engagement as well as alcohol reduction.* |
| **Study Population:** | *The study population will be approximately 60 ALD patients recruited from Michigan Medicine hepatology clinics. Patients will be 18 years old or older, any gender or race/ethnicity, and diagnosed with advanced ALD (cirrhosis or alcoholic hepatitis).* |
| **Locations:** | *University of Michigan health system (Michigan Medicine) in Ann Arbor, MI* |
| **Estimated Study Start Date:** | *March 1st, 2020.* |
| **Study Duration:** | *Two years.* |

## 1 BACKGROUND & RATIONALE

### 1.1 Background

Alcoholic liver disease (ALD) causes nearly *half* the liver-related deaths in the US, and with recent increases in alcohol use disorders, ALD-related deaths are expected to increase(1-3). Unfortunately, medical treatments to arrest liver dysfunction in ALD are of limited efficacy(4, 5). Cessation of alcohol use, by contrast, is the only factor proven to curb long-term mortality, even in the most advanced stages of ALD(6, 7). However, many patients, in spite of severe liver disease, never cease alcohol use. While clinical interventions have focused on improving liver function, behavioral interventions to stop alcohol use have not been a large focus of hepatology research, despite the fact that alcohol cessation prevents ALD patients from dying. Motivational interviewing may have benefit, but alone may not be enough to stop these complex patients from continued drinking, even after experiencing severe negative consequences. ALD patients are frequently motivated to stop drinking after a diagnosis of liver disease, but only 10% will access AUD treatment at 1 year after their initial diagnosis(8-10). Patient preferences for alcohol use treatment are varied(8), but preference-sensitive treatment matching has not been tested in this population as a means of increasing AUD treatment engagement and improving rates of alcohol reduction or cessation.

### 1.2 Study Rationale

ALD patients frequently struggle to engage in AUD treatment, despite the fact that treatment improves clinical liver outcomes through increased alcohol cessation. Attitudinal barriers have been shown to be major barriers to engagement in AUD treatment in ALD patients(8). To correct these barriers, we propose to pilot test an online behavioral intervention tool, the Michigan Alcohol Improvement Network-Alcohol Reduction and Treatment (MAIN-ART) web application, in a population of recently drinking patients with alcohol-related cirrhosis or alcoholic hepatitis. We hypothesize that the intervention will be effective in increasing alcohol treatment engagement via two mechanisms: 1) finding and correcting errors in how patients view the risks of alcohol use, liver disease, and alcohol relapse and 2) tailoring recommendations for alcohol use treatment to patient preferences. Our primary outcome is alcohol use treatment engagement. Secondary outcomes are alcohol use reduction.

## 2 OUTCOMES

### 2.1 Primary Outcome

The primary goal of this trial is to determine feasibility and acceptability of the MAIN-ART web-application. Feasibility will be determined by recruitment and retention rates. Acceptability will be determined based on survey questions administered following administration of the intervention.

### 2.2 Secondary Outcomes

The secondary outcomes of this trial are: 1) alcohol treatment engagement. Alcohol treatment engagement will be defined as at least one visit with formal, external assistance in alcohol cessation or reduction. This would include at least one session of either in person or telehealth treatment with an addiction treatment professional (either inpatient or outpatient), in person or telehealth attendance to at least 1 session of a community-based support group for alcohol cessation (such as Alcoholics Anonymous, SMART Recovery, Refuge Recovery, faith-based support group via religious organization, for example), one-on-one or group counseling with an addiction treatment professional, counseling with a religious leader (such as a pastor or priest)

to address alcohol use)), etc.. 2) alcohol reduction or maintenance of abstinence. Alcohol reduction is defined as either a 1- or 2-level reduction in alcohol use as detailed in the World Health Organization risk drinking levels (11, 12). Alcohol use will be measured using the Timeline Followback method (13).

### 2.3 Other Pre-Specified Outcomes

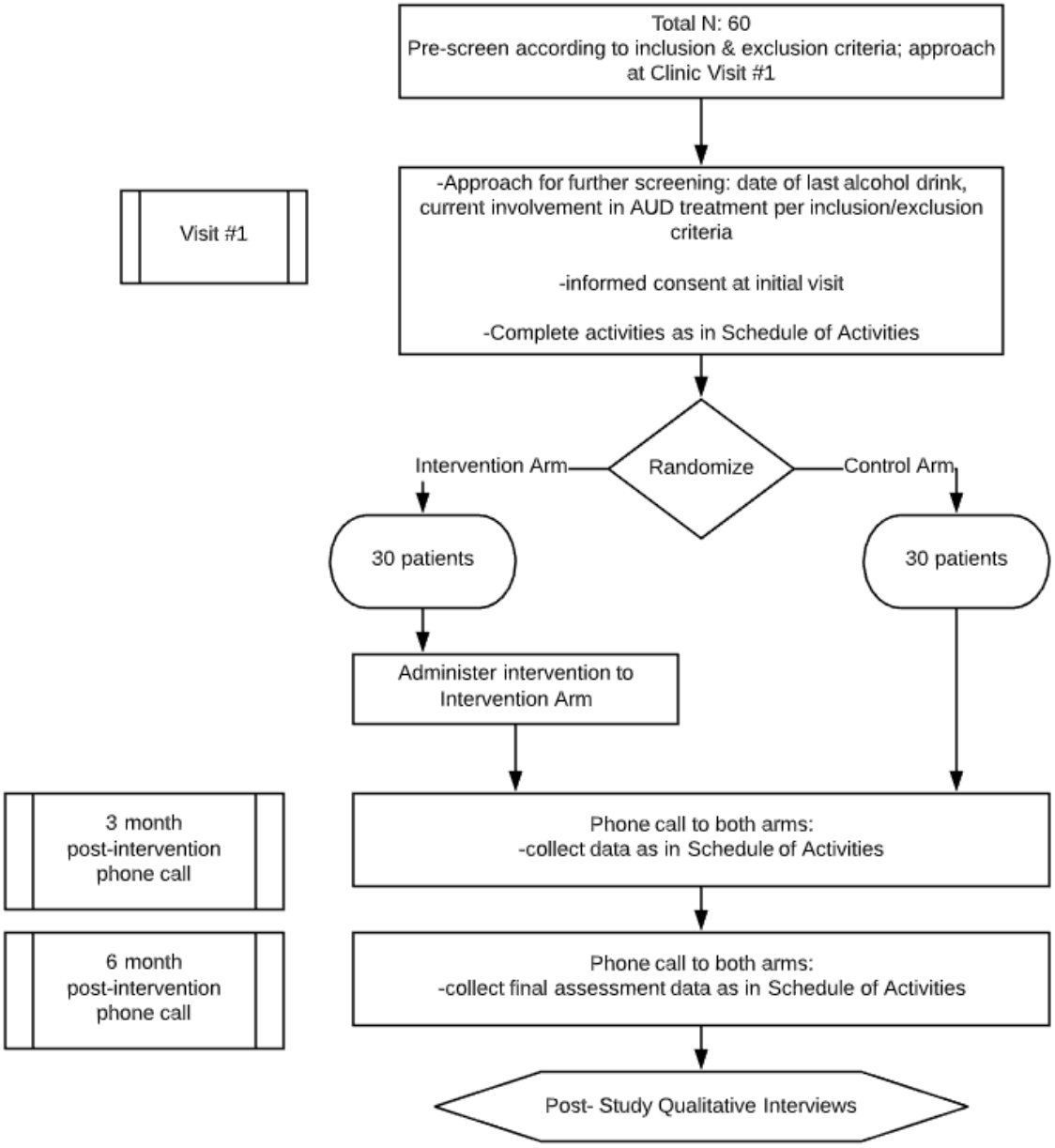
All other outcome measures will be exploratory.

## 3 STUDY DESIGN

### 3.1 Study Design

The study is a randomized clinical pilot trial that assesses preliminary feasibility and acceptability of a web-based application for alcohol misconception correction and tailored, preference-sensitive alcohol treatment engagement compared to usual care and evaluates intervention feasibility, fidelity, appropriateness, and acceptability. Study subjects will be outpatients at the University of Michigan Health System hepatology clinics and fulfill the study's inclusion criteria (see Section 4.1 below). Subjects will be randomized to one of two conditions: MAIN-ART Alcohol Treatment Engagement Tool or Usual Care (See Section 5 below).

## 3.2 Study flow



### 3.3 Inclusion Criteria

Subjects will be enrolled if they meet the following criteria:

- Stated willingness to comply with all study procedures and availability for the duration of the study
- Age 18 years or older
- Enrolled at University of Michigan general hepatology clinics
- Documented diagnosis of alcohol-associated cirrhosis or alcoholic hepatitis defined as follows:
    - *Alcoholic cirrhosis* is defined as evidence of cirrhosis based on 1 of the following 4 criteria:
        a. Positive liver biopsy
        b. Fibroscan score >12.5 KPa [in patients with ALT<100, no evidence of alcoholic hepatitis, no congestive heart failure, and no significant ascites at the time of Fibroscan measurement
        c. Evidence of nodular liver or portal hypertension on abdominal imaging;
        d. Presence of portal hypertension complications (hepatic encephalopathy, ascites, or varices or variceal bleeding) **and**
        e. History by chart review of prior or current heavy alcohol use or alcohol use disorder.
    - *Alcoholic hepatitis* is defined by either
        a. Liver biopsy
        b. Clinical criteria (any of the following: total bilirubin >=5.0 mg/dL, elevated AST (>2x ULN) and ALT levels in a 2:1 ratio with AST <=500 and ALT <=300; elevated International Normalized Ratio (INR)) **and** recent heavy alcohol use **and** the absence of any other cause of liver disease.
- Recent alcohol use of any amount within the past 6 months as assessed by either patient interview, medical chart review, or positive alcohol biomarker in the medical record.
- No alcohol use treatment within the past 1 month including, but not limited to:
    a. Professional mental health counselor led one-on-one therapy, group therapy, couples or family therapy with a primary aim of alcohol abstinence or reduction in alcohol use
    b. Community-based alcohol recovery groups (Alcoholics Anonymous, SMART Recovery, Celebrate Recovery, Refuge Recovery)
    c. Community-based church support groups primarily focused on alcohol abstinence or reduction in use
    d. Residential (inpatient) alcohol treatment
    e. Intensive outpatient programs
    f. Alcohol relapse prevention medications (disulfiram, acamprosate, naltrexone *or* prescriptions for non-FDA approved relapse prevention medications including gabapentin, topiramate, or baclofen when use of these medications is primarily for prevention of alcohol relapse)
    g. Any telehealth version of the above options
- Access to a phone for purposes of follow-up
- Life expectancy greater than 1 month
- Ability to speak and comprehend English

*Compensated cirrhosis* patients will be defined as those patients with a diagnosis of alcoholic cirrhosis who do not now and have not ever had have any decompensating signs of cirrhosis, defined as ascites, variceal bleeding, hepatic encephalopathy, or jaundice. *Decompensated cirrhosis* patients will be defined as those who have a diagnosis of alcoholic cirrhosis OR alcoholic hepatitis who either currently or previously have had ascites, jaundice, variceal bleeding, or hepatic encephalopathy, as determined by chart review.

### 3.4 Exclusion Criteria

- Unable to provide voluntary informed consent for any reason (including incompetency);
- Substantially cognitively impaired as evidenced by lack of orientation to person, place, or time or lack of ability to repeat back and answer screening questions
- Unable to read or understand English
- Active alcohol use treatment as defined in Section 3.3.
- Undergoing active evaluation for liver transplantation, is listed for liver transplant, or is post-transplantation.
- Is enrolled in the multidisciplinary alcohol-related liver disease clinic at Michigan Medicine
- Any other medical condition or circumstance that precludes safe and meaningful participation in the study
- Lack of telephone access

### 3.5 Recruitment

Participants (n=60) will be recruited in-person or via phone from Michigan Medicine Hepatology Clinics. We will seek a waiver of informed consent to identify potentially eligible patients from the medical chart. This waiver will only apply to the initial medical pre-screen for eligibility criteria. Recruitment letters or emails will be sent to identified patients explaining the study briefly and indicating that we will contact them for further recruitment. When the screening survey is administered and patients are determined eligible for enrollment, patients will be asked to read the consent for screening on the tablet or the consent will be emailed to them for their review. The study team will then review the consent over the phone, ask the participants if there are any questions, and answer any questions prior to administering the intervention remotely.

Research staff will be given tablets or laptops to complete the screening process via electronic data capture. Patients who are recruited remotely will use their own tablet, laptop, or smartphone to complete the study questions and intervention. Paper study screening questionnaires will be used as backup, if needed, and may be distributed by research or clinic staff. The screening assessment will determine patient eligibility to participate in the randomized control trial. The participant will be assigned a random screen ID number. If the participant is eligible and is interested in participating, we conduct the consent process at that time.

All patients approached will be tracked in the study database. To ensure generalizable recruitment, demographic and clinical information on severity of liver disease and other medical comorbidities will be retained for all subjects eligible to determine factors influencing enrollment. Identifiable information will only be retained for patients that enroll in the study. We will save only medical record numbers (MRNs) and names for all patients to ensure we do not attempt to recruit them more than once (e.g. if an eligible patient declines enrollment but returns to clinic at a later date and enters our recruitment list again, MRN cross check will allow us to ensure we don't contact them again). Recruitment outcomes,

including reasons for refusal or ineligibility will also be tracked in the study database to document eligibility, refusals and those the research assistant is unable to reach.

### 3.6 Enrollment

When the screening survey is administered and patients are determined eligible for and interested in enrollment, patients will be asked to read the consent for screening on the tablet or have consent read to them over the phone and emailed to them for review. Following screening, staff will document the outcome of screening, including: eligible, ineligible, refused, reason for refusal etc. Participants who meet study eligibility criteria and have not met any of the exclusion criteria, will be given the option to participate in the study. Eligible participants who complete the informed consent will review it with the study research assistant and be given time to read the consent and ask any questions. Reasons for refusal will be documented. Completion of informed consent will be documented and tracked in the study database. Paper informed consent documents will be stored in locked files. Each participant will be a given unique patient identifier (separate from the screening identifier)

### 3.7 Withdrawal

If subjects withdraw or decline to finish treatment, we will make every effort to gather primary outcome data at regularly scheduled follow-ups via medical chart review or in-person research staff interaction. We will also query for an adverse event over the phone or in person. For subjects who wish to withdraw completely from the study, we will make every effort to collect the data as soon as the individual lets us know they wish to withdraw. We will continue to use data that was obtained prior to withdrawal date unless the participant asks for it to be destroyed. The data will be kept secure until it is destroyed.

## 4 STUDY INTERVENTIONS

The MAIN-ART study will offer one intervention which will be given during the enrollment visit (whether this occurs in-person or over the phone). The intervention is the MAIN-ART web-based behavioral tool, as described below and will be compared to usual care. The intervention will be delivered by a trained member of the research team.

### 4.1 Intervention Arm: MAIN-ART Behavioral Tool

Participants randomized to the behavioral intervention condition will receive the intervention at the initial enrollment visit. For those seen in clinic, it will be administered on a research tablet or computer. For those recruited over the phone, a link to the intervention website will be emailed to them or texted to their smartphone, depending upon patient preference. After completion of structured surveys and data collection, as detailed in the Schedule of Activities, participants randomized to the intervention will complete the online behavioral tool. This will take approximately 15 minutes. Patients will receive a printout or PDF of their results for alcohol treatment preferences and will also receive a pamphlet for referral to the University of Michigan Addiction Treatment Services. The patient will also continue with standard care through the UMHS hepatology clinics department.

The intervention will consist of administering a single session of the MAIN-ART behavioral tool. The behavioral tool is a web-based application consisting of two modules which are completed in the same session. Patients enter their age and gender into the first screens. They also enter their zip code, but this information is not stored in any manner and is used only to link to an external substance use treatment locator (https://findtreatment.samhsa.gov/) which will aid in display of treatment locations near the subject's home. The first module is a 10 question true/false survey assessing patient beliefs

about alcohol use, liver disease, and risk of relapse. After each question, brief written education within the behavioral tool is given regarding the correct answer. The second module is a 19-question preference survey which assesses preferences for a range of attributes of alcohol treatment. After completion of the treatment preference module, an algorithm matches patients to their top three choices of treatment and provides them with brief explanations of each treatment option, reasons why this option featured in their top choices based on their preferences, and a short list of potential treatment locations, based upon the zip code they entered. The final treatment preference option output page will be printed and given to the patient in clinic or emailed to them as a PDF. The initial enrollment session, inclusive of eligibility screening and intervention administration, will last approximately 30-40 minutes.

### 4.2 Delivery

All intervention sessions will be delivered by a trained member of the research team.

### 4.3 Intervention Targets (mechanistic and clinical outcomes)

The goal of the pilot trial is to assess the acceptability and feasibility of the interventions. This study is underpowered to assess mechanisms of change.

### 4.4 Supportive Theories

Supportive theories include the Health Action Process Approach.

### 4.5 Usual Care

Patients randomized to usual care will receive a pamphlet for alcohol treatment referral to the University of Michigan Addiction Treatment Services, but will receive no further education from the research team. The patient will also continue with standard medical care through the UMHS hepatology department. Subjects randomized to the control condition will receive all necessary clinical care, as in the intervention condition, including labs and alcohol biomarkers and any alcohol use information provided by the primary hepatology provider's usual care strategy. From research staff, they will receive a brochure about University of Michigan Addiction Treatment Services which contains information on alcohol treatment resources and a phone number for them to call should they desire to do so.

### 4.6 Addiction Treatment Brochure

All randomized participants will receive a brochure for alcohol treatment referral options at the University of Michigan.

### 4.7 Concomitant Treatment

We will not exclude participants enrolled in other studies and/or health programs except as specified in the edibility criteria

### 4.8 Lifestyle Considerations

None

### 4.9 Intervention Discontinuation

Withdrawal of consent will result in true study discontinuation with no follow-up interview or other

assessment performed. Any information collected before withdrawal will be kept as part of the subject's record. The study will document the patient's reason for withdrawal, if available, to track for study purposes.

### 4.10 Treatment Fidelity

Fidelity to session content will be assured by the standardized nature of the behavior tool. All subjects randomized to the intervention arm will complete the behavior tool. Research staff will be present but will not be permitted to assist in interpretation of questions.

#### 4.10.1 Overall compliance

A participant will have completed the behavior tool intervention after completing both modules. We will track intervention completion in the study database.

#### 4.10.2 Treatment Design

The treatment is designed to correct misconceptions about alcohol and liver disease, provide health education, psychoeducation and increase alcohol treatment engagement through shared decision-making regarding patient preferences. It is a single-session web-based education and decision-assistance tool.

#### 4.10.3 Interventionist or Provider Training

All staff delivering sessions will be trained in administration of the Timeline Follow-back alcohol assessment (13) and will be given training in informed consent, best practices for research, and data safety and security.

#### 4.10.4 Delivery of Treatment

Participants will engage with the behavioral tool online using a tablet, laptop, or smartphone. It is self-directed and will be completed either in clinic or via phone with the subject's own personal computer, tablet, or smartphone.

## 5 STUDY PROCEDURES

We will conduct a randomized pilot trial test of the MAIN-ART behavioral tool compared to usual care to increase alcohol treatment engagement in ALD patients. The goal of the pilot trial is to assess initial acceptability and feasibility of the intervention and, as a secondary goal, to determine if the tool increases alcohol treatment engagement. Participants who agree to enroll in the study will be given the intervention at the initial, in-person study visit or via a phone recruitment visit. This is expected to take 30-40 minutes for the total enrollment visit. Two follow-up phone assessments will be performed at 3- and 6-months after enrollment (see below for content of assessments). We will be screening medical records to determine some patient eligibility criteria such as age and liver disease diagnosis. We are requesting a waiver of consent for recruitment purposes.

Due to the large number of patients receiving hepatology care in the liver clinics, it would be difficult to obtain consent from each patient prior to screening. The risk to patients is minimal in order to allow staff to pre-screen medical records. Patients who are interested in participating will provide informed consent before study activities begin. Participants who appear eligible after medical record screening will be approached in person or via letter or email to notify them of the study, then by phone to be asked additional screening questions, for which they will provide verbal consent. These questions will further assess for eligibility based on recent drinking pattern (within 6 months) and recent alcohol

treatment (within past month). Participants eligible after the screening survey will provide informed consent before performing any baseline study-related procedures.

Outcome assessments are performed three times across an individual's time in the study: baseline, 3 months after initial visit and 6 months after initial visit. Assessments performed at each time point are listed in the Schedule of Activities. Follow-up assessments will be completed by participants via phone unless there is a corresponding clinic visit during which the assessments could be done in-person. The schedule of assessments is indicated in the Schedule of Study Activities.

### 5.1 Participant Incentives

Participants will be compensated as follows: $30 for the initial enrollment visit, $30 for the first phone follow-up, and $40 for the final phone follow-up for a total of $100 compensation for study completion. Subjects who do not complete a follow-up study visit will not be compensated for that visit.

### 5.2 Randomization

We will use computer-generated urn randomization to ensure balanced groups based on gender. Research staff will be blind to participant study condition (with the exception of those delivering the intervention). We will track participant recruitment and retention as a measure of study feasibility. Retention strategies include, collecting multiple forms of participant and collateral contact information, sending reminders by e-mail, phone, and text, and increasing incentive payments in a stepped fashion for completing all parts of the study. We aim to retain 80% of patients (48/60) using these strategies and those reported in the literature for ALD patient research(14).

### 5.3 Outcome Assessments and Measures

#### 5.3.1 Baseline Assessment

Baseline assessment will take place in-person or via phone at the time of enrollment. The baseline assessment will take approximately 25 minutes to complete. Thus, the first enrollment appointment will take up to 40 minutes for those randomized to receive the intervention (25 minutes for consent form review, eligibility assessment, completion of AUDIT-10 and additional questionnaires (see Schedule of Activities) (15) and Timeline Follow-Back assessment, and 15 minutes for intervention completion).

All baseline and follow-up assessments will be designed and administered using an online survey platform like the University of Michigan instances of Qualtrics Research Suite (http://www.qualtrics.com) or REDCap. These and similar systems are protected with a researcher-designated login name and password. They house the surveys and compile data which are all stored on Michigan Medicine servers. There are security precautions in place to protect against unauthorized access, but there is a small risk of unauthorized access. Information regarding Qualtrics security and privacy statements can be found at http://www.qualtrics.com/security-statement and http://www.qualtrics.com/privacy-statement.

#### 5.3.2 Self-Report Measures

Acceptability will be assessed by survey questions administered at the end of the intervention as well as a modified Systems Usability Scale (https://www.usability.gov/how-to-and-tools/methods/system-usability-scale.html) to evaluate the usability of the intervention. Alcohol treatment engagement will be assessed by self-report. Alcohol use assessments administered at baseline and follow-up include the

Alcohol Use Disorders Identification Test (AUDIT)(15) and the Alcohol Timeline Follow-back (TLFB)(13). The secondary outcome data for alcohol reduction (1-level or 2-level reduction in weekly alcohol use using World Health Organization risk drinking levels) is gathered here. All other self-report measures are exploratory.

Measures of readiness to change and treatment readiness include the Stages of Change and Treatment Eagerness Scale (SOCRATES)(16) and alcohol use problems include the Short Inventory of Problems (SIP)(17). Health and functioning assessments include the Short-Form Survey 12 (SF-12)(18).

### 5.4 Other Measures

#### 5.4.1 Liver, Alcohol and Drug Use biomarkers

We will collect clinical data already collected for clinical care, as available, including comprehensive metabolic panel, INR, urinary ethyl glucuronide, urinary ethyl sulfate, blood alcohol levels, and phosphatidylethanol. Data will be abstracted in a one-month window around initial and follow-up time frames. This measure is exploratory.

#### 5.4.2 Medical Chart Review

The research team will extract and analyze de-identified data from patient's medical records to evaluate the impact of the alcohol brief intervention measures of liver function, alcohol use, and health-care utilization. These measures will include, but are not limited to, labs (to calculate Model for End-Stage Liver Disease Sodium (MELD-Na) score), clinical descriptions of worsening or improving portal hypertensive complications (ascites, variceal bleeding, hepatic encephalopathy) collected as part of routine clinical care, and things like ER visits and hospital admissions. Of note, no labs will be drawn for research purposes. We are underpowered to detect between group effects of interventions on these secondary outcomes

No HIPAA identifiers will be collected from the patient medical record, except dates of death (if applicable). This dataset will not be linked to patient identifying information. This measure is exploratory.

### 5.5 Satisfaction and Acceptability

#### 5.5.1 Post-Intervention Assessment

Participants will also complete brief assessments following intervention completion regarding usefulness of the intervention, effectiveness of the two modules (misconception correction and treatment matching), and any improvements that should be made.

#### 5.5.2 Qualitative Exit Interview

After the study is complete (N = 10) participants that indicated willingness to be re-contacted (in consent form) will be asked to complete an exit interview (open-ended researcher-delivered questions) about why they did or did not change their alcohol use, and what the role of the intervention was in that decision-making process. The purpose is to further refine the intervention conditions for further development and dissemination. This measure is exploratory.

Five who did respond and engage in treatment and 5 who did not will be selected for an interview at study completion. Selection will be balanced between intervention and control arm. Qualitative

interviews with patients will occur during a single interaction with research staff. Qualitative interviews will be audio recorded. Interviews will focus on why patients did or did not engage in alcohol treatment, how the intervention did or did not play a role in their decision (for those who received the intervention), and what could be improved or changed about the intervention.

### 5.6 Schedule of Activities

**Schedule of Activities**

| | Pre-Screening (Pre-Consent) | Visit 1 (Day 1) | Phone Visit 2 (Day 90 +/- 14d) | Phone Visit 3 (Day 180 +/- 14d) |
|---|---|---|---|---|
| EMR Review Eligibility | X | | | |
| Confirm Eligibility * | | X | | |
| Informed Consent | | X | | |
| Demographics | | X | | |
| Clinical history | | X | | |
| Intervention delivered<br>-Module 1: Misconception Survey[$]<br>-Module 2: Treatment Matching[$] | | <br>X<br>X | | X |
| Outcome Evaluation | | | | |
| Engagement in AUD Treatment | | | X | X |
| Date of Last Alcohol Use | | X | X | X |
| AUDIT-10 | | X | | |
| TLFB | | X | X | X |
| SOCRATES | | X | X | X |
| SIP | | X | X | X |
| SF-12 | | X | X | X |
| Acceptability survey[$] | | x | | |
| Brief interview on behavior tool effectiveness, appropriateness and usefulness [$] | | | | X |
| Randomization | | X | | |
| Adverse Events Reporting | | X | X | X |

*Query date of last alcohol use and any ongoing alcohol use treatment within past 6 months
[$]Survey will be given only to those in intervention arm.
*Note. All self-report measures are listed in the assessment section*

## 6 SAFETY

### 6.1 Potential Risks

There is a minor potential risk for breaches of confidentiality with assessment data. The risk of a violation of confidentiality exists because human participants will be disclosing personal information, both in assessments and intervention sessions. This risk is related to the damage that could be caused by an inadvertent release of sensitive information (e.g., psychiatric symptoms, substance use, etc.). Our research team has considerable experience in maintaining the confidentiality of study datasets and will have procedures in place to ensure data confidentiality. (See details of protections below) All investigators have completed training in the requirements for handling protected health information as outlined by the Health Insurance Portability and Accountability Act (HIPAA). Participants will be informed of the procedures taken to protect their confidentiality. The focus of this study is not on child

abuse or intention to harm others. However, because of the nature of the study (hazardous drinking and/or dependence) these issues may arise. The consent form will contain a statement explaining mandatory reporting requirements for information regarding child abuse and intention to harm self or others prior to participating in the study.

There is also a slight risk of psychological discomfort to study participants as a result of being asked personal questions, particularly during the assessments. Participants may also become anxious or upset during discussions about hazardous drinking that occur. Study staff will be trained to respond to this emotional distress and to refer participants to appropriate resources as necessary. All participants will be free to terminate the study at any time or refuse to respond to any questionnaire item. We are not directly assessing for suicidality. However, if study subjects make statements indicating an intent to self-harm, we will make a further clinical assessment and refer appropriately for follow-up. The study team contains a senior psychologist (Dr. Blow) and a psychiatrist (Dr. Winder) who will provide guidance in assessing risk.

### 6.2 Potential Benefits

Patients participating in the MAIN-ART trial may benefit as follows: 1) Improved knowledge of the risks of alcohol use and liver disease as well as the risks of alcohol relapse on their liver and overall health. Correctly understanding these risks may allow for increased willingness to reduce or stop alcohol use and engage in alcohol use treatment, which has benefits for patients with ALD in reducing risk of decompensation and mortality. 2) Improved understanding of alcohol use treatment options available. Many patients with ALD do not understand the full range of alcohol treatment options available to them. Completion of the tailored preference-sensitive alcohol treatment tool will allow them to view and contemplate different alcohol treatments and determine what their own values and preferences are for engaging in alcohol treatment. This may reduce barriers to participation in alcohol treatment, which may increase engagement in treatment resulting in reduction in or total cessation of alcohol use.

### 6.3 Assessment of Potential Risks & Benefits

The degree of risk to which study participants will be exposed in the proposed protocol is low. By contrast, the potential benefits to the individual and society are substantial, insofar as the results of this study will be used to develop and implement interventions to improve alcohol use treatment uptake and reduce alcohol use in ALD patients. These interventions have the potential to assist ALD patients in reducing or stopping alcohol use entirely, which would have substantial benefits on ALD morbidity and mortality as well as potential for improving healthcare utilization by reducing need for liver transplant as well as hospital and health resource utilization over the long-term. When considering the minimal risks entailed with the data collection and tests proposed, in combination with the extensive efforts to limit/eliminate these risks, we feel that the potential benefits to the research community and future interventions far outweigh the potential minimal risks.

### 6.4 Event Reporting Schedule and Classification of Adverse Events

Project staff will notify PI of SAEs immediately. All adverse events will be reported to the Institutional Review Board (IRBMED) per standard reporting guidelines; and an annual report will be submitted to the NIAAA Project Officer summarizing all adverse events. Per standard reporting guidelines, related and unexpected SAEs will be reported as soon as possible but within 7 calendar days, related and expected SAEs will be reported within 14 calendar days, unrelated and unexpected SAEs will be reported annually, and expected and unrelated SAEs will not be reported unless they exceed the rate expected for the study population. Dr. Mellinger will be responsible for determining the severity of an event, and whether

such adverse events were expected (i.e. listed as expected in the DSMP or included in the informed consent). The person responsible for reporting adverse events will be Dr. Mellinger; she will also be responsible for reporting amendments to the protocol to IRBMED prior to implementation of any changes.
In the event that a participant either withdraws from the study or the PI decide to discontinue a participant due to an AE or SAE, the participant will be monitored by Dr. Mellinger, PI, via ongoing status assessment until (a) a resolution is reached (e.g., the problem has resolved or stabilized with no further change expected), (b) the SAE is determined to be clearly unrelated to the study intervention, or (c) the SAE results in death. Actions taken by the IRB in response to adverse event will also be reported to the funding agency, as will reports of changes or amendments to the protocol resulting from an adverse event. Outcomes of AEs and SAEs will be regularly reported to NIH and IRB (as outlined above). A summary of the AEs and SAEs that occurred during the previous year will be included in the annual progress report to NIH and the annual IRB renewals at the University of Michigan. Events that do not meet the criteria of an AE or SAE will also be included in the project's annual progress reports to NIH.

## 6.5 Definitions for Adverse Events and Serious Adverse Events

### 6.5.1 Monitoring, Grading, Documentation, and Reporting of Adverse Events

It is unlikely that the study protocol will lead to an adverse event (AE) or serious adverse event (SAE). However, we have established procedures for dealing with these events. In the proposed study we will use the FDA definition of adverse events (AE) and serious adverse events (SAE). An adverse event is any undesirable experience, serious and non-serious, in a participant that may have a causal relationship with study participation. Symptoms or conditions present at or before the study that manifest themselves with the same intensity or frequency after study participation will not be recorded as adverse events. At the time of each contact, all participants will be monitored for the development of adverse experiences. Any concerns will be immediately reported to the PI who will review the information.

### 6.5.2 Relationship to Participation

The PI will classify the relationship of the study protocol to the event according to University of Michigan IRB definitions of adverse event categories: Definitely related, Probably related, Possibly related, Unlikely Related, and Unrelated. These definitions can be found at https://az.research.umich.edu/medschool/guidance/adverse-event-reporting.

### 6.5.3 Severity of Event

The scale below will be used to estimate the grade of severity of the adverse event:

- *Grade 1 Mild*: Transient or mild discomfort, no limitation of activity, no or minimal intervention/therapy required.
- *Grade 2 Moderate*: Mild to moderate limitation in activity; some assistance may be needed; no or minimal intervention/therapy required.
- *Grade 3 Severe*: Marked limitation in activity; some assistance usually required; intervention/therapy required; hospitalization possible.
- *Grade 4 Life –threatening*: Extreme limitation in activity; significant assistance required; significant intervention/therapy required; hospitalization probable (SAE)

### 6.5.4 Expectedness

*Expected adverse events:* The study population consists of patients with advanced ALD (alcohol-related cirrhosis [compensated or decompensated] and acute alcoholic hepatitis) with recent alcohol use and minimal recent alcohol use treatment involvement. Such patients are expected to potentially have medical complications including, but not limited to, worsening liver disease, ascites, variceal bleeding, hepatic encephalopathy, infection, and acute kidney injury. These adverse events are unlikely to be related to the intervention. Study staff may become aware of these complications during review of medical charts, or from participant self-report during follow up assessments.

## 7 DATA AND SAFETY MONITORING

### 7.1 Data Management

Project staff will be educated on the latest policies regarding the ethical treatment of participants and the protection of confidentiality. Several procedures will be utilized to guarantee the validity, integrity, accuracy and completeness of the data. Identifiers and study data will be maintained in HIPAA-compliant study and/or password-protected databases which are accessible only to project personnel and whose access is restricted based on role and responsibility.
Files used in data analysis will not have any identifying information in them – just randomly assigned ID numbers. All paper data will be filed in locked cabinets inside locked rooms that only the PI and research staff will have access to. No patient identifiable information will be released or published without written permission unless required to do so by law.

### 7.2 Data Monitoring Plan

The Principal Investigator (PI), Dr. Mellinger, ultimately will be responsible for monitoring the data safety and quality with involvement from all of the study investigators. Data will be collected using standardized paper or online forms. Quality control and reliability of screening, baseline and follow-up assessments will be monitored by Dr. Mellinger throughout the trial via regular meetings and observation of the research staff conducting standardized assessments and throughout the study via regular meetings. Drs. Mellinger and Blow will monitor the quality of the data files via supervision of the data manager and through the use of regular audits and data queries.

The MAIN-ART behavioral tool itself does not collect any PHI. Only numerical age (no dates) and gender are collected. Responses to questions within the tool are stored in a secure environment which meets requirements set by Information Assurance at the University of Michigan. Additional demographic and chart review data is collected separately and stored in secure password protected files as noted above. The MAIN-ART tool has been approved for use for research purposes by Information Assurance.

Data will be entered in the computer independently by trained data entry staff, and discrepancies will be corrected by a supervisor, based on source documents. The quality of the data will be monitored throughout the study. Data will be analyzed using a data analysis program, such as Stata software. Data quality will be monitored by random inspection of the completed forms by the study coordinator and any problems detected will be discussed with the PI.

In terms of delivery of the intervention, clinicians who will be delivering the interventions will receive standardized training in conducting them. Adherence to intervention techniques and protocols will be monitored with individual supervision. All clinicians will receive ongoing training. Post-intervention

evaluative interviews will be performed by research staff. The qualitative interviews will be audio-recorded. The audio-recordings of the sessions and interviews will be destroyed after the files are uploaded to a password-protected, secure server with restricted access. Once collected, participant data will remain confidential.

Because of the small size of this study, no DSMB will be utilized. Data and safety monitoring will be conducted by the PI (Dr. Mellinger) and overseen by Dr. Blow.

### 7.3 Entities conducting monitoring

The Michigan Medicine IRB (IRBMED) will review this protocol and all procedures and will provide oversight. Monitoring will be done by the PI, mentors, and IRBMED.

### 7.4 What is monitored?

Monitoring is done of all procedures to ensure that they conform to approved protocol; of unforeseen circumstances that might arise and affect safety; of all reports of serious adverse events as defined in 38 CFR 46 (death, new prolonged hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defect); of other significant adverse events (adverse events that lead to drop out by participant, termination by the investigator, termination or reduction of treatment); of unexpected adverse events resulting from the study; and of expected adverse events.

### 7.5 Safety Monitoring

The Principal Investigator, Dr. Mellinger, will ultimately be responsible for monitoring the data safety and quality of the study with involvement from all of the study investigators. It should be noted that all research projects involving human participants, including the proposed one, require approval from the University of Michigan Institutional Review Board. Dr. Mellinger, with the guidance of Dr. Blow, will ensure that all relevant IRB policies, procedures and stipulations are being followed. Dr. Mellinger also will be responsible for ensuring that other investigators and project staff adhere to the IRB policies including: (1) all participants will understand, agree to, and sign a written consent form before participating; (2) strict adherence to a participant's right to withdraw or refuse to answer questions will be maintained; (3) the assessments will be completely confidential; (4) consent forms will be kept separately from the actual participant data; (5) identifying information will be kept locked at all times and computer files will require passwords; (6) participants will be informed in writing in the consent form how to contact the PI, the project manager, and IRB office with any questions and/or concerns.

Dr. Blow and Dr. Mellinger will be responsible for providing training to all research staff working with participants with regard to procedures for managing issues that could arise given the patient population, including potential crisis situations and/or adverse events. Specifically, this training will include information regarding evaluating warning signs of distress that could occur as a result of the screening or assessment, and means of addressing such issues and minimizing distress. Such strategies will include maintaining an empathic response, acknowledging the distress through reflection, avoiding blame, processing in a non-blaming non-confrontational manner, intervening early, and eliciting or encouraging use of relaxation and cognitive calming strategies. Crisis procedures, effective in previous projects conducted by the study investigators, will also be utilized, including immediately paging Drs. Mellinger, Winder or Blow for consultation and conference call discussions with other investigators, as necessary.

In addition, staff will receive training from Dr. Blow in crisis assessment and management procedures in the event that participants reveal suicidal or homicidal ideation, child physical/sexual abuse, or concerns about safety. These crisis procedures will include a review of the study protocol regarding the limits of confidentiality, how to liaison with University of Michigan staff (i.e., emergency department) to arrange for an assessment, circumstances in which it may be necessary to notify authorities regarding intent to harm self or others, and the development of safety plans and resources. Study procedures also will include immediately paging Dr. Mellinger in cases in which this may arise.

Study staff will also be trained in safety procedures to ensure their own safety when conducting follow-ups interviews. The same crisis reporting procedures for staff safety concerns will apply in terms of immediately contacting Drs. Mellinger or Blow. As part of our follow-up interview protocol, written safety procedures for conducting follow-ups, include informing other staff members about one's whereabouts, positioning oneself to ensure a quick exit, if needed, and being appropriately assertive. All safety concerns regarding follow-up assessments will be reported immediately to Drs. Mellinger or Blow.

Dr. Mellinger is responsible for reporting amendments to the protocol to the University of Michigan Institutional Review Board prior to implementation of any changes. The timing of the reporting of any adverse events to the IRB and DSMB by Dr. Mellinger will be dependent on the severity of the event, and whether such adverse events were expected (i.e., included in the informed consent). Any SAE related to study intervention, will be reported to the IRB and DSMB according to their reporting guideline.

## 8 STATISTICAL CONSIDERATIONS

### 8.1 Sample Size

The sample size (N = 60) was primarily chosen to facilitate conclusions regarding study feasibility, acceptability, and provide experience with study protocol (e.g. recruitment, retention, assessment, and analysis) in addition to preliminary data on the effectiveness of the intervention in improving alcohol use treatment engagement. Participant retention (n = 48; 80%) is achievable using methods utilized in mentor's past research and described in the retention section. This study is underpowered to detect effects. For this reason, hypothesis testing is considered 'exploratory.' Therefore, this study will primarily provide pragmatic information and experience with the study protocol to inform a fully-powered RCT.

### 8.2 Data Preparation

Prior to analyses, we will examine patterns of missing data, research dropout, intervention fidelity, distributional properties of measures, and correlations among outcome measures. Given the small sample, we will pay particular attention to data distribution and use transformations when appropriate.

### 8.3 Data Analysis

We will examine between group effects on alcohol treatment engagement using General Estimated Equations (GEE). We expect balanced groups on key variables as a result of urn randomization but will test the following covariates for systematic effects on outcome; gender, age, degree of liver disease. These analyses will use regression modeling using GEE due to the correlated structure of our data from repeated measures at baseline and follow-up. The GEE methodology properly estimates the regression coefficient and variance of the regression coefficient when correlated data are used in regression analysis will use all data available for participants including those subjects lost to attrition. Appropriate

distributions will be used based on the nature and distribution of the response variable. Relevant covariates will be included such as gender, age, race/ethnicity, and degree of liver disease.

### 8.3.1 Primary Outcome

The primary outcome is alcohol treatment engagement. Alcohol treatment engagement will be defined as at least one visit with formal, external assistance in alcohol cessation or reduction. This would include, but is not limited to, at least one session of either in-person or telehealth treatment with an addiction treatment professional (either inpatient or outpatient), in-person or telehealth attendance to at least 1 session of a community-based support group for alcohol cessation (such as Alcoholics Anonymous, SMART Recovery, Refuge Recovery, faith-based support group via religious organization, for example), one-on-one or group counseling with an addiction treatment professional, counseling with a religious leader (such as a pastor or priest) to address alcohol use), etc.). Our hypothesis is that patients who receive the MAIN-ART behavioral intervention will have greater engagement in AUD treatment compared to usual care.

### 8.3.2 Qualitative Analysis

All qualitative interviews will be digitally audio-recorded and transcribed verbatim using a HIPAA-compliant transcription service. Transcripts and codes will be analyzed using MAXQDA software. We will analyze data using applied thematic analysis. Emerging themes and data interpretations will be used for intervention refinement.

## 9 REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

### 9.1 Informed Consent Process

Except for when identifying potential participants through MiChart, data will be accessed and collected only with informed consent. Consent will be obtained in writing (either via paper or tablet) at the time of enrollment. Signed paper consents will be filed in a locked, confidential research file, or electronically on study provided tablet computers and stored in a secure database. Copies of consent forms will be given to the participant. Unique identification numbers will be assigned to participants who consent. All data forms will be coded with this number rather than with a name. Computer data files will be saved with passwords. Consent forms will be stored separately from other study data because they contain identifying information. Furthermore, we will receive a Certificate of Confidentiality from the NIH to protect the confidentiality of our data from legal requests.

### 9.2 Confidentiality and Privacy

To minimize the risk of breaches of confidentiality, every effort is made to ensure that study data are always confidential, and web- and paper-based data are stored to minimize the likelihood of information breach. Training of research staff will include information about the importance of confidentiality and techniques to maintain confidentiality of all information reported by research participants. In addition, all research personnel will complete the required UM confidentially certification training.

### 9.3 Future Use of Stored Data

We will retain identifiers after study conclusion until publication of all results in order to provide the ability to confirm accuracy of data prior to publication. After collection of study data, all identifiers will

be stripped from research datasets and housed in separate password-protected files on secure UMich servers. Only research staff will have access to identifiers.

### 9.4 Quality Assurance & Quality Control

Throughout the proposed research investigation, participants' names and contact information will be stored in a secure, restricted access, password-protected database. Patient audio from intervention sessions and exit surveys will also be kept in a restricted access folder on a secure server. All information collected will be accessible only to research staff who have completed and maintain mandatory training in the protection of human subjects (see 9.4.2)

Electronic data capture and database systems like REDCap and/or Qualtrics will be used to collect and house study related data and information (e.g. subject demographics, medical details, study data, screening scores, and level of study completion, etc.). These systems use several methods to protect data from vulnerability and exploitation. The study investigators will ensure that Research Assistants (RAs) and other study staff will only have access to the data and information they need to complete their work by creating and updating user rights in

A project-specific Qualtrics site is protected with a researcher-designated login name and password. The site houses the surveys and compiles data that staff will then transfer to a password protected database on the Department of Medicine secure network. There are systems in place that prevent the survey from being taken by the same user more than once. There are security precautions in place to protect against unauthorized access, but there is a small risk of unauthorized access. Information regarding Qualtrics security and privacy statements can be found at http://www.qualtrics.com/security-statement and http://www.qualtrics.com/privacy-statement.

#### 9.4.1 Training

All hired members of the research team will complete training and receive certification in Human Subjects Research Protection, HIPAA regulations, and research best practices; the investigators will keep current certifications up to date. All members of the research team will also complete PEERRS training. All staff shall attend and successfully complete the University of Michigan Recipient Rights training within the first 90 days of employment.
The investigators will be responsible for providing training to all research staff who are interacting with participants via the intervention regarding procedures for identifying, managing, and responding appropriately to acute warning signs of distress. Staff will receive training in risk assessment as outlined in previous sections.

#### 9.4.2 Protocol Deviations

Study protocol deviations are not expected unless related to missed and rescheduled visits. Any protocol deviations will be addressed, tracked, and reported per the procedure below.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported NIAAA Program Official. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

### 9.4.3 Monitoring

We will monitor through routine data monitoring, weekly review meetings, staff training and annual re-training, and regular record reviews for assuring protocol compliance, and data quality, including regular record review and data double-entry to test for errors in data entry.

## 10 COMMITTEES

N/A

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