

5. Chapter 5: Randomization

5.1 Introduction to Randomization

The medication group to which a participant is assigned is determined by an allocation schedule developed by the COMBINE Coordinating Center based on the 9-cell design for the main trial. Study medication will be dispensed in individual participant medication cards packaged by the New Mexico VA Cooperative Studies Clinical Research Pharmacy. Because the order of medication assignment for each participant is determined through a chance process, this procedure is called “randomization.” However, controlled, documented, and accurate execution of this process is absolutely essential to the scientific validity of the trial.

If you have any uncertainty about whether a participant is eligible to be randomized or about the procedure to follow, contact your clinical center supervisor or the Coordinating Center before proceeding.

Participants who are randomized (are informed of the treatment assignment) but who fail to return will not be replaced. These participants will be included in intention to treat analysis but not in the evaluable participant analysis.

5.1.1 Overview

Randomization of participants in COMBINE will be made by use of an allocation schedule designed by the Coordinating Center for medications packaged by the study research pharmacy. COMBINE has a goal of randomizing 1375 participants who complete the full protocol. Those participants will be evenly recruited among 11 centers at a level of approximately 125 per site. Should a participant discontinue prior to study completion, staff should follow procedures outlined in section 8.1.1.1 (re-engaging non-adhering participants). They should also be invited back for a final week 16 visit to collect Form 90 data. No provisions have been made for replacement of participants that do not adhere to the protocol once treatment intervention has been assigned and medication has been taken. However, medication blister packs that have been allocated, but not actually used can be made available to the next eligible participant in the event of “early” (before initial MM visit) discontinuation. In some cases, after learning the therapy assignment, the participant may either never return for their first MM visit, or be excluded due to failure to meet the abstinence criteria. Should this occur prior to any drug being dispensed to and used by the participant, contact the Coordinating Center immediately for specific instructions.

5.2 Randomization of a Participant

5.2.1 Initial Preparation for the Randomization Process

- 1) Review the Eligibility Checklist (ELG) for the participant.
Before randomizing a participant into the study, each component of the eligibility screening process **MUST** be complete, and all baseline data recorded on the appropriate forms. In addition, the urine drug screen panel (and pregnancy test for females) must be reviewed for positive results prior to randomization. If there are any discrepancies between interpretation of the checklist, and the COMBINE protocol, the wording in the protocol supersedes the eligibility checklist.
- 2) Complete the Randomization Worksheet for the participant.
The randomization worksheet (RAN) is designed as a prompt to cover the key entry criteria, and record screening scores for measures of addiction, craving, readiness to change, and percent days abstinent. The RAN form is thus a formal mechanism for the site to certify the overall eligibility of

the prospective participant at the time of randomization. For this reason, no blank responses are allowed, and each question must be able to be verified against the source documents. The form provides a place for you to record the 5-digit study medication ID number and the 6-digit initial (week #01) study medication card number used to verify that the study medication was assigned following the standard COMBINE procedures. The intervention arm (MM, MM+CBI, CBI only) is also recorded on the worksheet.

- 3) Call the COMBINE Telephone Randomization System for a study treatment assignment (see detailed discussion in the next section).

5.3 Introduction to the Telephone Randomization System (TRS)

The treatment group a participant is assigned to is determined by a telephone call to the COMBINE Coordinating Center. Before participants can be enrolled, the study project office at NIAAA must receive IRB approval from the center and issue a written Certificate of Confidentiality covering the main trial for that site. No treatment assignments can be made for a center until NIAAA notifies the Coordinating Center that the certificate was awarded, and in turn the Coordinating Center provides that center with written clearance to screen and randomize participants into the trial.

Each clinical center staff member must be trained and certified in the use of the system before being authorized to randomize participants. Upon certification, you will receive a five digit "PIN", which must be used in addition to your COMBINE staff ID number in order to access the system.

5.3.1 Overview of Randomization Process

The COMBINE Telephone Randomization System allows authorized users at COMBINE clinical centers to make a telephone call to the Coordinating Center, respond to a series of questions using the telephone keypad and receive a treatment assignment for a specified participant. Written confirmation of the assignment will be faxed to the clinical center.

The TRS program runs on a computer located at the Coordinating Center and is available 24 hours each day. Experience from previous studies using a similar system had an overall system availability exceeding 99.9%. In the rare event of a system failure, designated Coordinating Center personnel will perform randomizations manually.

5.4 Using the Telephone Randomization System

5.4.1 Interacting with the System

The system uses pre-recorded speech samples to generate all instructions and prompts. The user responds to questions and provides information by pressing keys on the telephone keypad. The numeric keys are used for most choices. The pound key (#) is used to confirm a response or to indicate the end of a multi-digit response. The star (*) key is used to indicate a prior response is incorrect and should be ignored. The system always indicates what keys should be used to respond to a question.

As you become familiar with the sequence of prompts, you can interrupt a prompt at any time by responding with the appropriate key.

5.4.2 Steps in the Telephone Randomization Process

- 1) Complete the Randomization Worksheet (RAN) for the participant.

The date documented on the RAN header should be the date that you call the TRS.

The System will prompt you to enter most of the information from the Randomization Worksheet. It also provides a place for you to record the intervention assignment, card number of the first week of study drug, and a treatment ID number used to verify that the intervention was assigned following the standard COMBINE procedures.

- 2) Call the TRS at **800-472-2595**

You must use a touch-tone telephone when calling the Telephone Randomization System. The telephone number is 800-472-2595. Most phone calls require less than 3 minutes to complete. Since an average of four randomizations per day are expected study-wide, more than two simultaneous calls are extremely unlikely.

The system should answer the call on the second or third ring. If the line is busy, call back a few minutes later. If the line continues to be busy or if the line rings with no answer over an extended period, call the Coordinating Center for assistance (see section 5.4, getting help).

The system will announce an introductory message to the caller.

- 3) Enter your COMBINE Staff ID number.

The system will prompt you to enter your three-digit Staff ID number, followed by the pound (#) key. Each staff member will have their own Staff ID and should use their own ID when calling the TRS. Contact the Coordinating Center for assignment of additional Staff IDs when new users are certified to use the system.

The entered Staff ID number is spoken by the system and you are prompted to confirm or correct it.

Press the pound key (#) if the value is correct. If you have made a mistake, press the star key (*). If you press the star key you are asked again to enter your ID. This sequence will repeat until you press the pound key to confirm your entry.

- 4) Enter your Personal Identification Number (PIN)

The system will prompt you to enter your 5-digit PIN, followed by the # key. Staff members who are authorized to call the TRS will have their own PIN.

The entered PIN is spoken by the system, and you are prompted to confirm or correct it.

Press the pound key (#) if the value is correct. If you have made a mistake, press the star key (*). If you press the star key you are asked to reenter your PIN. This sequence will repeat until you press the pound key to confirm your entry.

- 5) The Staff ID and PIN entered are checked against a list of valid Staff IDs and PINs.

If the ID and PIN are valid, the center for which the user may randomize participants is spoken. You are allowed to randomize participants from your center only.

If the Staff ID or PIN is invalid, you are asked to enter and confirm the invalid value or values again. You are given three chances to enter a valid Staff ID and PIN. If you fail to do so, the call is terminated by the system. Check your assigned Staff ID number and PIN with your clinical

center supervisor. If you are certain you used both numbers correctly during the terminated phone session, contact the Coordinating Center for assistance.

To discourage attempts by unauthorized persons to access the system, the number of unsuccessful attempts at use over time is monitored. If the frequency exceeds a limit, the system is made completely unavailable for a period of time. Users calling during this time-out period hear a message that the system is currently unavailable. Contact the Coordinating Center for assistance.

6) Enter and verify the Screening ID for the participant.

The Screening ID# is the combination of the 2-letter center code and the 7 digit Participant ID number. Enter only the numeric portion of the Screening ID. Press the pound key after 7 digits have been entered.

The Screening ID you entered is spoken.

To insure accurate entry, you are asked to reenter the Screening ID.

In order to confirm the Screening ID, two consecutive entries must match. If your two entries are not identical, you will be prompted to try again. You are given three chances to enter two consecutive matching values, or the call is terminated.

7) The Screening ID is checked for validity:

- the center must be the one for which the user is authorized to enter participants
- the participant ID number must be a valid COMBINE participant number
- the participant ID number cannot be for someone already randomized.

8) Enter the information from items 1-5 on the Randomization Worksheet.

These responses are entered only once. They are not confirmed by re-entry.

The system checks the responses and determines whether the participant meets the general eligibility requirements for COMBINE.

If the participant is eligible, the system speaks the treatment ID, initial study drug card number, and intervention assignment to the user. This information is repeated once by the system. Record the treatment assignment and treatment number on items 8, 8a, and 9 of the Randomization Worksheet. (Note: CBI only participants will have a dummy six-digit card number of 999999). This information will also be faxed to a designated number at your center.

If the participant is not eligible, the user is informed and given the chance to randomize another participant or hang up to exit the system.

9) The system prompts you to randomize the next participant, or hang up to end the session.

5.5 Study Drug Assignment

The study medication for COMBINE can be stored locally either at the research pharmacy affiliated with your institution, or kept in a secure area within the COMBINE clinical center. The initial (week #01) and second (week #02) weeks of study medication are supplied together. Subsequent weeks of follow-up study medication, or maintenance cards need to be reordered from the NM VA Clinical Research Pharmacy (phone #: 1-866-228-0256). Maintenance medication is shipped for overnight delivery after placing the phone order.

After maintenance cards are ordered the NM VA will send a confirmatory fax to the site within 24 hours. For more detailed information see section 6.12.

5.6 Preparing for the Randomization Visit (Initial Treatment Session)

Once all eligibility information is obtained, the Project Coordinator should review, with the participant, his or her responsibilities as a research participant (expectations regarding attendance, completion of research forms, and follow-up visits) before randomization takes place. In this way, future adherence and retention problems can be avoided by allowing an ambivalent participant an opportunity to decline participation. It also allows a motivated participant an additional opportunity to formally express interest in the study, thus reconfirming commitment.

Once the telephone randomization system has provided a treatment assignment on the day of randomization (or the day before in order to schedule clinician and/or therapist) and the medication card number and/or intervention is known, the participant should be scheduled for his or her initial MM and/or CBI visit as soon as possible. The participant should **not** be informed of the treatment assignment until the participant arrives for the visit and has completed the remaining assessments (see section 5.7). It is best to have both sessions scheduled on the same day. If this is not possible and scheduling conflicts arise, the MM visit should take precedence. If the participant is assigned to both interventions, they should attend the MM session before the CBI session.

If staff call the TRS before the day of the actual randomization visit (for scheduling purposes), and the participant does not show up for the randomization visit, staff should keep the treatment assignment, treatment ID#, and the titration card # until the person becomes ineligible.

If, after finding out the treatment assignment, a participant says s/he does not want to participate, staff should continue to link the treatment assignment, treatment ID#, and titration card # with that participant as s/he could change his or her mind about participation. When it becomes clear that the participant is not going to continue with the randomization process s/he can be de-randomized.

5.6.1 De-Randomization

If, after calling the TRS, the participant becomes ineligible or it is apparent that the participant is not going to continue with the randomization process, the participant can be “de-randomized”. De-randomization can only take place if the participant has no knowledge of the treatment assignment. Once a participant is informed of their treatment assignment, that participant cannot be de-randomized. These participants will be included in intention to treat analysis but not in the evaluable participant analysis.

5.6.1.1 De-Randomization Procedures

- 1) Note the reason for randomization failure on the Eligibility Checklist (ELG).
- 2) Write “Failure” on the person’s Randomization Worksheet (RAN) and fax it to Marston Youngblood at the Coordinating Center at (919) 962-3265.
- 3) Delete the Randomization Worksheet (RAN) from the COMBINE Data Management System.

The treatment assignment and week 1 card number for randomization failures should not be given to the next eligible participant. The medication will be wasted. Staff should call the TRS in order to obtain another treatment assignment and week 1 card number for the next eligible person.

5.7 Evaluations and Assessments

Before the participant is notified of the treatment assignment, breath alcohol content and vitals should be recorded on the Vital Signs Form (VSB) and the Concurrent Medication Form (COM) should be updated. BAC will be collected for all participants, however, vitals will not be taken for those participants assigned to CBI-only, unless they request this. The BAC should be 0.00 on the day of randomization because the participant should have been abstinent for at least four days.

The Clinical Institute Withdrawal Form (CIWA) should also be completed prior to informing the participant of the treatment assignment. The CIWA score must be less than 8 on the day of randomization.

If the BAC is 0.00 and CIWA score is less than 8 and the participant wishes to continue with the randomization process, s/he will be asked to complete some research assessments before s/he is informed of the treatment assignment. The assessments that are to be completed prior to notification of treatment assignment consist of the Profile of Mood States (POM), Perceived Stress Scale, Obsessive Compulsive Drinking Scale, Drinking Questionnaire and the Clinical Institute Withdrawal Assessment Form. The baseline Concurrent Medication Form should also be updated.

Note that, in general, if there are more than 30 days between the first screening day and randomization, the Drinker Inventory of Consequences (DRB) and the lab samples need to be repeated. Judgment should be used to determine whether or not the entire baseline assessment battery needs to be completed again.

Table 5.1 Randomization Assessment Schedule

Visits			
	<i>BL screening</i>	<i>Randomization</i>	<i>Comments</i>
Profile of Mood States (POM)		X	Complete before participant is notified of treatment assignment
Perceived Stress Scale (PSS)		X	Complete before participant is notified of treatment assignment
Drinking Questionnaire (DRQ)	X	X	Complete before participant is notified of treatment assignment
Obsessive Compulsive Drinking Scale (OCD)	X	X	Complete before participant is notified of treatment assignment
Clinical Institute Withdrawal Assessment (CIW)	X	X	As needed during the screening process but it is necessary to complete on the day of randomization prior to notification of treatment assignment.
Concurrent Medication (COM)	X	X	Inquire about concomitant medications at each visit/contact
Eligibility Checklist (ELG)		X	Complete before participant is notified of treatment assignment
Randomization Worksheet (RAN)		X	Complete before participant is notified of treatment assignment

5.7.1 Profile of Mood States

The POMS-short form is a standardized 5-point interval rating scale comprised of adjectives describing different moods or feeling states. The 37-item self-report version scores eight factors including Vigor, Fatigue, Friendly, Anger-Hostility, Tension-Anxiety, Depression-Dejection, Confusion-Bewilderment, and Elation.

The POMS will be administered on the day of randomization (prior to being informed of treatment assignment). The score should be communicated to the CBI therapist for the Personal Feedback Report. The POMS is also administered during weeks 1, 2, 4, 8, 12, and 16.

5.7.2 Perceived Stress Scale

The Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) will be used to assess one dimension of stress. This 14-item scale assesses the degree to which individuals appraise situations in their lives as stressful. It appears to have two factors, one dealing with adaptational symptoms and one with coping ability (Hewitt, Flett, & Mosher, 1992). The PSS has demonstrated high levels of reliability and validity (Cohen, et al., 1983; Cohen & Williamson, 1988).

An abbreviated 4-item scale has been developed; while its level of reliability is somewhat lower than the two longer measures (14- and 10-item), it was judged to be adequate for use in situations requiring a very brief measure of the perception of stress (Cohen & Williamson, 1988).

The PSS will be administered at the randomization visit (prior to participant being informed of treatment assignment) and at weeks, 1, 2, 4, 6, 8, 10, 12, 16, and 52.

5.7.3 Obsessive Compulsive Drinking Scale and Drinking Questionnaire

The primary instrument that will measure baseline and change in “craving” will be the Obsessive Compulsive Drinking Scale (OCDS) which has been determined to be reliable, and to have good construct, congruent and face validity (Anton, Moak, & Latham, 1995, Moak et. al. 1998, Bohn et. al. 1996) and to be capable of measuring change during a pharmacotherapy trial (Anton, Moak, & Latham, 1996).

The OCDS is a 14-item self-administered rating scale with two sub-scales, which quantifies thoughts of alcohol, urges to drink, resistance to these thoughts and urges, and social interference of these thoughts and urges. The OCDS will be given during the baseline visit, on the day of randomization (before the participant is informed of treatment assignment) and at weeks 1, 2, 4, 6, 8, 10, 12, 16, and 26.

The OCDS will be supplemented by two additional questions that are taken from the 5-item Craving Questionnaire developed by Weiss et al. (1995, 1997). These items will assess 1) conditioned craving (i.e., the strength of one's desire to drink when exposed to a stimulus previously associated with drinking, such as a beer ad), and 2) the participant's perception of his/her likelihood of drinking if he/she were in the environment previously associated with drinking. They will be used to complete the evaluation of craving during the trial.

The Drinking Questionnaire is self-administered and is given during screening at the baseline visit, on the day of randomization (before the participant is informed of treatment assignment) and during weeks 1, 2, 4, 6, 8, 10, 12, 16, and 26.

5.8 Informing Participant of Treatment Assignment

After the BAC and vitals are taken and the remaining assessments and evaluations have been completed, the participant should be informed of the treatment assignment and given an outline of his or her responsibilities, based on the specific treatment assignment (Treatment Assignment Tools are located in Appendix B). They should also be given the CBI therapist's and/or MM clinician's name, session location, starting and ending dates and times. The participant will then attend the initial session(s).

After a participant has been randomized to treatment, the goal is to maintain a good research relationship, prevent attrition from the study, and maximize the collection of data in a complete and timely manner.

Should a participant miss their scheduled appointment, arrive intoxicated, or indicate they have not been abstinent for the last 4 days (96 hours), the first MM visit should be rescheduled.

In some cases, after learning the therapy assignment, the participant may either never return for their first MM visit, or be excluded due to failure to meet the abstinence criteria. Participants who are randomized (informed of the treatment assignment) but who fail to return will not be replaced. These participants will be included in intention to treat analysis but not in the evaluable participant analysis.

5.9 Getting Help with a Randomization

If, after reviewing the protocol and the Manual of Operations, you encounter difficulty qualifying a participant using the inclusion and exclusion criteria contact the PI at your site. If s/he is unable to resolve the question/issue contact the Coordinating Center.

If you have problems with the Telephone Randomization System contact Marston Youngblood or Kelly Tobin at the Coordinating Center.

If there are any problems with the initial study medication cards contact the primary pharmacy coordinator at New Mexico VA Cooperative Studies Clinical Research Pharmacy (505-248-3203), or you can contact COMBINE staff in the order listed:

Marston Youngblood (CSCC, Chapel Hill):	(919) 962-3083
Kelly Tobin (CSCC, Chapel Hill):	(919) 966-7825
Jim Hosking (CSCC, Chapel Hill):	(919) 962-3085

If you are not successful in reaching anyone, contact the Coordinating Center at (919) 962-6971. Ask to speak to someone who can provide assistance concerning a COMBINE trial randomization.

5.10 Tracking Systems

Chapter 3 describes tracking systems used through the screening and recruitment phase. There should also be a way to track participants through the study after they are randomized. Some information that should be tracked includes: 1) participant ID; 2) assessment “due dates”; 3) scheduled appointment date; 4) actual appointment date; 5) schedule window (3 days on either side of the due date); 6) attendance; 7) correspondence (phone calls, letters, etc.). Contact information for both the participant and the locator should also be updated on a regular basis (from screening through follow-up visits).