

# 1. Chapter 1: Overview of Study Design

## 1.1 Study Objectives

COMBINE is a multi-center, randomized clinical trial, evaluating three interventions and their combinations for the treatment of alcohol dependence. Two of the interventions will be pharmacological treatments (naltrexone and acamprosate). The third intervention will evaluate the addition of a moderate intensity behavioral therapy to a minimal therapy focused on enhancing compliance to medications and supporting reduction in drinking.

The primary objective of COMBINE is to assess the efficacy of combined behavioral and pharmacological interventions in the treatment of alcohol dependence. The goal is to determine if improvement in treatment outcomes can be achieved by various combinations of pharmacotherapy and behavioral interventions.

## 1.2 Study Design

Participants will be randomized to one of nine treatment combinations (cells). Eight cells will form a complete 2x2x2 factorial design. The ninth cell will receive the moderate intensity behavioral therapy without any medication (i.e., no active or placebo pills); this cell will also not receive Medical Management. Figure 1 presents the nine treatment combinations (see below).

Figure 1. COMBINE Treatment Combinations

### Medical Management

	Placebo	Acamprosate
Placebo	1	2
Naltrexone	3	4

### Medical Management + Psychotherapy

	Placebo	Acamprosate	No Pills
Placebo	5	6	
Naltrexone	7	8	
No Pills			9

Eleven clinical centers will recruit and randomize 125 participants (a total of 1375). All randomized participants will receive sixteen weeks of therapy, with subsequent long-term follow-up assessments. All participants will be followed for a total of 16 months post-randomization.

### **1.3 Participant Eligibility**

All study participants will be 18 or older, have a current DSM-IV diagnosis of alcohol dependence and be abstinent for a minimum of 4 and a maximum of 21 days prior to randomization. Participants currently meeting dependence criteria for any psychoactive drug other than alcohol, caffeine, nicotine, and marijuana are excluded. Detailed eligibility criteria are presented in Chapter 2.

### **1.4 Interventions**

#### **1.4.1 Behavioral Interventions**

The mandate of the RFA was to develop two behavioral interventions to provide a platform for testing the combined effects of these interventions with the pharmacotherapies selected. Two such interventions were developed, Medical Management and Combined Behavioral Intervention. There were several primary considerations guiding the development of these two interventions. Regarding Medical Management (MM), it was important that the intervention be of low intensity so as to be ecologically valid in a managed care setting. Its primary aim is the enhancement of medication compliance and support of sobriety, so as to maximize sufficient exposure to the medications to permit evaluability of their effects.

Regarding the moderate intensity behavioral intervention (CBI), it was important that it incorporate the putative strengths of the Project MATCH behavioral therapies, so as to maximize potential therapeutic gains.

Regarding the contrast of the two therapies, an additive design was chosen so that CBI was added to the MM condition. We also sought to make the two behavioral interventions sufficiently different that addition of CBI to MM would be likely to make a positive difference for a substantial proportion of participants.

Regarding both treatments, primary aims were that each treatment be manual guided so that dissemination efforts would be possible, should either or both prove to be of value; and that the manuals developed be unique to COMBINE so that they could be freely disseminated to the field without concern about copyright limitations. Lastly, both treatments were designed to be a maximum of 16 weeks duration.

##### **1.4.1.1 Medical Management**

The goal of MM is to provide a basic, minimal form of clinical intervention supporting the use of effective pharmacotherapy and reduction in drinking (sobriety). MM involves 9 sessions, with the initial session an hour long, and subsequent sessions of 15-25 minutes. During the first two weeks of treatment, sessions would be weekly; during weeks 2-12, bi-weekly; with a final visit at week 16. The therapy is delivered by a medical professional (M.D., nurse, or clinical pharmacologist).

The initial visit involves evaluation of the participant, a rationale for the treatment, education regarding the disorder, advice to abstain from alcohol, information about the pharmacotherapy, a discussion of the rationale for focusing on medication compliance, and encouragement to participate in mutual help groups. Subsequent visits include assessments of the participant's drinking status; monitoring and discussion of medication compliance; and discussion of problems that may have arisen since the prior visit. Strategies include procedures for handling medication noncompliance and dealing with participant drinking.

### **1.4.1.2 Combined Behavioral Intervention**

CBI integrates several elements of treatments tested in Project MATCH: motivational enhancement therapy, cognitive behavioral skills training, and facilitation of involvement in mutual help groups. CBI involves four phases: motivational enhancement, developing a self-change plan, implementation of selected skill modules, and monitoring and maintenance of therapeutic gains.

Phase 1 involves motivational interviewing to elicit and understand the participant's intrinsic motivations for change, followed by more structured feedback to enhance this motivation.

As the participant evidences readiness to consider change, phase 2 focuses on helping the participant to identify areas in need of change and to develop a self-change plan. This phase includes a functional analysis of the participant's drinking, as well as an assessment of psychosocial functioning. These assessments lead to the construction of an Options chart, which identifies areas upon which the next phase to treatment might focus. From the options chart a specific change plan is negotiated, using a Change Plan worksheet.

In phase 3 treatment modules selected from the menu of options are implemented. The length of each module is negotiated rather than being fixed, being determined by the relative needs of the participant for strengthening coping skills in each area. The number of sessions to be provided in phase 3 is guided by the achievement of goals identified in the change plan.

Once goals are achieved, the participant enters phase 4, consolidation and maintenance of gains. In this phase the therapist reviews with the participant the progress made with regard to each of the goals, renews participant motivation and reaffirms commitment. During phase 4 the therapist and participant may negotiate a return to phase 3 when desired. At the completion of phase 4 therapy is terminated.

The entire therapy is planned for a maximum of 20 sessions (including emergency sessions) tapered according to phase of treatment. When the participant has a spouse or significant other, it is expected that this person will also participate in therapy unless such involvement is contra-indicated. Phase 1 involves 2-3 sessions, conducted bi-weekly. Phase 2 may take the participant through sessions 4-5, also scheduled for bi-weekly meetings. Phase 3 occurs on a weekly basis and continues until goals have been accomplished or modified. Phase 4 occurs on a once a month basis.

Therapy is delivered by an experienced clinician trained in a mental health profession.

In order for the therapies to be delivered uniformly and competently, MM clinicians and CBI therapists are trained and certified by the training center. Once therapy has commenced with study participants sessions are audiotaped and randomly selected for review and feedback by the training center. CRU senior therapists who receive regular feedback regarding therapist performance from the training center conduct supervision.

## **1.4.2 Pharmacotherapy**

### **1.4.2.1 Naltrexone**

Naltrexone 50 mg and matching placebo will be obtained from the manufacturer. The dosage of naltrexone will be titrated as follows: 25 mg in the morning for days 1-4; 50 mg in the morning for days 5-7; 100 mg in the morning thereafter. The same titration schedule will be used for naltrexone placebo.

### **1.4.2.2 Acamprosate**

The manufacturer will supply Acamprosate 500 mg and matching placebo. The dosage will be constant at 3 g per day, administered as 2 tablets TID.

- 1) If an acamprosate dose is missed, it should not be taken simultaneously with the next scheduled dose; there should be a minimum of 2 hours between doses. If this is not feasible, do not take the skipped dose. Instead, wait until your next scheduled dose, and take only that dose.
- 2) Acamprosate pills should not be crushed due to an enteric coating. The destruction of this coating could result in exacerbation of GI side effects.

## **1.5 Assessments**

Assessment and data collection for COMBINE has been designed to consider the temporal needs of measuring changes that may result from both behavioral and pharmacological interventions. Initial screening will focus on participant eligibility and reasons for participation or nonparticipation. Baseline assessment domains include physical/medical/physiological, expectancies about pharmacotherapy and psychotherapy approaches to alcohol treatment, alcohol consumption and alcohol / drug involvement, readiness to change, alcohol-related craving, psychological functioning and psychiatric symptomatology, social support, involvement in mutual support groups, and quality of life. Measures of alcohol consumption and drinking patterns will be collected during treatment. In addition, measures of medication compliance, adverse consequences, mood states, perceived stress, therapeutic alliance, and processes of change will also be collected during treatment. In addition to collecting repeat information on a number of variables initially assessed at baseline, follow-up assessments will focus on alcohol consumption and drinking patterns and service utilization. These follow-up assessments will take place at weeks 8, 16, 26, 52, and 68 will provide long term data on drinking and psychosocial outcomes. Refer to Chapter 4 for a more detailed description of the psychosocial assessments and medical-related measures.

## **1.6 Study Size and Duration**

Eleven clinical centers will recruit and randomize a total of 1375 participants over 40 months, an average of 125 participants per site.

Randomized participants will receive sixteen weeks of therapy with subsequent long-term follow-up assessments. All participants will be followed for one year post-treatment, for a total of 16 months post-randomization. All participants will have follow-up assessments at weeks 8, 16, 26, 52, and 68.