Combining Medications and Behavioral Interventions for the Treatment of Alcoholism

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# Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AA</td>
<td>Alcoholics Anonymous</td>
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<tr>
<td>AAI</td>
<td>Alcoholics Anonymous Inventory</td>
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<tr>
<td>AASE</td>
<td>Alcohol Abstinence Self Efficacy</td>
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<tr>
<td>ACRDNF</td>
<td>Address Correction Requested Do Not Forward</td>
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<tr>
<td>ADS</td>
<td>Alcohol Dependence Scale</td>
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<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
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<tr>
<td>ASI</td>
<td>Addiction Severity Index</td>
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<td>AST</td>
<td>Aspartate Aminotransferase</td>
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<tr>
<td>AUDIT</td>
<td>Alcohol Use Disorders Identification Test</td>
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<tr>
<td>BAC</td>
<td>Breath Alcohol Content</td>
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<tr>
<td>β-HGC</td>
<td>Beta-Human Chorionic Gonadotropin</td>
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<tr>
<td>BSI</td>
<td>Brief Symptom Inventory</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood Urine Nitrogen</td>
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<tr>
<td>CASAA</td>
<td>Center on Alcoholism, Substance Abuse and Addictions</td>
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<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
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<tr>
<td>CBI</td>
<td>Combined Behavioral Intervention</td>
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<tr>
<td>CBT</td>
<td>Cognitive Behavioral Therapy</td>
</tr>
<tr>
<td>CC</td>
<td>Coordinating Center</td>
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<tr>
<td>CDT</td>
<td>Carbohydrate Deficient Transferin</td>
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<tr>
<td>CIWA-AR</td>
<td>Clinical Institute Withdrawal Assessment for Alcohol-revised</td>
</tr>
<tr>
<td>CRA</td>
<td>Community Reinforcement Approach</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<td>CRU</td>
<td>Clinical Research Unit</td>
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<tr>
<td>SSO</td>
<td>Supportive Significant Other</td>
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<tr>
<td>DrInC</td>
<td>Drinker Inventory of Consequences</td>
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<tr>
<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders-v. IV</td>
</tr>
<tr>
<td>DWI</td>
<td>Driving While Intoxicated</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
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<tr>
<td>GAF</td>
<td>Global Assessment of Functioning</td>
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<tr>
<td>GGT</td>
<td>Gamma Glutamyl Transferase</td>
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<tr>
<td>HMO</td>
<td>Health Management Organization</td>
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<tr>
<td>ID</td>
<td>Identification</td>
</tr>
<tr>
<td>IND</td>
<td>Investigational New Drug</td>
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<tr>
<td>IP/IPA</td>
<td>Important People Scale</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
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<tr>
<td>LFT</td>
<td>Liver Function Test</td>
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<tr>
<td>MA</td>
<td>Medical Attention</td>
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<tr>
<td>MEMS</td>
<td>Medication Event Monitoring System</td>
</tr>
<tr>
<td>MET</td>
<td>Motivation Enhancement Therapy</td>
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<tr>
<td>MM</td>
<td>Medical Management</td>
</tr>
<tr>
<td>NIAAA</td>
<td>National Institute of Alcohol Abuse and Alcoholism</td>
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<tr>
<td>NIH</td>
<td>National Institute of Health</td>
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<tr>
<td>NMDA</td>
<td>N-Methyl-D-Aspartate</td>
</tr>
<tr>
<td>OCDS</td>
<td>Obsessive Compulsive Drinking Scale</td>
</tr>
<tr>
<td>PC</td>
<td>Project Coordinator</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>PCQ</td>
<td>Processes of Change Questionnaire</td>
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<tr>
<td>PDA</td>
<td>Percent Days Abstinent</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
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<tr>
<td>POMS</td>
<td>Profile of Mood States</td>
</tr>
<tr>
<td>PSS</td>
<td>Perceived Stress Scale</td>
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<tr>
<td>RA</td>
<td>Research Assistant</td>
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<tr>
<td>RCT</td>
<td>Randomized Clinical Trial</td>
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<tr>
<td>RR</td>
<td>Rational Recovery</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAFTEE-GI</td>
<td>Systematic Assessment for Treatment Emergent Events-General Inquiry</td>
</tr>
<tr>
<td>SCID</td>
<td>Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum Glutamic Oxalacetic Transaminase</td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum Glutamic Pyruvic Transaminase</td>
</tr>
<tr>
<td>SMART</td>
<td>Self-Management and Recovery Training</td>
</tr>
<tr>
<td>SOS</td>
<td>Secular Society for Sobriety</td>
</tr>
<tr>
<td>TEE</td>
<td>Treatment Experience and Expectancies Questionnaire</td>
</tr>
<tr>
<td>TLFB</td>
<td>Timeline Followback Interview</td>
</tr>
<tr>
<td>TSF</td>
<td>Twelve-Step Facilitation</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper Limit of Normal Range</td>
</tr>
<tr>
<td>URICA</td>
<td>University of Rhode Island Change Assessment Scale</td>
</tr>
<tr>
<td>WAI</td>
<td>Working Alliance Inventory</td>
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<tr>
<td>WFS</td>
<td>Women for Sobriety</td>
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<tr>
<td>WHO/WHOQOL</td>
<td>World Health Organization Quality of Life</td>
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CHAPTER 1: Introduction

1.1 Background and Significance

Alcoholism is a disorder with substantial morbidity and mortality, and the development of efficacious treatment methods is essential to reduce medical, social and human costs. The approval of new pharmacological treatments, including naltrexone in the United States and acamprosate in Europe, and the development of behavioral and psychosocial interventions, represent significant advances in the methods available to treat alcoholism.

Over the past decade research on medications to treat alcoholism has rapidly expanded (Litten et al., 1998). In particular, advances have been made in understanding the biology underlying drinking behavior, thereby suggesting new possibilities for pharmacological treatments. For example, it is now known that multiple neurotransmitter systems are involved in problem drinking. These include opioid, serotonin, dopamine, gamma-aminobutyric acid (GABA), and glutamate systems. Several medications that affect these neurotransmitter and neuromodulator systems have been tested in humans, including opioid antagonists, selective serotonin reuptake inhibitors, 5-HT3 antagonists, 5-HT2 antagonists, 5-HT1A agonists, dopamine agonists, and GABAergic agents.

Naltrexone, a nonspecific opioid antagonist, is the only non-aversive pharmacotherapy for alcoholism that is approved by the US Food and Drug Administration. Acamprosate, the calcium salt of acetylhomotaurine, is used to treat alcoholism in Europe, but it is not yet approved for use in the US. Several studies have shown that it is superior to placebo in promoting abstinence from alcohol (Paille et al, 1995; Pelc et al, 1997; Whitworth et al, 1996). The mechanism of action of acamprosate may involve alteration of neuronal excitability at the N-Methyl-D-Aspartate (NMDA) receptor and other non-opioid effects.

Naltrexone and acamprosate have very different mechanisms of action and presumably target different aspects of the alcohol dependence syndrome. As a result, the combined use of these two medications may yield a more effective treatment. Acamprosate may be particularly useful in helping participants avoid initial alcohol consumption and enhancing treatment retention by attenuating protracted alcohol withdrawal. Naltrexone may be particularly efficacious in reducing the likelihood of heavy drinking following a slip.

Likewise, important advances have been made in the development of behavioral interventions to treat alcoholism, including motivationally based, targeted behavioral strategies and interpersonal support treatments. Pharmacological and behavioral treatments are not mutually exclusive and indeed may enhance each other. Thus, pharmacotherapies may reduce craving for alcohol and/or the reinforcement experienced from drinking alcohol. Behavioral therapies provide skills for patients to maintain sobriety for extended periods of time. Recent studies have demonstrated that the addition of pharmacotherapy to psychosocial treatment improves outcome in alcohol dependence (O’Malley et al., 1992; Volpicelli et al., 1992).

COMBINE is a clinical trial designed to evaluate the efficacy of acamprosate, naltrexone, and psychotherapy, individually and in combination, in the treatment of alcohol dependence. The remainder of this chapter summarizes the studies providing the scientific basis for the project.
1.2 Promising pharmacological interventions

1.2.1 Naltrexone

1.2.1.1 Efficacy

It has been hypothesized that the reinforcing effects of alcohol are mediated in part via activation of the endogenous opioid system, and that the opioid antagonist naltrexone attenuates the reinforcing effects of alcohol via blocking opioid receptors (for a review see Froelich, 1993). Naltrexone was approved for use in the treatment of alcoholism based on two studies demonstrating that the drug was efficacious when provided as an adjunct to psychosocial treatment (O'Malley et al., 1992; Volpicelli et al., 1992). In a combined analysis of data from these two studies (O'Malley et al., 1996), patients who received 50 mg daily of naltrexone for 12 weeks were more likely to remain abstinent and to avoid relapse to heavy drinking compared with placebo treated patients. Among the set of nonabstinent patients, naltrexone also reduced the risk of relapse to heavy drinking following an initial drink. Retrospective reports of patients in clinical trials who lapsed suggest that naltrexone reduced craving, intoxication levels and the incentive to continue drinking (O'Malley et al., 1995; Volpicelli et al., 1995). Thus, naltrexone appears to target craving for alcohol and loss of control over drinking following a lapse in abstinence. Naltrexone does not appear to reduce the symptoms of acute withdrawal (Spanagel & Ziegglansberger, 1997).

Optimal doses of naltrexone for alcoholism therapy have not been studied adequately. Although a 50 mg daily dose is efficacious, clinical experience and unpublished studies suggest that higher doses may be necessary for some patients (Volpicelli, unpublished; McCaul, unpublished). Furthermore, the therapeutic role of 6-beta naltrexol, the major metabolite of naltrexone, remains uncertain. It has been known for over 20 years that plasma levels of 6-beta naltrexol are variable among subjects (Cone et al 1974; Vereby et al, 1976; Wall et al, 1981). The plasma ratios of metabolite to parent drug varied from 1.5:1 to 10:1 in one study (Vereby et al, 1976). Urinary ratios were 10:1 in a more recent study (King et al, 1997). The potency of the opiate antagonizing effect of 6-beta naltrexol is less than that of naltrexone, with ratios ranging from 1:12 to 1:53 in animal models (Cone et al, 1974; Fujimoto et al, 1975). Clinical studies indicate that levels of 6-beta naltrexol may correlate positively with adverse effects (King et al, 1997) and efficacy (McCaul, unpublished). Higher doses may also provide greater protection against the effects of missed doses, an important consideration in light of recent research which has found that the outcome of naltrexone therapy is related to medication compliance (Volpicelli et al., 1997). These findings suggest the need for further study of the 100 mg dose of naltrexone and monitoring of plasma levels of naltrexone and 6-beta naltrexol during trials of efficacy.

1.2.1.2 Toxicity

The safety of naltrexone in alcoholics has been demonstrated in a large multicenter study (Croop et al, 1997). In that open-label study of 570 alcohol dependent patients treated with doses of naltrexone as high as 200 mg daily the most common new-onset adverse effects were nausea (9.8%) and headache (6.6%). Fifteen percent of naltrexone patients discontinued the drug due to adverse effects, most commonly nausea. Preliminary findings also indicate that naltrexone is well tolerated in adolescents (Lifrak et al, 1997) and elderly patients (Oslin et al, 1997). Clinical experience in opioid addicts supports the safety of 100-150 mg doses administered three times weekly (Kleber 1985). The most serious adverse effect of naltrexone is liver toxicity, although the largest studies found that mean levels of liver enzymes decreased over the course of naltrexone therapy of alcoholism (Croop et al, 1997; O’Malley et al 1995). Doses higher than 50 mg have also been studied. The safety of both a 300 mg daily dose (Huntington’s Disease, Sax
et al, 1994) and a 400 mg daily dose (eating disorders, Marrazzi et al, 1997) has been reported. On the other hand, studies of dementia and obesity using doses as high as 300 mg daily found elevated transaminase levels in some patients (Atkinson et al, 1985; Pfohl et al, 1986). Clinical experience with 100 mg daily doses in alcoholic patients indicates that it is not associated with elevated liver enzymes or clinically significant liver damage (Volpicelli, unpublished).

There have been no systematic studies of drug-drug interactions with naltrexone. The most important potential interaction is insensitivity to opioid analgesics for 72 hours after the naltrexone dose. If alternative agents cannot be used, increased doses of opioids are used with respiratory monitoring. Older studies have reported that the metabolism of naltrexone to 6-beta naltrexol is carried out by a cytosolic reductase, although specific cytochromal pathways have not been studied (DuPont Product Information). It is not certain whether naltrexone alters the metabolism of other drugs although it appears unlikely. Naltrexone does not alter antipyrine clearance (an older test to screen for drug interactions), although in one species it did increase the microsomal fraction.

1.2.2 Acamprosate

1.2.2.1 Efficacy

Several European studies suggest that acamprosate increases abstinence rates and retention in treatment among recently detoxified patients (Lhuintre et al. 1990; Paille et al., 1995; Poldrugo, 1997; Sass et al., 1996; Whitworth et al., 1996; Pelc et al., 1997). Whitworth et al., (1996) completed a study with 455 alcohol dependent patients. At the end of the 1-year treatment, 18 percent of acamprosate-treated patients had been abstinent in contrast with 7 percent of placebo-treated subjects. One year after termination of treatment the acamprosate group still demonstrated a significantly higher rate of abstinence than did the placebo group (12 percent versus 5 percent). Sass et al., (1996) reported results from a 12-site study with 272 detoxified alcohol dependent patients. Following 48 weeks of treatment, 43 percent of the acamprosate-treated subjects had sustained sobriety versus 21 percent for the placebo group. The side-effect profiles were identical for acamprosate- and placebo-treated subjects. Mann et al., (1995) analyzed pooled European data consisting of over three thousand alcohol dependent subjects from 11 independent acamprosate studies. The acamprosate group had significantly more sustained abstinence, better treatment retention, and those who drank did so on significantly fewer days than did the placebo-treated subjects.

While drugs such as benzodiazepines are used routinely to manage severe complications of withdrawal (i.e., delirium, seizures), less severe signs and symptoms of withdrawal may also influence the course of alcohol rehabilitation. For example, these mildly aversive effects of abstinence may lead to withdrawal-induced craving for alcohol and drinking, thus providing negative reinforcement of drinking (Hershon, 1977; Koob and Bloom, 1988). While relatively unexplored, mild withdrawal symptomatology may also contribute in part to the high dropout rate (19-70%) from outpatient alcohol and drug abuse treatment programs (Pettinati et al., 1996).

Acute alcohol withdrawal is associated with glutamatergic hyperactivity and down-regulation of GABA function (Tsai et al 1995; Abi-Dargham et al. 1995 RSA; Behar et al 1996 RSA). Acamprosate, an acetylhomotaurine derivative, is hypothesized to attenuate signs and symptoms of protracted alcohol withdrawal, by altering glutamate activity and GABA transmission (Littleton 1995). Both NMDA antagonists and GABA agonists suppress alcohol withdrawal (Glue & Nutt, 1990). In rats, acamprosate suppresses ethanol withdrawal (GeWiss et al 1991; Gutierrez et al 1987) and reduces ethanol administration (Biozzi et al 1984). The mechanisms
through which acamprosate suppresses withdrawal and drinking are not completely clear at this
time. Acamprosate may facilitate GABA function via inhibition of GABA-transaminase.
Consistent with this view, acamprosate inhibits bicuculline and pentylentetrazole induced
seizures (see Nalpas et al 1990 for review). However, recent data questions the behavioral
significance of acamprosate's actions on GABA systems (Lovingier and Zieglsangberger 1996 for
review). Similarly, acamprosate may suppress withdrawal and drinking by reducing
glutamatergic tone. Consistent with this view, acamprosate has been reported to block both
NMDA and non-NMDA (kainate) glutamate receptor medicated electrophysiological effects in
the cerebral cortex. However, facilitatory effects on NMDA receptors have been reported in
hippocampus and nucleus accumbens (Madamba 1996). Thus, the exact mechanism of
action of acamprosate remains to be determined.

Present preclinical and clinical data suggest that acamprosate may suppress protracted alcohol
withdrawal, that it is well tolerated, and that it increases retention in treatment and abstinence
rates. Very little is known about the effects of acamprosate on alcohol craving, alcohol
intoxication, or on the amount consumed following a "slip" in alcohol dependent patients in
treatment. While the amount consumed on an occasion is a typical outcome in pharmacotherapy
studies conducted in the United States, the clinical trials conducted in Europe on acamprosate
have not collected this information. Given that the clinical trials of acamprosate have focused
on abstinence as the primary outcome measure, additional research is needed to determine
whether acamprosate can affect other outcomes such as drinking amounts or craving for more
alcohol.

1.2.2.2 Toxicity

Acamprosate is well tolerated when administered in 3 daily doses of 1.2-2 grams. The most
common adverse effects are gastrointestinal, with diarrhea reported in 7-20% patients in clinical
trials, roughly twice that of the placebo group. Other adverse effects that have been reported, but
not at rates consistently greater than placebo, include abdominal pain, nausea, vomiting, pruritis,
skin rashes, dizziness, confusion, drowsiness, headache, and altered libido. It is notable that the
percentage of patients withdrawn from the European clinical trials did not differ between
acamprosate and placebo groups.

European clinical trials suggest that 2 grams daily have greater efficacy than 1.3 grams. The
multicenter US trial is comparing both 2 and 3 grams to placebo. Findings from that trial will
provide safety and efficacy data for the 3-gram dosage. Acamprosate is slowly absorbed from the
gastrointestinal tract, with large interindividual variation. Concomitant food decreases
bioavailability by approximately 20%. The drug is eliminated unchanged by renal excretion, with
an apparent half-life of 13 hours after oral administration. No clinically significant drug-drug
interactions have been reported, and ethanol does not alter acamprosate elimination. Impaired
renal function lowers acamprosate clearance.

There are no data currently published on the use of naltrexone with acamprosate, however safety
and tolerability studies of the combination will be completed and analyzed prior to the initiation
of the current study. Although it is possible that naltrexone could alter either absorption or renal
elimination of acamprosate, this seems unlikely. Any effects of naltrexone on hepatic function
should not alter acamprosate clearance because acamprosate is not metabolized and is excreted
unchanged in urine. Given that both medications have gastro-intestinal side effects (nausea for
naltrexone, diarrhea for acamprosate), it is conceivable that these added effects might be a
drawback of the combination for some patients. Available evidence, however, suggests that
naltrexone and acamprosate should be well tolerated when administered concomitantly.
1.3 Promising Behavioral Interventions

COMBINE was undertaken with the expectation that alcoholism treatment outcomes can be enhanced by combining effective behavioral and pharmacological therapies. Two modalities of behavioral treatment were developed for the study, the COMBINE Behavioral Intervention (CBI) and Medical Management (MM). CBI, a moderate intensity intervention, takes advantage of the Project MATCH findings. It incorporates the putative strengths of each of the three Project MATCH treatments: Twelve-Step Facilitation, Motivational Enhancement Therapy and Cognitive Behavioral Therapy. On the other hand, Medical Management (MM), a less intensive intervention, was designed to enhance medication compliance and support of sobriety, while being able to be readily incorporated into the daily routine of busy health care practitioners in primary care or managed care settings. It is intended to maximize exposure to the medications, facilitating evaluation of their effects. It represents a potentially cost-effective alternative to CBI. Other features, described below, were also incorporated into the behavioral treatments.

1. The two behavioral interventions are incorporated into an additive design, such that the more intensive intervention is an add-on treatment to the less intensive treatment.
2. The difference between MM and CBI is large enough so that the addition of the moderate intensity therapy to the less intense behavioral intervention is likely to improve outcome.
3. Each treatment is manual-guided, to ensure standardization across multiple sites and so that dissemination of the treatments will be maximized should one, the other or both be found to be valuable.
4. The therapy manuals are unique to COMBINE, so that they can be freely disseminated to the field, without concern about copyright limitations.

Since the study medications will be administered over a sixteen-week period, both the low and moderate intensity treatments are provided over the same sixteen-week duration. Consideration of the ecological validity of treatment delivery led to a decision that both treatments would be delivered in a protocol where the frequency of treatment would be initially more intensive, followed by a tapering of intensity throughout the remainder of the sixteen-week period.

1.3.1 Medical Management Treatment: Background and Rationale

Medical Management was derived from what has been generically termed minimal or brief treatment approaches (Heather, 1995). These approaches have been employed opportunistically as part of health care promotion packages in nonspecialized settings, with individuals seen primarily for health-related concerns rather than alcohol problems (Fleming, et al., 1997). Brief interventions have also been employed as stand-alone treatments in specialized settings with individuals seeking help for alcohol-related problems (Edwards & Taylor, 1994; Zweben, et al, 1988; Drummond, et al, 1990). Depending upon the setting and/or circumstances and conditions of patients, brief interventions may vary in terms of the levels of intensity and the kinds of the intervention strategies employed in the sessions. In primary care settings, brief intervention usually consists of one or two 15-30-minute sessions where feedback is provided on the personal risk and negative consequences of drinking behavior and advice is offered about how to change the drinking behavior (Fleming, et al, 1997). These sessions are usually conducted by nonspecialists or health care practitioners. In specialized settings, brief interventions are typically carried out by specialists and entail a more extensive assessment and feedback session (e.g., 90 minutes) with greater emphasis devoted to enhancing motivation and improving coping resources of patients. (Orford, et al, 1977; Zweben et al, 1988; Donovan, et al, 1994). The number of sessions in the brief intervention approaches can range from one to six 30-60 minute sessions depending upon the aims of the particular treatment approach (Heather, 1995, 1996; Bien, et al, 1993).
Initially, brief interventions were employed as minimal or control treatment conditions in studies examining the efficacy of more intensive traditional approaches. However, by virtue of their effectiveness, brief interventions have become a viable alternative to more intensive interventions for treating alcohol dependent patients. Bien and his colleagues (1993) in a meta-analysis found that brief interventions produced drinking outcomes that were at least similar to those observed following more intensive or conventional treatments with help-seeking patients having varying levels of severity of alcohol problems.

Trials of pharmacotherapies have adopted many of the components of brief intervention such as the provision of self-help pamphlets and referral to self-help groups, while adding a series of strategies aimed at facilitating patients’ compliance with the medication regimen. Such strategies have been systematically employed for dealing with failure to comply with medication administration. These minimal or brief treatments are intended for patients in short-term ambulatory pharmacotherapy trials where alcohol problems are viewed as a medical illness and treatment is provided in the context of a health care provider/patient relationship.

Principal investigators who had completed and/or were conducting on-going pharmacotherapy studies made available their brief intervention manuals and allowed them to be adapted for COMBINE. A review of these manuals revealed that many of them contained elements of the more intensive CBI treatment condition, such as cognitive-behavioral (CB) skills (e.g., relapse prevention) and/or aspects of motivational enhancement therapy (MET) (e.g., addressing patients’ underlying ambivalence by using techniques such as eliciting self-motivational statements). Since both cognitive behavioral and motivational enhancement techniques are included in the CBI condition, it was important to ensure that MM treatment did not contain aspects of either of these treatments.

Similarly, detailed discussions of 12-step groups (beyond encouraging people to go to 12-step or other mutual help meetings) were excluded from the MM manual, since CBI contains mutual group program facilitation. Each of these elements was excluded from the MM manual in order to maximize the contrast between the MM alone and MM + CBI treatment conditions.

Conversely, because referral to a mutual self help group is a practice that does not involve additional contact between MM clinician and participant and because the referral to mutual self help groups is a common feature of primary care interventions, this was retained as part of the MM condition.

In order to increase the probability that participants would comply with the medications, care was taken to limit the number of MM contacts and consequently, the number of MM sessions was set at 9 over a 16-week period. To enhance ecological validity, (i.e. the feasibility of the approach for use in a primary care setting), apart from the initial treatment appointment of 40-60 minutes, MM sessions are 15-25 minutes in duration, depending upon participant status and need.

In choosing the MM treatment, emphasis was placed on strategies that could be learned with minimal training and delivered rapidly with an orientation compatible with the delivery of other types of medical care. The major goal of Medical Management (MM) treatment is to provide a basic, brief form of clinical intervention that supports the use of effective pharmacotherapy. Detailed strategies for dealing with sources of failure to comply with medication administration were devised by combining the most useful strategies developed in prior pharmacotherapy trials. All participants in COMBINE (except those in the CBI alone cell) will receive MM therapy.
Half of the participants will receive the COMBINE Behavioral Intervention (CBI) as well.

In sum, the MM treatment was developed from common themes in existing treatment manuals for brief therapy, while eliminating references to CBT, MET, and detailed 12-step techniques, and focuses primarily on effective techniques to enhance medication compliance while also supporting the participant’s efforts to change his or her drinking habits and abstain from alcohol. The primary objectives of this low intensity behavioral intervention are to facilitate medication compliance and abstinence from alcohol.

1.3.2 COMBINE Behavioral Intervention: Background and Rationale

While a number of verbal therapies have evidence of efficacy, none have been studied in a multisite, large sample study as was done in Project MATCH. In this multisite study (Project MATCH Research Group, 1997), 1726 patients were randomized to one of three therapies for 12 weeks: Twelve-Step Facilitation (TSF), Cognitive Behavioral Therapy (CBT) or Motivation Enhancement Therapy (MET). Project MATCH findings showed marked improvement in drinking for the three MATCH treatments during the 12-month follow-up. This improvement was sustained at the subsequent 3-year follow-up (Project MATCH Research Group, 1998). In addition, these interventions demonstrated relatively high retention rates and high levels of patient satisfaction and were feasible to implement in a clinical trial. In clinical practice, therapists are likely to employ a range of techniques from each of these three distinct treatments. Thus, it is highly desirable to examine the efficacy of a broader model of treatment that incorporates the putative active ingredients of each of these Project MATCH therapies.

The COMBINE 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 includes some standard elements that are delivered to all participants in Phase 1 and Phase 2, an individualized Phase 3 in which modules are selected from a menu of options in order to address participants personal needs and preferences, followed by Phase 4, a maintenance period during which therapeutic gains are monitored and strengthened. All of the elements in CBI have been tested in prior studies, and showed reasonable evidence of efficacy for the treatment of alcohol problems. They are combined here to create a state-of-the-art treatment approach that is both empirically sound and sufficiently flexible to be applicable in routine clinical practice.

CBI relies on the principles of social learning theory and motivational psychology in choosing modules, which are most likely to be effective with each individual participant. The bases for matching modules to participants have varied widely including clinical judgement of the therapist and the participant’s choice from a menu of options (Miller, 1989). An alternative model would be to employ matching algorithms based on hypothesized interactions between certain participant characteristics and treatment modalities. However, the findings of Project MATCH provided little evidence that treatment effectiveness can be enhanced by matching patients to treatments (Project MATCH Research Group, 1997). Instead, COMBINE opted to analyze the problem behavior in the context of the person's social environment while trying to understand what functions the problem behavior has served. Treatment modules are selected on a classic behavioral approach involving a functional analysis of the problem behavior. The CBI therapist looks for stimuli (i.e., antecedents) that are related to the problem behavior (i.e., drinking) and searches for factors that reinforce (i.e., consequences) such behavior.

Thus, the underlying framework employed in CBI includes: (1) a menu of empirically sound treatment components and (2) a process of functional analysis for matching participants to these components. Moreover, the philosophy and principles underlying MET provide the therapeutic
approach to guide the participants’ choice of modules available from cognitive and behavioral therapies and to maximize the likelihood of their being utilized to the participants benefit. Incorporation of a strong referral to a mutual help group takes advantage of one of the active ingredients in TSF, increased use of AA, with its associated better drinking outcomes (Project MATCH Research Group, 1998). Combining many of the putative ingredients of the three MATCH therapies and conducting a functional analysis of the problem behavior are expected to produce better outcomes than prior behavioral treatment approaches.

Reviews of prior studies of behavioral interventions such as CBT indicate that comparisons between alternative theoretically coherent treatments generally yield non-significant differences, while add-on designs are likely to yield significant differences favoring the add-on component (Morgenstern and Longabaugh, 1998). Therefore, an add-on design was employed to maximize the likelihood that a moderate intensity behavioral treatment would show incremental benefits. Thus as previously stated *all* participants in CBI (except those in CBI alone condition, i.e. cell 9) will also receive MM treatment.

### 1.3.3 Research Basis for the Four Key Elements of CBI

#### 1.3.3.1 Community Reinforcement Approach

COMBINE has drawn upon the Community Reinforcement Approach (CRA) in developing a framework for integrating functional analysis, behavioral skill training, and family involvement in the treatment of alcohol problems. In the current approach emphasis is not placed on insights or transactions that occur within the therapy room, but on changing environmental contingencies to provide a lifestyle that is more rewarding than drinking. Within this model drinking is viewed as a behavior maintained and modifiable by positive reinforcement in the individual's real-life community context.

Such a comprehensive and systematic approach was developed for the treatment of alcohol problems by Nathan Azrin and his colleagues in their pioneer CRA study (Azrin et al, 1982; Hunt & Azrin, 1973). With few exceptions (Miller, 1985) CRA has been supported as more effective than conventional methods with inpatients (Azrin, et al, 1982; Hunt & Azrin, 1973) outpatients (Azrin, Sisson, Meyers, & Godley, 1982), and homeless individuals (Meyers & Smith, 1995). Other studies have supported the efficacy of the CRA in treating heroin (Abbott, Weller, Delaney, & Moore, 1998) and cocaine dependence (Higgins et al., 1991). The volume and methodology of the CRA studies have placed it on the list of most strongly supported treatment methods for alcohol problems in virtually every review of empirical studies (Finney & Monahan, 1986; Holder et al., 1991; Mattick & Jarvis, 1992; Miller et al., 1998).

#### 1.3.3.2 Motivational interviewing

Other research from the past two decades points to the importance of participant motivation as a determinant of treatment outcome. In Project MATCH (1997), for example, participant motivation proved to be one of the strongest predictors of both short- and long-term drinking outcomes. As reviewed below, studies have also documented the efficacy of certain interventions designed to enhance participant motivation for change.

Project MATCH (1993) tested a four-session motivational enhancement therapy (MET) as a stand-alone aftercare and outpatient treatment. Despite the fact that MET differed in intensity, philosophy and theoretical orientation from CBT and TSF, it (MET) had efficacy equivalent to the other two treatments (CBT and TSF). While TSF and CBT yielded slightly greater (2 abstinent days per month) reductions in alcohol consumption during the active treatment of
outpatients, post-treatment follow-up of drinking rates did not significantly differ among the three treatments (Project MATCH Research Group, 1997; 1998).

Others have tested the efficacy of motivational interviewing and closely related approaches with diverse populations. Significantly improved outcomes have been reported in clinical trials with methadone-maintained opiate users (Saunders, Wilkinson, & Phillips, 1995), marijuana users (Stephens, Roffman, Cleaveland, Curtin, & Wertz, 1994), severely dependent drinkers (Allsop, Saunders, Phillips, & Carr, 1997), pregnant heavy drinkers (Handmaker, 1993), and heavy drinkers in college (Baer, Marlatt, Kivlahan, Fromme, Larimer, & Williams, 1992), or identified through health care settings (Heather, Rollnick, Bell, & Richmond, 1996; Senft et al., 1997; Woolard, Belin, Lord, Puddey, MacAdam, & Rouse, 1995). Adaptations of motivational interviewing have also been demonstrated to be effective in trials of cardiovascular rehabilitation (Scales, 1997) and diabetes management (Smith, Heckemeyer, Kratt, & Mason, 1997). One negative trial has been reported by Kuchipudi et al. (1990) in treating relapsed alcohol dependent patients with gastrointestinal disease.

In sum, motivational enhancement methods have been found in at least 16 controlled trials to improve compliance and/or outcomes in treatment for a range of chronic problems. The three primary components of MET - structured assessment feedback, therapeutic empathy and motivational interviewing techniques (i.e., methods employed to address patient ambivalence/resistance) have been tested separately as well as in combination. Personal feedback alone, without therapist contact, was also found to suppress heavy drinking, although the effect was smaller than that observed in the in-person Drinker's Check-up Study conducted by Miller and his colleagues (1988) (Agostinelli, Brown, & Miller, 1995). Therapeutic empathy, (Miller et al., 1980, Valle, 1981) and motivational interviewing (e.g., Handmaker, 1993; Heather et al., 1996; Saunders et al., 1995) appear to exert beneficial effects apart from the context of assessment feedback. In combination, they enhance the outcomes of diverse treatment programs. For this reason, motivational interviewing and assessment feedback comprise the first phase of the COMBINE Behavioral Intervention (CBI). This is consistent with earlier, albeit less systematic, attempts to address motivational issues at the outset of CRA treatment (e.g., Azrin et al., 1982; cf. Meyers & Smith, 1995).

1.3.3.3 Mutual Help Group Involvement

A third element encompassed in CBI is involvement of the participant in a mutual help group. Research, for example, consistently supports a modestly positive association between participant involvement in Alcoholics Anonymous (AA) and more favorable treatment outcomes (Emrick, Tonigan, Montgomery, & Little, 1993), a finding upheld in Project MATCH (1997). The consistency of this finding, in the context of matching research, led Glaser (1993, p. 392) to opine that "everyone should be encouraged to try AA" but that "no one should be required to attend." Participants in Project MATCH (1997) who were assigned to the twelve-step facilitation therapy also showed a modest but enduring advantage when continuous abstinence was used as the outcome criterion.

For these reasons, encouragement to participate in a mutual help group was incorporated as a standard module in CBI. Because a range of other mutual help organizations has become available (though little is yet known of their effectiveness), the module emphasizes sampling from AA or other options available in the participant's vicinity. It incorporates systematic encouragement procedures developed within the community reinforcement approach, and which have been shown to be effective in increasing group attendance (Sisson & Mallams, 1981).
1.3.3.4 Supportive Significant Other Involvement (SSO)

The fourth component entails the involvement of the Supportive Significant Other (SSO) as an active participant in CBI. Conceivably, the SSO could be a child, parent, friend or clergyman but in most cases it has been a spouse or live-in partner. The SSO can play a valuable role throughout all phases of CBI treatment. By providing emotional support, identifying obstacles to change, sharing activities incompatible with drinking (e.g., church attendance and participating in alcohol-free events) and helping to facilitate medication and treatment compliance, SSOs can help participants achieve a sustained period of abstinence.

Evidence clearly supports the value of SSO involvement in the treatment of alcohol problems. Studies on SSO-involved alcoholism treatment have reported favorable outcomes regardless of theoretical approach (i.e., systems theory or social learning theory) and especially if positive ties have existed between the parties involved (SSO and participant) prior to the initiation of treatment (cf., O'Farrell, 1993, Sisson & Azrin, 1986; Zweben, Pearlman & Li, 1988; Longabaugh, Beattie, Noel, Stout, & Malloy, 1993; Miller et al., 1998). Longabaugh and his colleagues (1993) found that individuals who have strong investment in the patient’s abstinence and whose support for abstinence is highly valued by the participant are optimal candidates for SSO involvement.

1.4 Integration of Psychosocial and Pharmacological Treatments

The literature reviewed above provides much promising evidence of the efficacy of a number of psychosocial treatments and new pharmacological agents. It is timely to now conduct studies of regimens which systematically combine these two approaches to determine if outcomes can be further improved. Several features are desirable for inclusion in this new generation of studies. The methodological advantages provided by multisite clinical trials, such as large sample size and enhanced power over single site studies, are important generic considerations in the design of these new studies. More specific features that are desirable to advance over past work are mentioned below. COMBINE was designed to address features 1-3, with feature #4 remaining a future goal for both behavioral and neuropharmacologic research.

(1) A key requirement is that the clinical trial design be appropriate to address two critical questions: (a) Do combinations of drugs produce more favorable outcomes than when given singly?, and (b) Do combinations of drugs and psychosocial therapies produce better outcomes than either component given alone? COMBINE is designed to evaluate the efficacy of the two most promising medications currently available (naltrexone and acamprosate), singly, and together, when provided with two levels of psychosocial treatment. The two levels of psychosocial therapy consist of a minimal and highly portable treatment, and a moderately intensive specialized treatment. The project will compare the efficacy of these medications (alone and jointly) within two levels of psychotherapeutic intensity in a large sample, an approach hitherto not undertaken.

(2) Past studies have not articulated what constitutes the optimal parameters of intensity, content, duration, and sequencing of the two kinds of treatment. COMBINE will attempt to address the first two of these parameters. The study will employ two intensities of psychosocial treatment, with differing content, and two medications, naltrexone and acamprosate, given within a treatment duration of 16 weeks. Related to the content and intensity of the psychosocial interventions are the practical requirements of care as it is given in today’s cost controlled environment. The
tendency is for less specialized providers to give first line treatment, with specialized settings reserved for more difficult cases. Advantages for both levels of treatment intensity can be argued for based on experience with other addictive behaviors and mental disorders, although the optimal prescription for alcoholism treatment is unclear. For example, while it seems likely that weekly contact with a treating professional is important in the early phases of treatment, the frequency and type of psychosocial intervention needed subsequently remains to be determined. Based on the history of antidepressant therapy, primary care providers will probably be increasingly important providers of pharmacological treatments for alcoholism. Thus it is essential that the efficacy of these medications be evaluated in the context of relatively minimal psychosocial treatments that could be utilized by them. However, it is also conceivable that offering a more intensive psychosocial treatment together with pharmacotherapy can maximize overall treatment outcomes. For example, overall smoking cessation rates are increased when the nicotine patch is combined with behavioral counseling compared to patch alone (Fiore et al., 1994). Similarly, the overall effectiveness of methadone maintenance is increased by the provision of more intensive concurrent psychosocial treatment (McLellan et al., 1993).

(3) It is essential that the clinical trial psychosocial intervention be standardized and fully described to enable comparison of outcomes when similar psychosocial treatments are paired with different pharmacological agents. A drawback of previous work is that most of the research with acamprosate has been conducted with unstandardized psychosocial treatments. The set of studies done in Europe of acamprosate did not control the psychosocial intervention, with variations occurring depending upon individual practices at different sites. Most of the research with naltrexone has been conducted with more intensive treatments and the effects of the drug with more minimal interventions are unknown. Therefore, the use of manual-guided, standardized interventions employing well-trained and supervised therapists and quality control monitoring throughout the trial is critical.

(4) An ultimate goal for the field is the development of models for the mechanisms of conjoint action when drugs and psychosocial agents are combined. We are beginning to understand some of the neurochemical mechanisms of drugs such as acamprosate and naltrexone and they appear to act upon two different neurotransmitter systems. Initial clinical observations have suggested that these drugs appear to affect different stages in the cessation process (i.e., abstinence versus later relapse prevention). As evidence accumulates from the many ongoing laboratory studies, the drugs’ mechanisms of action will be better understood. Likewise, studies of the processes of change occurring during behavioral interventions will identify the "active ingredients" of psychosocial interventions and the components most important in promoting behavior change. It is likely that COMBINE will contribute information on the latter and generate testable hypotheses regarding the mechanisms of action of the behavioral and pharmacological interventions.

As understanding of these complex mechanisms progress, the goal will be to complement the neurochemical effects produced by drugs with psychotherapeutic interventions in order to provide fuller support of the process of drinking cessation and relapse prevention.
CHAPTER 2: Overview of Study Design

2.1 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.

2.2 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.

Figure 1. COMBINE Treatment Combinations

<table>
<thead>
<tr>
<th>Medical Management</th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Management + Psychotherapy</th>
<th>Placebo</th>
<th>Acamprosate</th>
<th>No Pills</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>No Pills</td>
<td></td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

Eleven clinical centers will recruit and randomize a total of 1,375 participants. Randomized participants will receive sixteen weeks of therapy, with subsequent long-term follow-up assessments. All participants will be followed for a total of sixty-eight weeks post-randomization.

2.3 Participant Eligibility

All study participants will be outpatients, 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 marihuana are excluded. Detailed eligibility criteria are presented in Chapter 3.
2.4  **Interventions**

2.4.1  **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 pharmaco therapies selected. Two such interventions were developed: Medical Management and COMBINE 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 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 sixteen weeks duration.

2.4.1.1  **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 an initial session and 8 subsequent 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 3-12, 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.

2.4.1.2  **COMBINE 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 skills 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, 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 once every four weeks.

Therapy is delivered by a Masters level clinician trained in a mental health profession.

In order for the therapies to be delivered uniformly and competently, MM counselors 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. Supervision is conducted by CRU senior therapists who receive regular feedback regarding therapist performance from the training center (University of New Mexico Center on Alcoholism, Substance Abuse, and Addictions—CASAA).

2.4.2 Pharmacotherapy

2.4.2.1 Naltrexone

Naltrexone 50 mg and matching placebo will be obtained from the manufacturer. The dosage of naltrexone will be titrated as follows: 25 mg (1/2 tablet) in the morning for days 1-4; 50 mg (1 tablet) in the morning for days 5-7; 100 mg (2 tablets) in the morning thereafter. The same titration schedule will be used for naltrexone placebo.

It is permissible for naltrexone to be administered BID when evidence of side effects dictate twice a day dosing.

2.4.2.2 Acamprosate

Acamprosate 500 mg and matching placebo will be supplied by the manufacturer. The dosage will be constant at 3 g per day, administered as 2 tablets TID.
2.5 **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 the active treatment phase. 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, which will take place at weeks 8, 16, 26, 52, and 68 will provide longer term data on drinking and psychosocial outcomes.

2.6 **Endpoints**

The efficacy of the therapies will be evaluated with two co-primary outcome measures: percent days abstinent and time to relapse to heavy drinking.

2.6.1 **Percent days abstinent**

Percent days abstinent (PDA) will be evaluated using a revised version of the Form 90-AIR/ED interview developed by Project MATCH, the Form 90-AIR/ED, described in Section 7.6.1.

2.6.2 **Time to relapse to heavy drinking**

Drinks consumed per day will be evaluated using Form 90-AIR/ED. Heavy drinking will be defined as consumption of 5 or more drinks per day for males and 4 or more for females.

2.6.3 **Secondary Endpoints**

A wide variety of secondary outcome measures will be evaluated, including other measures of drinking outcomes, psychological assessments, quality of life, and measures of adverse experiences. Measures of drinking outcomes will include duration of abstinence, other measures of drinking frequency and intensity, the Drinker Inventory of Consequences, and the Alcohol Dependence Scale. Psychological assessments will include the Brief Symptom Inventory, Profile of Mood States, and the Clinical Global Assessment Scale. Quality of life will be assessed with the WHO scale. Adverse events will be assessed using the SAFTEE-GI. A standard battery of laboratory tests will be administered to evaluate physiological toxicity.

2.6.4 **Hypotheses**

The primary hypotheses will be the traditional main-effect and interaction ANOVA contrasts, based on the eight cells in the 2x2x2 factorial design. The principal aim is to evaluate the efficacy of each intervention as monotherapy and to assess the incremental efficacy of combinations of interventions.

Primary hypotheses 1-3 are the main effects of acamprosate, naltrexone, and psychotherapy. These test whether, averaged over the two other factors, there is a mean difference between the two levels of the third factor. For example the main effect of acamprosate tests whether,
averaged over the two other factors, there is a mean difference between acamprosate and placebo.

Primary Hypotheses 4-6 test the two-way interactions among pairs of interventions. For example, primary hypothesis 4 is the 2-way acamprosate by psychotherapy interaction: This tests whether the effect of psychotherapy is the same when combined with acamprosate as when combined with placebo (both averaged over naltrexone or placebo). Equivalently, it tests whether the effect of acamprosate is the same when combined with medication management as when combined with psychotherapy (both averaged over naltrexone or placebo).

Primary hypothesis 7 evaluates the 3-way acamprosate by naltrexone by psychotherapy interaction: This tests whether the simultaneous effect of all three interventions differs from that which would be predicted by the main effects and two-way interactions.

2.7 Study Size and Duration

Eleven clinical centers will recruit and randomize a total of 1,375 participants over 30 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 52 weeks post treatment, for a total of 68 weeks post-randomization. All participants will have follow-up assessments at weeks 8, 16, 26, 52, and 68.
CHAPTER 3: Eligibility

3.1 Inclusion criteria

The following inclusion criteria are to be met:

1. Male and female outpatients ≥ 18 years of age.
2. Participants will have a current DSM-IV diagnosis of alcohol dependence.
3. Participants will have signed a witnessed informed consent.
4. Participants must have been drinking a minimum of ≥ 14 drinks (females) or ≥ 21 drinks (males) on average per week over a consecutive 30-day period in the 90-day period prior to initiation of abstinence, and have two or more days of heavy drinking (defined as 4 drinks for females and 5 drinks for males) in the 90-day period prior to initiation of abstinence.
5. Participants must have had a minimum of 4 consecutive days (96 hours) of abstinence and have a CIWA < 8 prior to randomization.
6. Participants can be abstinent for a maximum of 21 days prior to randomization.
7. Participants will have no more than 21 consecutive days of planned absence during the 16 week active treatment period.
8. Participants who are able to identify at least one "locator" person to assist in tracking the participant for follow-up assessment.
9. Participants who are able to speak and understand English.

3.2 Exclusion criteria

The following exclusion criteria rule out participants:

1. Participants who meet current DSM-IV criteria for bipolar disorder, schizophrenia, bulimia/anorexia, dementia, or a psychological disorder requiring medication.
2. Participants requiring concomitant therapy with any medications that pose safety issues (see Appendix B).
3. Participants with a current diagnosis of dependence on any drug except for nicotine, cannabis, and alcohol, or habitual caffeine use. If there is a positive urine screen the participant can be retested after the (metabolic) interval appropriate to that drug. If the second urine drug screen is positive the person is excluded.
4. Participants who meet DSM-IV criteria for opiate dependence or abuse within the past 6 months, chronic treatment with any opiate-containing medications during the previous month, or urine positive for opioids.
5. Participants who have significant medical disorders that will increase the potential risk of study treatment or interfere with study participation, and participants with sensitivity to study medications or related drugs as evidenced by adverse drug experience, especially with opiate-containing analgesics, opioid antagonists, or acamprosate.
6. Participants with abnormal AST or ALT (more than 3 times the upper limit of the normal range(ULN)) or elevated bilirubin (more than 10% above the ULN). Tests may be repeated if initial results are out of range.
7. Participants who are pregnant or nursing infant(s), and women of childbearing potential not using a contraceptive method judged by the investigator to be effective.
8. Participants who intend to engage in additional formal treatment for alcohol-related problems, or who intend to continue in current treatment for alcohol-related problems during the active treatment period. Self-help treatments are not considered formal treatment.
9. Participants who have had more than seven days of inpatient treatment for substance use disorders in the 30 days previous to randomization.
10. Participants who have prior use of study medication(s) in the last 30 days.

Any question concerning the interpretation of or application of the inclusion/exclusion criteria will be referred to the medical expert at the Coordinating Center. If he is unavailable, the question will be referred to the Chairperson of the Treatment Subcommittee.
CHAPTER 4: Recruitment and Screening

4.1 General Approach to Screening and Recruitment

4.1.1 Recruitment
Methods of recruitment will vary depending upon study site and budget constraints. There are three potential sources for recruitment: 1) "In house" from in- and outpatient referrals within the study site; 2) "external sources" in- and outpatient referrals from treatment centers outside of the test site; and 3) media sources. Participant motivation could differ substantially between those recruited from a population coming in to seek treatment and those who come to treatment in response to an advertisement. Experience demonstrates that external sources and media advertisements generate the most contact with study personnel by telephone. In-house recruitment, on the other hand, will usually involve direct contact of participants by study personnel.

4.1.1.1 In House
At each of the COMBINE sites, there may be other clinics within the setting that may not be included in COMBINE, but may attract patients eligible for COMBINE. Therefore, staff within the facility but external to the test site should be informed of the existence of the study and eligibility criteria. Ensuring the local visibility of the study can provide an additional source of participant referrals.

4.1.1.2 External Sources
External sources within the vicinity of the test site can be tapped to increase recruitment. Moreover, some of these sources can be useful for enhancing the recruitment of minority participants who may be under represented at the test site. Because additional meetings may tax the resources of the staff, presentation of the study can be added onto regular staff meetings. Study sponsored breakfasts or lunches can enhance attendance and commitment to referrals. The meeting should be used to present the protocol capitalizing on the benefits for the participants, particularly participants with few resources and alternatives. Contact information with study logos can be left with staff members, and a staff member who is willing to serve as a monthly contact should be identified. When considering external sources, it is important to approach programs that do not offer the same kinds of services as those that will be offered by COMBINE. Agencies that only offer detoxification without any additional services or agencies that offer both detoxification and follow-up only to participants with insurance are good examples of appropriate external sources.

4.1.1.3 Media
Before using media be aware of the requirements of your institution and the law. Some institutions require that media advertisements have a particular form, carry the institution’s logo or be reviewed prior to placement. In addition, the Americans for Disabilities Act requires that University public service announcements must be close-captioned.

4.1.1.4 Television
Public Announcement Stations may be utilized and are free. Hospital PR departments should be made aware of the trial and the prestige it brings to the hospital. The study can be promoted by having local news stations cover the trial in one of their regular medical segments (which is a regular segment on most local news stations). Once again, this coverage is free and will generate many phone calls.
4.1.1.5 Radio
Radio advertising is among the most expensive, depending on the frequency of announcements and the time slot. It is important to consider the target population. Some study sites will do well with Country music stations whereas other study sites might consider "Oldies" stations. Prices for airtime can vary by $1,000. With some negotiation, sales representatives will occasionally include extra airtime during non-peak hours. Obtain several quotes and promote some competition for the price between sales reps.

4.1.1.6 Newspaper
Newspaper advertisements in the main local newspaper are also expensive, but less costly than radio. Furthermore, newspapers and radio announcements seem to reach different populations. Alternating radio and newspaper can increase recruitment during a lull. Responses to these advertisements, however, may vary with site. Different newspaper sections can be differentially effective in reaching different types of prospective participants. For example, some newspapers have special sections targeted to women readers or to a particular minority group. Also, placement in the paper can be important. For example, advertisements by the television section can be more effective than one in the financial section.

4.1.2 Screening
In general, the approach to screening and recruitment is one of using multiple tiers characterized by relatively higher sensitivity and lower specificity questions early on and relatively lower sensitivity and higher specificity as screening continues. The intent is to assume that all participants are eligible until proved otherwise. Such an intent, combined with relatively general screening early and more specific, labor-intensive screening later (e.g. medical qualification) should maximize the number of eligible participants and minimize cost. The flow chart in Fig 1 illustrates this process. This flow chart is meant to be a guide through the screening process but some modifications can be made as needed. For example, a consent form to collect demographic data may not be required by some IRBs, and may be omitted. Furthermore, the baseline assessment battery may be distributed throughout the screening process, again with the idea of minimizing of labor-intensive assessment early in the screening.

4.1.2.1 Initial participant contact via phone or in person
Although initial phone contact is fine, and may be the best that can be accomplished, generally it is preferable to conduct only the most superficial screens on the telephone. This is a complicated study and it may be easy for the participant to be overwhelmed by the time requirement. The interpersonal dynamics and the willingness to becoming part of the trial are enhanced by personal contact, preferably by a senior COMBINE staff member. The research assistant should brief the candidate on the study objectives and time commitment. Interested candidates will be interviewed using the initial screening questionnaire, which is designed to rule out obviously ineligible candidates. A verbal consent needs to be received at this point. Questions include general demographic information (i.e. age, gender, permanent address), medical questions designed to detect obvious reasons for disqualification (i.e., pregnancy), and drinking patterns. The screen, whether administered via phone or in person, should be completed within 15 minutes. Candidates will also be assigned an identification number at this time, which will be used to track screening failures. Those still apparently eligible will then be given an in-person Quickscreen and if still eligible given the first full written Informed Consent. Because some candidates will be ruled out during the phone screen but will still be in need of treatment, the interviewer should have a list of treatment alternatives that can be recommended for candidates with and without medical insurance. Also, because many phone inquiries will be made by individuals calling on behalf of a potential candidate, the interviewer should provide study
information, and then explain that it is essential that the candidate contact study personnel directly.

### 4.1.2.2 Assessment Battery and Initial Medical Evaluation

This will take place over at least a 2-day period because blood samples need to be submitted to a laboratory and results are not received immediately. However, questionable bloods or urine specimens might pose some problems for meeting the abstinence criteria for alcohol or cocaine. Although consecutive test days are preferred, non-consecutive days are allowed. The initial assessment battery will consist of obtaining signed and witnessed consent, a breathalyzer, and a clinical interview to rule out major psychiatric disorders. The first step will include all screening instruments necessary to determine study eligibility. Assessments that are required to gather baseline information will be reserved for the second study visit. In this way, the burden of the assessment battery will be reduced by having part of the medical examination follow the first 3 hours of assessment, and will prevent gathering information only to find out that the participant is ruled out in the final stage of the screening process. The medical evaluation will include obtaining a medical history, the CIWA, and blood and urine tests. It is recognized that some flexibility in the scheduling of assessments of medical evaluation will be necessary according to the availability of the study personnel.

Because compliance and retention begins with the initial participant contact, it is imperative that the RA obtain agreement with the participant about the participant's responsibilities so as to avoid future compliance problems. Participants may initially appear motivated to carry out the study requirements in order to gain access to innovative and free study treatments or reimbursement for the initial assessment interview. Others may participate to look good for an impending court appearance. To decrease the odds that participants of questionable motivation for participation are included, participants must be thoroughly acquainted with the demands of the study. In order to establish the rules and boundaries of the study, the following points should be addressed.

- The assessment and follow-up procedures should be thoroughly described and reviewed. It is better to explain this initially than to surprise the participant with this information during the follow-up phase.
- The notification process should be reviewed with an emphasis on the importance of notifying the researcher if an appointment must be changed. This is especially true if the participant's circumstances change, since any change, positive or negative, can make it difficult to contact the participant for an appointment.
- The procedures for laboratory work that may be necessary should be reviewed, with specific target dates, during the follow-up.
- A portion of the interviews will be audiotaped on a random basis. Thus, participants must be notified about the possibility of an audiotaping.
- The importance of a locator person for maintaining contact with the participant if they move or become otherwise unavailable must be addressed.
- Informed consent to utilize enhanced measures including naming a locator or person who can be trusted to forward a message in the event the RA is unable to reach the participant by the usual means should be reviewed.
- The participants need to be reassured that the RA will not disclose the nature of their inquiry except to say that it is "personal business". On the rare occasion when someone refuses to answer questions regarding the whereabouts of the participant, the research staff will leave a telephone number for a return call. If that call is returned, confidentiality is maintained because the telephone is answered simply with "Good afternoon, this is (name)." That way, people who want to gather more information than the staff is able and willing to divulge are prevented from retrieving it in unscrupulous ways.
4.1.2.3  Assessment Battery and Medical Evaluation
This will be completed on the second day of screening. The assessment battery will begin with a physical examination, review of laboratory tests and medical history, and ECG (as clinically indicated). Study eligibility should be determined at this time. Successful candidates will then complete the remaining assessment to collect baseline information, and schedule the participant for psychotherapy and study visits.

4.2  Tracking Systems/Screening Logs to Monitor Recruitment

4.2.1  Pre-Randomization
Recruitment Sources: Tracking all phone and participant contacts will likely be too burdensome and unnecessary. It is recommended, however, that a log be kept of the number of phone contacts received and the sources of referrals. This will determine the rate of contact (to inform advertisement scheduling) and to identify the most fruitful recruitment source (i.e. radio and time slot, newspaper ads, in-house or external sources). Because media advertising is expensive, tracking initial contact can help to reduce costs. Forms for tracking recruitment sources need not be standardized across sites, although a systematic tracking system yields important information. This information can be shared across sites to enhance recruitment in sites that experience difficulties or slow periods.

4.2.1.1  Screening Failures
Because of the importance of collecting information on screen failures, a screening log will be kept on location with an ID number designed to identify individuals in screening but not yet randomized. The screening log will include basic demographic information such as date of birth, sex, race and reason for screen failure. In order to ensure that participants who do not meet criteria are not re-screened, the identifying information must be complete enough to facilitate quick identification of repeat self-referrals.

4.2.2  Randomization

4.2.2.1  Screen Successes
Successful candidates will be assigned a treatment ID (different from screening ID) which will be recorded on a randomization worksheet, keyed, and transferred to the Coordinating Center on a weekly basis. The Coordinating Center will then monitor study enrollment across all treatment sites.

The basic information required for monitoring and tracking randomized participants includes demographic information that can be used in maintaining contact and in relocating a participant. Basic information should include:

♦ Name, address, day and evening phone numbers.
♦ Name under which the telephone numbers are listed.
♦ Time of day participant is available for contact, appointments.
♦ Permanent address if different from above.
♦ Date of birth.
♦ Ethnic background.
♦ Social security number.
♦ Locators: 1-2 people who know the participant and will forward a message; preferably one of the locators does not live with the participant.
♦ Personal identifying information such as hobbies and unique physical traits.
CHAPTER 5: Pharmacological Interventions

5.1 Introduction

Recent studies have demonstrated that the addition of pharmacotherapy to psychosocial treatment improves outcome in alcohol dependence (Litten and Allen 1998). Despite recent advances, pharmacotherapy for alcoholism remains in its early stages. Naltrexone, a nonspecific opioid antagonist, is the only non-aversive pharmacotherapy for alcoholism that is approved by the US Food and Drug Administration. Acamprosate, the calcium salt of acetylhomotaurine, is used to treat alcoholism in Europe, but it is not yet approved for use in the US. Several studies have shown that it is superior to placebo in promoting abstinence from alcohol (Paille et al., 1995; Pelc et al., 1996; Whitworth et al., 1996). The mechanism of action of acamprosate may involve alteration of neuronal excitability at the N-Methyl-D-Aspartate (NMDA) receptor and other non-opioid effects. Most evidence suggests that acamprosate and naltrexone act via different neuronal mechanisms, supporting the rationale that combined therapy may have additive or synergistic effects in treating alcohol dependence.

5.1.1 Naltrexone

Naltrexone has been approved for the treatment of alcohol dependence by the US Food and Drug Administration. In a study of men with alcohol dependence, naltrexone (50 mg) was superior to placebo in reducing craving for alcohol and relapse to heavy drinking (Volpicelli et al, 1992). Another study examined the interaction of psychosocial therapy and naltrexone (O’Malley et al, 1992). That study also found subjects taking naltrexone (50 mg) were less likely to relapse than placebo subjects. The cumulative rate of abstinence was greatest for subjects receiving naltrexone and supportive therapy. For subjects who drank, those receiving naltrexone and coping skills were least likely to have a full relapse. These findings suggest that the interactions of psychosocial interventions and pharmacotherapy of alcohol dependence merit further study.

5.1.2 Acamprosate

Several multisite European studies have shown that acamprosate is superior to placebo in preventing relapse in patients with alcohol dependence (Paille et al, 1995; Pelc et al. 1995; Sass et al, 1996; Whitworth et al, 1996). The 3-, 6-, and 12-month outcome measures demonstrating consistent drug-placebo differences were cumulative duration of abstinence, time to first drink, and percentage of patients with no alcohol consumption during the study period. Some, but not all studies found differences in liver enzymes. A multi-center United States trial is being conducted to compare 2g and 3g of acamprosate to placebo (Lipha Pharmaceuticals, Inc.) Interactions of psychosocial therapies with acamprosate have not been studied.

5.2 Dosing And Titration

The target therapeutic doses of the study medications are naltrexone 100 mg daily and acamprosate 3 g (in three divided doses) daily. Naltrexone dosage will be titrated as follows: 25 mg daily for 4 days, 50 mg daily for 3 days, and 100 mg daily thereafter. Medications will be dispensed from blister packs, and participants will take 4 tablets in the morning, 2 tablets midday, and 2 tablets in the evening. Naltrexone 50 mg and matching placebo tablets will be supplied by the manufacturer. Participants will take 2 tablets in the morning. Acamprosate 500 mg and matching placebo tablets will be supplied by the manufacturer as a white, coated, beveled, ovoid tablet. Participants will take 2 tablets in the morning, 2 tablets midday and 2 tablets in the evening.
It is permissible for naltrexone to be administered BID when evidence of side effects dictate twice a day dosing.

5.3 Medication Ordering, Dispensing, And Drug Accountability

5.3.1 Medication Supply and Packaging
The Biomedical Research Institute of New Mexico Clinical Research Pharmacy is the qualified organization for packaging and dispensing of the medications used in COMBINE. The BRI-NM-CRP will receive 500 mg acamprosate, along with an identical-appearing placebo from Lipha Pharmaceuticals, Inc. The BRI-NM-CRP will repackage the blister packs into dosage packages containing the appropriate number and dosage strengths (500 mg or placebo) as required by the study design and study drug randomization schedule.

The BRI-NM-CRP will obtain naltrexone 50 mg tablets from Amide Pharmaceuticals, Inc. The BRI-NM will package the naltrexone and matching placebo capsules into individual blister packs, and collate the blisters together with the acamprosate blisters.

5.3.2 Medication Labeling
Each study drug blister pack will contain space to record the following: participant number, study number, Clinical Center’s name and address, as well as the IND number for the study. In addition, each sleeve for the blister pack will have space for participant’s initials and visit number, the number of tablets the blister pack contains, and dosing directions.

5.4 Adverse Effect Management

5.4.1 Adverse Medical Events
An adverse medical event is any negative event that the participant experiences during the study (e.g., adverse experience, treatment emergent signs and symptoms, new intercurrent illness, clinically significant abnormal laboratory findings). All such events must be recorded on the SAFTEE (adverse experience form), and must include the following information when applicable: the specific condition or event and direction of change; indication if the condition was present pre-study; the dates of occurrence; severity; assessment of relationship to study drug; countermeasure(s); specific drug therapy used in countermeasure; and outcome.

Serious and unexpected adverse experiences, which are thought to be associated with the use of the study drug, require special reporting to the sponsor at 1-800-547-4299. FDA 21CFR312.32 defines a “serious” adverse drug experience as “any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.” For the purposes of this protocol, “sponsor” refers to Lipha Pharmaceuticals, Inc and the COMBINE Coordinating Center on behalf of NIAAA.
The information recorded should be based on the signs or symptoms detected during the physical examination and clinical evaluation of the participant. In addition to the information obtained from those sources, the participant should be asked the following nonspecific question; “How have you been feeling since your last visit?” Signs and symptoms should be recorded clearly in a concise manner using standard, acceptable medical terminology to eliminate vague, ambiguous or colloquial expressions.

In the event of a serious adverse experience(s) or participant death from any cause, the sponsor is to be notified immediately by telephone (Lipha at 1-800-547-4299, and by fax to the CC at 919-962-3265). The experience(s) must be completely described in the CRF, as indicated in the preceding paragraph.

5.4.2 Overview of Adverse Effects of Naltrexone

The usual naltrexone dose of 50 mg daily appears to be well tolerated by most patients. In a multicenter non-randomized, open-label study with 570 alcohol-dependent patients treated with various doses of naltrexone, ranging up to 200 mg, for periods up to one year, the most common side effects (which were not dose related) were anxiety, sedation and nausea in approximately 10% of patients (Croop, 1997). Patients taking naltrexone are insensitive to opioid analgesia for 72 hours after administration, but with respiratory monitoring can overcome this insensitivity. Although 300 mg daily doses of naltrexone have been associated with hepatotoxicity, significant hepatotoxicity is rarely observed at 50 mg daily doses or with 150 mg administered thrice weekly (Berg, et al, 1997). Indeed, serum transaminase levels are lower in naltrexone-treated subjects than placebo-treated subjects, presumably due to decreased alcohol use with naltrexone (O’Malley, et al., 1996, Volpicelli et al., 1997). A study of 11 cirrhotic patients receiving oral naltrexone showed impaired metabolism of naltrexone and higher blood levels than non-cirrhotic controls (Bertolotti et al., 1997). Thus, naltrexone should be used with caution in active hepatitis or severe liver disease and liver functions should be monitored prior to naltrexone treatment and periodically during treatment. In the present study liver toxicity risk will be minimized by limiting study participation to participants with liver enzymes (AST and ALT) no higher than 3 times the upper limit of normal. Liver enzymes will be monitored throughout the study and participants who have liver enzymes of 3 times the upper limit of normal the responsible physician will evaluate the patient clinically to determine whether naltrexone should be discontinued.

5.4.3 Overview of Adverse Effects of Acamprosate

Adverse events attributed to acamprosate tend to be mild and transient, occurring at the onset of treatment, and primarily involve the gastrointestinal tract. Diarrhea is the most common complaint, occurring in about 10% of patients in controlled clinical studies; however, gastrointestinal complaints infrequently resulted in premature termination of study participation.

5.4.4 Management of Adverse Effects

The first step in dealing with adverse experiences involve taking either over the counter medication such as Pepto Bismol® (for GI side effects) or acetaminophen (for headache) and/or adjusting the time of dosing (i.e., taking naltrexone at night) and/or taking the medication with meals. If this is unsuccessful or insufficient, the second step should involve the dose reduction strategy (section 5.4.4.6). The third step, if necessary, should be the use of prescription medication (i.e., hydroxyzine) if appropriate. Adverse effects are reported on the SAFTEE CRF (adverse experience report form).
5.4.4.1 **Gastrointestinal Symptoms**

Instructions for the management of adverse effects (Section 5.4.4) should be followed. If symptoms persist and the patient continues to experience nausea 3 days after the doses of both medications are reduced, nausea may be treated with hydroxyzine pamoate (Vistaril) 25-50 mg orally, provided that the patient does not report prior adverse effects from hydroxyzine. The medication should be taken 30 minutes prior to the scheduled dose of study drug. If nausea persists despite hydroxyzine treatment, the morning dose of the study medications should not be administered for 1-2 days. If after 2 days, nausea persists, do not administer study drugs until the patient is no longer nauseous. When the patient no longer reports the nausea, prescribe 25 or 50 mg of hydroxyzine 30 minutes prior to the morning dose of study medications. Dose reductions should also be considered as described in Section 5.4.4.6 below.

Diarrhea should also be treated by following the instructions for management of adverse effects.

5.4.4.2 **Hepatic Symptoms**

Elevated liver enzymes are a serious potential adverse event associated with naltrexone. The AST and ALT may be the better markers of naltrexone-induced toxicity than GGT, which reflects recent ethanol consumption. If ALT or AST reach values of 3x ULN, the responsible physician will evaluate the patient clinically to determine whether study medications should be discontinued. If GGT is elevated, the responsible physician will determine the course of action which may include more intensive monitoring, for example, more frequent monitoring of liver function tests. If GGT remains elevated, the study physician should use clinical judgment to determine if naltrexone should be discontinued.

5.4.4.3 **Renal Insufficiency**

Individuals whose serum creatinine level is 1.3 or 1.4 will be evaluated by a study physician to ascertain whether study medication should be discontinued. However, a creatinine level of 1.5 should be cause for discontinuation of study medication.

5.4.4.4 **Central Nervous System Symptoms**

Dizziness, nervousness, anxiety, and insomnia will be treated by following the instructions for management of adverse effects (Section 5.4.4).

Headaches may be treated with over-the-counter medications, such as aspirin, acetaminophen, or ibuprofen.

5.4.4.5 **Dermatologic Symptoms**

Minor dermatologic side-effects, primarily pruritus and/or erythematous rash, and variable effects on libido and sexual performance have also been reported in small numbers of participants treated with acamprosate, but without any consistent differences between acamprosate and placebo groups in controlled clinical trials.

Among spontaneously reported adverse events in post-marketing experience with acamprosate, a single case of presumed mild erythema multiforme (without mucus membrane involvement) has been reported, occurring in a female participant with an active herpetic infection, simultaneously started on acamprosate and spironolactone. Causality attribution to acamprosate, as well as the diagnosis, has been disputed.
However, accordingly, any participant experiencing a dermatologic event will be managed as follows:

1) Localized rash or pruritis, no intervention required and other etiology to be explored.

2) Generalized erythema and/or macular or maculopapular rash and/or pruritis, without other etiologic explanation:
   a) Discontinue vitamin B supplements;
   b) Symptomatic treatment with oral antihistamines (e.g., hydroxyzine hydrochloride [Atarax®], 25 mg t.i.d.) and topical corticosteroids (e.g., triamcinolone acetonide cream) for up to one week:
      (i) If rash/pruritis improves or disappears, study drug may be continued;
      (ii) If rash/pruritis worsens, study drug is to be discontinued. Code this as an adverse experience on the SAFTEE page of the CRF and refer participant to dermatologist for evaluation and possible biopsy. (NOTE: Written report of such a consultation must be incorporated into CRF).

3) If rash is atypical (i.e., other than maculopapular) or if rash is urticarial or if there is mucous membrane involvement, in the absence of another etiologic explanation, study drug is to be discontinued. Code this as an adverse experience on the SAFTEE page of the CRF and refer participant to dermatologist for evaluation and possible biopsy. (NOTE: Written report of such a consultation must be incorporated into CRF).

5.4.4.6 Dose reductions to manage adverse events

Participants who are unable to tolerate their assigned dosage of study medication because of side effects will be permitted a dose reduction of one medication initially. The reduction will consist of taking one acamprosate in the morning and one in the afternoon, rather than taking two in the morning and two in the afternoon. The participant will be contacted three days after the dose reduction. If this reduction is not sufficient, naltrexone will also be reduced. The participant will be instructed to take one naltrexone capsule in the morning rather than two. Dose adjustments may be made at the time of the scheduled visit or before, if warranted. The dose of naltrexone can be reduced to 25 mg for all side effects, including elevated bilirubin, if the patient cannot be maintained on the 50 mg dose. Every effort should be made to increase the dose of naltrexone whenever possible, but if the patient cannot tolerate the increase, s/he can remain on a maintenance dose of 25 mg of naltrexone.

If the participant agrees to have the dose increased, the naltrexone should be increased first. If the participant is able to tolerate it, the acamprosate should be increased. If the participant is unable to tolerate the second dose increase, s/he should be instructed to go back to the reduced dosage level.

If a patient’s bilirubin levels increase by 50% over baseline values but remain within the normal range, the naltrexone dose can be reduced prior to the acamprosate, rather than run the risk that the bilirubin level will continue to rise and meet the threshold for withdrawal from the study medications altogether. If the naltrexone dose is reduced to 25 mg and the patient cannot tolerate the dosage, all study medications should be discontinued.

See Appendix A for participant instructions and guidelines for the Medical Management therapists regarding management of adverse effects.
5.4.5 Serious and Unexpected Adverse Experience Reporting

FDA defines a “serious” adverse drug experience as “any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.” See Code of Federal Regulations, Title 21, Volume 5, Section 312.32, Revised as of April 1, 1999.

FDA defines “unexpected” as “not identified in nature, severity, or frequency” in the current investigator brochure. In addition, FDA requires that “the sponsor notify FDA by telephone of any unexpected fatal or life threatening experience associated with use of the drug no later than three working days after receipt of the information.”

As per Federal Regulation 21 CFR part 312.64(b), the “investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.” In that case, immediate reporting by telephone followed by a detailed written report (within one week) to both the sponsor (at 1-800-547-4299) and the IRB is necessary. The SAE report form should also be faxed within 24 hours to the Coordinating Center (919-962-3265) and NIAAA (301-443-8774).

Any participant who suffers adverse reactions will be followed until the outcome is determined, and written reports will be provided to the sponsor on a periodic basis as appropriate.

5.5 Assessment of Medication Compliance

Medication compliance is a particular concern for the treatment of addictive disorders. Typically medications used to treat psychiatric disorders, such as mood or anxiety disorders, reduce an unpleasant emotional state. Thus, there is a strong motivation to comply with these medications. In contrast, medications, which successfully reduce alcohol use (e.g., naltrexone), do not have any inherent positive reinforcing effects (at least over the short term). We can, therefore, anticipate that medication compliance will be a challenge. In fact, experience with naltrexone treatment for opioid dependence is severely compromised by non-compliance unless participants are intrinsically motivated. Thus, a fair test of any pharmacological non-agonist treatment for addictions depends on excellent medication compliance. For this reason, a major focus of Medical Management treatment (see Section 6.1), which all participants on medication will receive, is the enhancement of medication compliance.

Placebo controlled studies showed that the treatment size of naltrexone in alcoholism treatment is very sensitive to medication compliance (Volpicelli et al., 1997). For example, in a recent study, naltrexone was not more effective than placebo for subjects who took <90 percent of their prescribed medications. In contrast, for subjects who took more than 90 percent of their prescribed medications, 52% of the highly compliant placebo subjects relapsed compared to 14% of the highly compliant naltrexone subjects. Thus, in order to evaluate medication adequately for alcohol dependence, attempts should be made to measure and enhance medication compliance.
Several techniques are used to measure medication compliance. The most simple and least expensive, is to use pill counts based on returned medication. Pill counts, however, often lead to missing data, as participants often forget to bring back their unused medication at the follow-up visit. By supplementing returned medications with self-reports, the incidence of missing data can be reduced. Also, self-reports can be made more precise when medication diaries or the time line follow-back techniques is used to obtain self-reports.

In addition to pill counts and self-reports, objective measures of medication compliance can be utilized. The use of MEMS caps, drug markers such as riboflavin, or directly measuring serum medication levels add a measure of objectivity to measuring medication compliance but each technique has its limitations. Although MEMS caps provide data on the time and date that the pill bottle is opened, this method may not be as useful when monitoring medications in which the participant is prescribed several pills at each dosing time (e.g., three tablets of acamprosate). Alternatively, blister packs can have the advantage of organizing the pills for the participant in a way that may enhance compliance. Medication markers measure only the recent ingestion of the marker (missed doses between samples are not determined). Measuring the actual medication levels in the serum is also insensitive to missed doses between serum levels and this technique does not assess compliance in placebo treated participants.

In summary, there are no universally accepted ways to assess medication compliance. A combination of returned medication and a self-report of medication compliance based on timeline follow-back procedures offers a satisfactory means of assessing compliance, with confirmatory drug plasma levels in the active drug conditions.

Randomized participants will be required to return their used medication blister packs at each visit for tablet count and discussion of compliance. Unused medication will not be redispensed. All used and unused blister packs should be returned to the study site and retained by the investigator for subsequent shipment to the sponsor.

If a participant should lose his/her study drug during study participation, the site will call the Coordinating Center for instructions as to which blister pack from the unused randomized drug supply will be designated to replace the lost drug.

5.6 Concomitant Medication

Allowable concomitant medications are listed in Appendix B. Exclusionary medications are listed in “Exclusion Criteria.” All concomitant medications must be listed on the Concurrent Medication form of the CRF.
CHAPTER 6: Behavioral Interventions

6.1 Medical Management (MM)

6.1.1 Overview
The goal of MM treatment is to promote recovery from alcohol dependence by facilitating compliance with medication using psychoeducational methods, and providing support for the participant in changing his or her drinking patterns. MM treatment is to be delivered by a medical professional (physician, nurse, physician assistant, and clinical pharmacist) as might occur in an HMO setting.

6.1.2 Frequency of Visits
MM is to be delivered 9 times in the 16-week treatment period: weeks 0 (initial), 1, 2, 4, 6, 8, 10, 12, and 16.

6.1.3 Length of Visits
The initial visit is designed to last 40 to 60 minutes, whereas each subsequent visit is designed to last 15 to 25 minutes, depending on the participant’s clinical status.

6.1.4 Content of the Initial Visit
The initial visit occurs after the participant has had a comprehensive evaluation. In the first MM visit, the clinician reviews the results of the evaluation with the participant; provides the participant with rationale, information and prognosis for the alcohol dependence diagnosis; educates the participant about the disorder; advises the participant to abstain from alcohol; provides the participant with information about the pharmacotherapy; establishes a history of the participant’s past experiences with taking medications and suggests strategies to enhance compliance; discusses the rationale for focusing on medication compliance at each subsequent visit; encourages the participant to participate in mutual-help groups such as Alcoholics Anonymous or SMART Recovery; provides the participant with pamphlets about alcohol dependence, medications, and mutual-help groups; reviews the schedule of future visits; and answers any questions that the participant might have about the disorder, the study, or the treatment.

6.1.5 Content of Subsequent Visits
Each subsequent visit includes a brief assessment of the participant’s drinking and functioning status; monitoring and discussion of medication compliance; an assessment of the participant’s medical status; and a discussion of problems that may have arisen since the previous visit. The clinician then helps the participant to deal with these trouble areas, and makes recommendations for the participant to follow until the next visit.

The MM manual organizes each of the subsequent visits around the 4 possible scenarios that might arise regarding drinking and medication compliance: 1) The participant is not drinking and is compliant with medications, 2) The participant is drinking and is compliant with medications, 3) The participant is not drinking and is not compliant with medications, and 4) The participant is drinking and is not compliant with medications.

6.1.6 Strategies for Handling Medication Noncompliance
The MM manual reviews a variety of reasons that frequently underlie medication noncompliance. These include: 1) forgetting to take medications, 2) experiencing medication side effects, 3) the belief by the participant that he or she is taking a placebo, 4) misconceptions
about what the medications will or will not do, 5) uneasiness about taking medications at all, 6) a
desire to drink or use drugs, 7) reluctance to accept a diagnosis of alcohol dependence or a belief
that he or she is ‘cured.’. If a participant is not compliant with pharacootherapy, the clinician is
advised to evaluate the pattern of noncompliance and the reason behind it. Based on this
evaluation, the clinician can make recommendations. For example, if the clinician establishes
that the participant is forgetting to take medications, the clinician can recommend certain
routines to help remind the participant to take the medications, e.g. wearing an alarm watch, etc.
If participants are uneasy about taking medications because they fear, for example, that
naltrexone will prevent them from experiencing natural pleasure, this can be dealt with using
medication education.

6.1.7 Strategies for Dealing with Drinking
In addition to the focus on noncompliance, MM is designed to encourage and support
participants’ abstinence from alcohol. Therefore, if participants continue to drink, this will be
addressed in MM sessions. Of course, the treatment approach to a participant’s continued
drinking will depend somewhat on whether the participant is complying with medications. If the
participant is not taking medications as prescribed, the participant will be encouraged to comply
with the medications and give them a chance to work. Moreover, the participant will be
encouraged to attend support groups (e.g., AA) that can help him/her develop strategies for
abstaining from alcohol. If, on the other hand, the participant has been taking medications
faithfully and drinking anyway, then the clinician would focus more on the benefits of attending
as many support group meetings as possible to attain and maintain abstinence.

6.1.8 Adjuncts to Medical Management Treatment
During the initial and subsequent visits, the clinician will use forms for reporting participant
status, providing information to the participant, and establishing the participant’s history and
strategies. These forms, found in Appendix A of the MM Manual, include the Clinician Report
Form; Naltrexone and Acamprosate Information Sheets; Medication Compliance Plan;
Medication (Non)Compliance Form; and SAFTEE. In addition to the visits themselves, all
participants in MM will receive educational materials including participant information sheets
describing the medications, their benefits and side effects; “Patient Instructions for Managing
Side Effects”; a handout entitled “Quick Reference Drug Info Grid”; “Facts about Drinking”
pamphlet; a pamphlet entitled “The AA Member - Medications and Other Drugs.” These can be
found in Appendix C of the MM Manual.

6.1.9 Monitoring of Medical Management Protocol Adherence
The Medical Management treatment has 2 adherence checklists: one for session 1, and one for
sessions 2 through 9. These are to be completed based on audiotaped sessions locally by the
study coordinator and centrally by the training site at a schedule that is included in the section of
the Policy and Procedures Manual entitled "Adherence Monitoring." The checklists can be be
found in Appendix B of the Medical Management Manual.

6.1.10 Medical Attention Treatment
Some participants who are receiving Medical Management treatment will experience difficulties
with medications such as side effects, elevated liver function tests, or concomitant illnesses or
other conditions (e.g., pregnancy) that might contraindicate the use of these medications. Such
participants are candidates for "Medical Attention" treatment, which is quite similar to Medical
Management, except without the focus on medication compliance. In some cases, these medical
issues may be temporary, so that the participant may be able to return to pharmacotherapy after a
period of time. Medical Attention (MA) treatment focuses on an assessment of drinking status; continued encouragement to abstain from alcohol; a reminder of the reasons that the person entered treatment; and continued encouragement for the participant to participate in mutual help groups. The MA clinician qualifications, the frequency and length of visits, and the policies regarding emergencies are identical to those of MM. Adherence monitoring procedures are also the same as those for MM. It is hoped that some participants receiving MA will be able to or will decide to return to MM if they are able to or decide to begin taking the medications again. The Medical Attention procedure can be found in Appendix A of the MM manual.

6.2 COMBINE Behavioral Intervention: An Integrated Cognitive-Behavioral Psychotherapy for Alcohol Dependence

6.2.1 Overview

The following is a brief overview of the content and procedures of the CBI Manual. The full CBI Manual contains details of sessions and sequences of therapist interventions. The CBI Manual is divided into four Phases: Phase 1: Building Motivation for Change, Phase 2: Developing a Plan for Treatment and Change, and Phase 3: Implementing Negotiated Treatment Modules, and Phase 4, Monitoring Goal Achievement and Maintenance. The expected duration of treatment is a minimum of 12 and maximum of 20 sessions, delivered over a period of sixteen weeks from the date of randomization. During the first four weeks of treatment it is recommended that sessions be held at least twice weekly (permissible range: 1-3 times weekly during the first four weeks in which treatment is delivered). In Phases 2 and 3 sessions will normally be reduced to once weekly (permissible range: 1-2 times weekly during Weeks 5-12). In Phase 4 sessions will be reduced to once every four weeks (permissible range 1-2 times every four weeks). The maximum number of CBI sessions with a single participant is 20, plus two additional emergency sessions that may be used only to deal with crises. The emergency sessions may not be used solely to extend the duration of treatment, and therefore they would almost never occur immediately after Session 20.

The CBI modules are divided into standard procedures to be delivered to all participants and elective modules that are chosen to address specific participant needs. The following is an overview of each phase, the corresponding modules and the pull-out procedures that are to be used in particular circumstances, and only as the need arises. Phase 1: Building Motivation for Change

6.2.2 Phase 1: Building Motivation for Change

The central purpose of Phase 1 is to enhance participant’s motivation for change. Some participants will come to treatment well along with readiness to change, and Phase 1 will go quickly. Others will come less ready to change, and building motivation is an important prerequisite to Phases 1 and 3. Motivational interviewing is a participant-centered yet directive style of counseling designed to do just that - to help resolve ambivalence about a problem behavior and initiate change (Rollnick & Miller, 1995). It is the clinical style to be used throughout CBI. Based on principles of motivational psychology, it is designed to initiate rapid, internally-motivated change.

Motivational Enhancement Therapy (MET; Miller, Zweben, DiClemente, & Rychtarik, 1992) was developed as a specific application of motivational interviewing for use in Project MATCH (1993, 1997). MET provides systematic feedback of the participant's assessment data, given within the supportive and empathic style of motivational interviewing. Motivational interviewing and MET constitutes Phase 1 of CBI, which focuses on increasing participant
motivation for change. This flows naturally into Phase 2, which centers on negotiating a change plan and sets the stage for the cognitive-behavioral skill-training components of CBI in Phase 3.

Motivational interviewing begins with the assumption that the responsibility and capability for change lie within the participant. The therapist's task is to create a set of conditions that will enhance the participant's own motivation for and commitment to change. The therapist seeks to mobilize the participant's own inner resources, as well as those inherent in the participant's natural helping relationships. The idea is to evoke and support *intrinsic* motivation for change, which will lead the participant to initiate, persist in, and comply with behavior change efforts.

Phase 1 of CBI involves two parts. The first is a less structured (but directive) period of motivational interviewing focused on drinking behavior, which will ordinarily continue for 20-30 minutes. The second is a period of systematic feedback of findings from the participant’s pretreatment assessment (MET) given within the style of motivational interviewing. This is likely to extend into the second session.

The second component of Phase 1 is Assessment Feedback. After an initial period of motivational interviewing, the first Phase 1 session proceeds with feedback to the participant from the pretreatment assessment. This is done in a structured way, providing participants with a written report of their results (Personal Feedback Report). The details of this feedback process are provided in the Manual. The next session is scheduled usually within a few days of the first session.

6.2.2.1 Phase 1 Modules:

6.2.2.1.1 MOTI Motivational Interviewing
At the beginning of treatment there is a period of motivational interviewing to establish rapport and enhance intrinsic motivation for participation and change

6.2.2.1.2 METF Motivational Enhancement Feedback
Each participants receives structured feedback of baseline assessment results, following the basic procedures of MET in Project MATCH

6.2.2.1.3 COIN Concerned Other Involvement
Whenever there is a concerned significant other (SSO) with whom the participant has a reasonably good relationship, the SSO is to be involved in treatment. This module contains procedures for contacting and engaging the SSO.

6.2.2.1.4 TRAN Transition from Phase 1 to Phase 2
There is a specific procedure for summarizing Phase 1 (enhancing motivation for change - above) and transitioning to Phase 2 (developing commitment to a change plan).
6.2.3 Phase 2: Developing a Change Plan

The key shift in Phase 2 is from focusing on reasons for change (building motivation) to negotiating a plan for change. The goal during this phase is to develop with the participant (and SSO) some ideas and ultimately a plan for what to do about the participant’s drinking.

The primary focus in Phase 2 is on alcohol use and completing the functional analysis that examines common antecedents and desired consequences of drinking behavior. The therapist uses the "New Roads" sheet in the manual to record the Triggers and Effects of drinking, and helps the participant to connect the two and find alternatives to drinking. Another focus in Phase 2 is to complete an assessment of the participants psychosocial functioning. Alcohol problems do not occur in isolation from the rest of a person’s life. Drinking can adversely affect virtually any area of functioning, diminishing quality of life. Phase 2 expands the focus of treatment for all participants by identifying areas of functioning that could, if enhanced, have a beneficial impact in the reduction of drinking and related problems. Eight broad areas are reviewed with and prioritized by the participant. This is a further step toward developing a treatment plan that will address the participant’s unique concerns and thereby enhance motivation for change. The purpose of discussing psychosocial functioning is to identify important life areas that may be related to drinking problems. This in turn informs the process of setting goals for treatment and change. The Personal Happiness Form (see CBI Manual) identifies areas of psychosocial functioning that sometimes affect and/or are affected by excessive drinking.

The final step in Phase 2 is developing a Treatment Plan. As issues have been identified (during the functional analysis and the review of psychosocial functioning) that could be addressed in this treatment, they have been put on the Options sheet. The Treatment Plan form mirrors a standard problem-oriented record format (Ryback et al., 1981) consistent with clinical practice standards. The plan is developed by a process of negotiation between the therapist and participant, based on all of the discussions thus far. Each problem identified is prioritized. Once a problem has been specified and numbered, the next step is to specify broad goals and specific objectives that you hope to achieve. The Treatment Plan specifies how the therapist plans to address the specified problem in order to achieve the stated goal(s). The therapist can identify specific modules that will be included in Phase 3. Referrals may be specified here, as may change activities that the participant is to pursue outside of treatment (such as attending AA meetings). The plan is stated in terms that are sufficiently specific to allow a clear judgment as to whether or not the plan was carried out. At least a tentative timeline is also stated for each problem: when will this be done? Progress notes that are kept throughout treatment correspond to the problems, goals, and plans stated. In addition, at some point during Phase 2, all participants are given modules on recommending Mutual-Help Programs and on Emphasizing Abstinence.

Toward the end of the Phase 2 commitment process, as the therapist senses that the participant is moving toward a firm decision for change, the participant is offered a broad summary of what has transpired. Emphasis is put on the participant's self-motivational statements, the SO's role, the participant's plans for change and goals for treatment, and the perceived consequences of changing and not changing. After the therapist has recapitulated the participant's situation, as above, and responded to any additional points and concerns raised by the participant (and SO), there is movement toward a formal commitment to change. In essence, the participant is to commit verbally to take specific, planned steps to bring about the needed change. Before beginning Phase 3, however, the participant agrees on and signs at least a provisional treatment plan.
6.2.3.1 Phase 2 Modules:

6.2.3.1.1 FUNC Functional Analysis
Every participant proceeds into a functional analysis of drinking behavior, using structured procedures.

6.2.3.1.2 ANPF Analysis of Psychosocial Functioning
A broader analysis of psychosocial functioning is performed as a further step toward a treatment plan.

6.2.3.1.3 CPWS Change Plan Work Sheet
Based on the above steps, a general change plan in negotiated with the participant setting intended goals and plans for change.

6.2.3.1.4 ABEM Abstinence Emphasis
There is a standard abstinence emphasis module to reinforce the treatment's goal of abstention from alcohol.

6.2.3.1.5 MUTU Mutual Help Group Involvement
Each participant is encouraged to consider involvement in mutual help group, drawing from resources available in the community. These included 12-Step groups like AA, SMART, RR, SOS and WFS. If the participant refuses or is already engaged in a group, no further action is taken.

6.2.3.1.6 TRPL Treatment Plan
Finally, Phase 2 is concluded by developing a Treatment Plan as a subset of the Change Plan. This corresponds to the normal clinical procedure of specifying a treatment plan in the chart. This includes selection of modules from the Phase 3 menu.

6.2.4 Phase 3: Implementing Selected Coping Skills Modules
The next step is for the therapist to administer the agreed upon modules in Phase 3 (as presented in a subsequent session). Phase 3 continues until the modules selected to assist the participant in achieving his/her self-change plan has been completed and the goals achieved or modified. At the end of phase 3 the therapist and participant negotiate and enter phase 4.

6.2.4.1 Phase 3: Modules for Individual Treatment Plan
These modules are intended to be administered after the therapist and participant have agreed upon a Treatment Plan that has identified areas to be addressed in Phase 3. The modules can be given singularly or in combination, but no more that two at a time is recommended.

6.2.4.1.1 ASSN Assertion Skills Training
Training in assertive communication skills; appropriate expression of emotions; making clear requests; setting limits. Training in self-control skills for managing angry feelings without aggression.

6.2.4.1.2 COMM Communication Skill Training
Training in skills for communication in relationships: starting and maintaining conversation, acknowledgment and reflective listening, (may be done with individual or couple)
6.2.4.1.3 CRAV Coping with Craving and Urges
Training in skills for managing craving and urges to drink; identification or urge triggers; urge surfing; distraction; social support.

6.2.4.1.4 DREF Drink Refusal and Social Pressure Skill Training
Training in refusing unwanted drinks; training in handling social support for drinking, dealing with prior drinking friends, and old and new social pressure situations

6.2.4.1.5 JOBF Job Finding Training
For participants who are unemployed and want to find a job.

6.2.4.1.6 MOOD Mood Management Training
ABC model of emotion; identification of automatic thoughts; thought replacement; identification of cognitive themes and antidote statements; mood monitoring.

6.2.4.1.7 RELA Relationship Skill Training
Training in skills for improving relationships; decreasing aversive control, increasing reinforcement and shared positives, making requests, negotiating, accepting partial responsibility, offering to help (may be done with individual or couple)

6.2.4.1.8 SARC Social and Recreational Counseling
Helping a participant pursue positive social and recreational activities to allow participants to engage in behaviors that will compete with drinking and will support their sobriety, by enhancing their self-esteem.

6.2.5 Phase 4: Monitoring Goal Attainment and Maintenance
Phase 4 of the CBI is referred to as the Maintenance Phase of treatment. It is implemented after the participant and therapist have reached a mutual agreement that they have completed the modules on drinking and psychosocial functioning that were identified in the Treatment Plan developed in Phase 2 and implemented in Phase 3. The objective of Phase 4 is to provide continued treatment contact with the participant up to the end of the sixteen-week treatment period of the main trial. At the completion of Phase 3 treatment, which may occur anytime between sessions 12 to 20 over the sixteen-week treatment period, the therapist and participant agree to meet every four weeks to provide a check-up of the gains already made in treatment. Some participants who needed the full sixteen weeks of CBI treatment in Phases 1, 2, and 3, may never reach Phase 4, while others who completed Phases 1, 2, and 3 within the minimum 12 sessions may be in Phase 4 for 12-16 weeks. The focus of Phase 4 sessions is to determine the drinking status of the participant as well as the maintenance of psychosocial treatment gains since the previous visit. If it is determined that the participant has maintained good sobriety and psychosocial functioning, then the participant is scheduled for another visit in four weeks if time to end of trial permits. If during the Phase 4 maintenance session it is determined that the participant needs further treatment for resumed drinking or continued difficulties in psychosocial status, then the participant and therapist will review and/or revise the original change plan to incorporate the current treatment needs of the participant. The revised treatment plan may include revisiting previously delivered modules from Phases 1, 2, or 3, and may include new modules that are appropriate to the participant's current treatment needs. Sessions can be scheduled on a more frequent basis (1-2 per week) until it is again mutually determined by the therapist and participant that the treatment modules have been completed. The participant may then be put back into monthly Phase 4 maintenance if time permits until the end of the sixteen-week treatment period. The number of sessions in Phase 4, therefore, depends on the amount of time remaining between the end of Phase 3 and the end of the sixteen-week treatment period, but
also depends on the extent of further treatment needed by the participant during Phase 4.

6.2.5.1 Phase 4: Modules for Monitoring and Maintenance

6.2.5.1.1 REV Review of Goals and Progress.
Reviewing with the participant progress towards achieving and maintaining the goals specified in the change plan.

6.2.5.1.2 SUM Concluding session.
Therapeutic termination and referral when needed.

6.2.6 Pull-Out Procedures As Needed:
The five "pull-out" procedures described in this section are to be used in particular circumstances, and only as the need arises. The need may arise anywhere during treatment, and thus these procedures may be used during Phase 3, Phase 2, or even Phase 1, as appropriate. There will also be cases in which none of these procedures will be needed. The five pull-out procedures are:

6.2.6.1 SOBR Sobriety Sampling
This procedure is to be used if the participant is not committed to long-term abstinence, or has been drinking throughout sessions to date.

6.2.6.2 CONC Concern for Participant
This procedure is to be used when the therapist's goal or sense of what is best for the participant differs from the participant’s own plan, or when for other reasons the therapist is concerned for

6.2.6.3 REFR Referral
This procedure is to be used when a participant needs help or social services that are not available within the treatment protocol, and is referred to community resources (e.g., clergy, cooking and household management, family therapy, money management, and parenting.)

6.2.6.4 RESU Resumed Drinking
This procedure is to be used when a participant who has been abstaining reports having resumed drinking since the last session.

6.2.6.5 SOMA Support for Medication Adherence
This procedure is to be used when the participant states a desire or plan to discontinue medication, or has stopped taking trial medication

6.3 Supportive Significant Other (SSO) Involvement

As indicated earlier, SSO involvement is an essential active ingredient of CBI. The SSO can play an important role in helping to facilitate treatment compliance and abstinence on the part of the participant. Critical guidelines for the selection of the SSO include: (1) That the SSO be supportive of the participant’s sobriety and treatment plan (2) That the SSO be generally supportive of the participant and (3) That the SSO be willing and able to become actively engaged in the participant’s treatment.

The extent to which a SSO will actively participate in the participant’s treatment will be
negotiated by the participant and therapist. This decision will be determined primarily by the following: (1) the nature of SSO/participant relationship - i.e., (a) that the relationship is highly valued by the participant and (b) that the SSO has strong investment in the participant's sobriety, and (2) SSO's willingness/ability to participate in the sessions. Some SSOs may attend all treatment sessions while others may attend only a few sessions. A SSO can be added later in the treatment if a SSO is initially not chosen or the original SSO withdraws from treatment. As always, the choice of the SSO is directed by the participant with the therapist and SSO having the right to refuse.

It is important to note that the presence of the SSO in treatment will not lead to marital or couples therapy. The therapist will outline this proscription in discussing the guidelines with the participant about SSO involvement. However, if a participant is in need of relationship enhancement, then she or he might elect to participate in the appropriate modules (e.g., communication skills) related to this need. Such a plan might result in having the SSOs focus their efforts on the task demands associated with the particular module rather than deal with other issues (e.g., medication compliance) in treatment.

In cases where the participant decides to discontinue treatment prematurely, the SSO will be permitted to have one appointment without the participant present. The purposes of this session are to review the available strategies for reinvolving the participant in treatment and/or to make a treatment referral for the SSO him/herself.

Therapists will be required to check off categories on a form indicating (1) whether the SSO is a spouse, parent, child, clergyman, friend, etc. to the participant and (2) the amount face-to-face and telephone contact on average, the participant has had with the SSO in terms of both the number of days and hours in a week. SSO attendance will also be recorded. These data can be used to account for outcomes differences that might result from the variability in SSO involvement.

6.4 **Coordination between MM and CBI Therapists**

The overall approach for each of the treatment models is that they should be delivered independently. Thus, the goal is to confine the interaction between MM clinicians and CBI therapists within specified boundaries.

Information to be passed on from the MM clinician to the CBI therapist will include alcohol consumption, side effects resulting from medications, use of concomitant drugs, and any physical problems that might preclude remaining on the trial medications. Other information to be shared involves potential compliance problems (i.e., intention to leave MM or CBI) and participant management or safety issues (i.e., psychiatric deterioration, spousal/child abuse, and suicidal/homicidal ideation). A checklist has been developed by the MM committee for gathering these data. The form will be completed by the MM clinician and forwarded to the CBI therapist via the study coordinator after each MM session. For accountability purposes, both MM and CBI therapists will be required to sign the checklist. A copy of the checklist is included in the appendix of the MM manual.

Face-to-face meetings or telephone contacts between CBI and MM clinicians will be "triggered" by any one of three issues: discrepancies in drinking data and drug use; immediate compliance problems (i.e., intention to leave MM or CBI); and safety or management issues.
In both MM and CBI conditions, a participant will be designated as "inactive" if he or she misses ("no shows") three consecutive scheduled sessions regardless of the reasons for missing the sessions. Also, a participant who directly expresses his or her unwillingness to reschedule subsequent treatment sessions will be declared "inactive".

When a participant is designated as inactive in MM, the MM clinician will send a formal note to the participant confirming his/her decision not to attend or resume MM sessions and/or take trial medication immediately after placing him/herself in an inactive status. The clinician's note will include a message encouraging the participant to return to MM and/or resuming trial medication at a later time if desired. A follow-up letter will be sent out two weeks later, reiterating the above. The CBI therapist will review the participant's decisions about not attending/resuming MM sessions and/or taking trial medication at each of the CBI sessions. Compliance strategies outlined in the CBI manual (e.g., support for medication adherence) will be utilized for dealing with participants who are inactive in MM and not taking trial medications.

When a participant is designated as inactive in CBI, the CBI therapist will provide a personal, handwritten note confirming the participant's decision not to attend or resume ("no shows") subsequent sessions, but will encourage him/her to attend future sessions if desired. A follow-up letter will be sent out two weeks later reiterating the above. The MM clinician will review the participant's decision about not attending or resuming CBI sessions at each of the MM sessions. Compliance procedures outlined in the MM manual should be utilized with participants who evidence an interest in resuming the CBI sessions.

When a participant is designated as inactive in both CBI and MM, the CBI therapist will provide a personal handwritten note confirming the participant's decision not to attend or resume subsequent CBI sessions. The note will include a message encouraging the participant to attend future CBI sessions, if desired. A follow-up letter will be sent out two week's later reiterating the above. The MM clinician will provide a formal note confirming the participant's decision not to attend or resume MM sessions and/or taking trial medication. The note will include a message encouraging the participant to attend future MM sessions and/or to resume trial medication, if desired. A follow-up letter will be sent out two weeks later reiterating the above.

### 6.5 Concomitant Therapy

In order to prevent contamination of treatment effects, participants will be ineligible to participate in the study at intake if they plan (1) to engage in other "formal" alcohol treatment(s) outside the protocol or (2) to continue in current alcohol treatment during the active treatment phase. However, despite a desire to limit a participant's exposure to nonprotocol alcohol treatments, some participants after entering the study, might express a desire to participate in concomitant therapy while involved in one of the COMBINE treatments (MM or CBI). Therapists will try to postpone participant involvement in concomitant therapy until the active treatment phase is completed. Participants who become involved in formal adjunctive treatment will not be removed from the treatment protocol. However, therapists will note such involvement in the monitoring report. Therapists will review the CBI or MM manual for specific guidelines on handling participant participation in adjunctive treatment.

### 6.6 Emergency or Unplanned Visits

Participants in MM treatment are allowed to have up to 2 emergency or unplanned sessions above and beyond the 9 visits prescribed by the study protocol. These visits may be necessary for the safety or protection of the participant (e.g., suicidal or homicidal ideation) or to stave off

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an impending relapse. In the CBI treatment, emergency or unplanned sessions will be handled as needed as long as the absolute number of therapy sessions does not exceed 20 in the sixteen weeks.

### 6.7 Training, Certification, and Quality Control for Clinicians and Therapists

It is vital in clinical trials to control and document the fidelity of treatments that are delivered. As described above, COMBINE will test two psychosocial treatments as part of its complex design joining medications and behavioral interventions. The first of these, Medical Management (MM), is intended to provide the type and quantity of service that might realistically be delivered through primary health care settings in the era of managed care. It will be provided by health practitioners (e.g., nurses and physicians) typically involved in primary care practices. The COMBINE Behavioral Intervention (CBI) is a flexible treatment approach with both core elements and optional modules selected from a finite menu through an individualized treatment planning process. It is intended to represent state-of-the-art behavioral treatment for alcohol dependence, integrating components with evidence of efficacy. It incorporates motivational enhancement and cognitive-behavioral treatment methods developed in Project MATCH, and includes participant involvement in mutual-help groups, as appropriate. Its design and flexibility are meant to be consistent with treatment services as delivered in specialist treatment programs. Both treatments will be manual-guided, and both will be delivered through individual counseling sessions that extend over a maximum of sixteen weeks.

At least five functions are crucial to quality control of behavioral treatments in a multisite trial:

1. **Standardizing** the delivery of trial treatments through therapist manuals and training procedures that are consistent across sites. That is, therapists who are to see trial participants should proceed through a specified and standard training procedure. This does not in itself ensure competency and adherence, but it does provide a common knowledge and conceptual base for therapists.

2. **Selection** of properly trained and qualified therapists. Initial selection, checking of professional credentials, evaluating candidates on minimum training criteria are best handled at the CRU level. For the CBI, however, skillfulness in accurate empathy is also required to facilitate initial training and ensure the therapist's ability to adhere to the treatment protocol. Consistent central assurance of this clinical skill is needed.

3. **Certification** of therapists to see trial participants. Again, standardized procedures and criteria should be used to approve therapists before they treat participants in the main trial.

4. Once therapists have been certified, there is an ongoing process of **monitoring** performance so that the content and quality of counseling do not drift from trial standards. This requires a standardized review of practice samples.

5. **Document the fidelity** of delivered treatments, so that adherence to and discriminability of protocols can be demonstrated in scientific peer review.

Thus for the success and credibility of the trial it is important to have centralized training, certification, monitoring, and documentation for treatments, in addition to local on-site supervision.

Pending necessary budget allocation, the University of New Mexico Center on Alcoholism, Substance Abuse, and Addictions (CASAA, hereafter called the Training Center) will be responsible for trial-wide training, certification, monitoring, and documentation of therapists in both treatments. The training plan is outlined separately by the two staff groups to be trained.
6.7.1 Medical Monitoring (MM) Treatment

6.7.1.1 Clinician Qualifications
Applicants for the MM clinician positions will have the following minimum qualifications:

1. Completion of either an M.D., R.N., LPN., PA, Clinical pharmacology degree or license.
2. A minimum of two years of clinical experience after completion of the qualifying degree.
3. Willingness to provide manual-guided treatment and be audiotaped for supervision and research purposes.
4. Willingness to complete a preliminary battery of confidential questionnaires to provide the project with documentation of therapist attributes.
5. Upon hiring agrees to make a two-year commitment to the study.
6. A therapeutic skill level, based on an audiotaped sample of a therapy session submitted to, and approved by both the site PI and the Training Center.

Applicants who meet criteria 1-4 will then submit a tape of a therapy session to be evaluated for therapeutic skill. This tape will be sent to the Training Center where it will be reviewed. The Training Center will notify the site P.I. of the results of this evaluation. Applicants who do not pass the first evaluation will be permitted to submit a second tape that will be independently evaluated. Applicants who do not pass either tape review will be precluded from being hired.

The site P.I. will choose from among the applicants who have met all six criteria. In addition the P.I. may consider the applicant's prior experience in dealing with alcohol problems and prior experience with research protocols. To ensure within site clinician variability, each site P.I. will hire at least two MM clinicians.

6.7.1.2 Training
A detailed clinician manual has been prepared by the MM Subcommittee of the Behavioral Interventions Committee, members of who are responsible for initial MM training. Initial training for the MM treatment occurred at a trial-wide training meeting held in Orlando on November 19-20, 1998. All Project Coordinators attended, and sites had the option of sending additional MM staff to this meeting for training. The Project Coordinator or designated MM monitor will be responsible for training and on-site monitoring of MM therapists at their own sites during the main trial. The Training Center plans to prepare one or more MM training videotapes that can be used both at local sites in future training of MM staff. Another trial-wide training meeting will need to be provided toward the end of Year 02 or early in Year 03, to accommodate staff from CRUs that were not funded during the first two trial years.

6.7.1.3 Certification
Before MM clinicians may see randomized participants in the main trial they will be certified by the Training and Monitoring Center. A minimum of two post-training cases per therapist will be required for certification. An MM clinician will be certified when the Training Coordinator determines that he or she is adhering closely to treatment procedures as described in the MM clinician manual. Additional practice cases may be required prior to certification.

6.7.1.4 Monitoring
The Training and Monitoring Center will be primarily responsible for monitoring trial-wide adherence to protocol. The local CRU will be responsible for clinician supervision (See section...
6.8 on MM supervision). This means that the local CRU will need to resolve issues or problems arising in maintaining clinician adherence to the protocol. The Training and Monitoring Center will request one tape for every two cases seen by the MM clinician. Audiotapes of all MM sessions will be retained at the CRU. The Training Coordinator will notify the PC of the tapes that are to be copied and sent to the Training and Monitoring Center. Thus clinicians will not know in advance which sessions will be monitored.

If average adherence slips below criterion level (average of 5 on 7-point Likert scales), a clinician may be “red-lined” (decertified) by the Training Coordinator. The clinician is thereafter prohibited from beginning new study cases until adherence returns to an acceptable level. Improved adherence may be demonstrated with cases that were already in treatment at the time of decertification, or with additional practice cases that will not be included in trial data. The density of session monitoring will be increased during a red-lined period. The Training Coordinator must recertify the clinician as consistently adhering to the MM protocol (ratings of 5 or higher) before he or she may see new research cases.

A red-line warning is issued by the Training and Monitoring Center as a preliminary step, prior to red-lining. The warning triggers an intensification of monitoring of recent and new sessions. Priority is given to monitoring these sessions, so that a determination can be made expeditiously as to whether to proceed to red-lining. In the interim, the practitioner may continue to see COMBINE patients, including new patients. The Training and Monitoring Center will request specific tapes to review, and role-play sessions may also be required.

### 6.7.1.5 Documentation

The fidelity of MM will be documented via clinician adherence checklists completed at the Training Center. This will further allow limited comparisons of adherence ratings given by the CRU Project Coordinators and by the clinicians themselves who complete a parallel checklist during treatment. The inter-rater reliability of adherence ratings at the Training Center will be ascertained by double-coding 5% of rated sessions, selected at random.

Separability of the two treatments (MM and CBI) is not an issue that can be addressed meaningfully in COMBINE because: (1) all trial participants (except those in CBI alone) receive MM, and (2) treatment group cannot be masked from coders because of salient differences in format (e.g., length) and in staff who provide the two treatments. Nevertheless, fidelity to each treatment protocol can be documented.

### 6.7.2 The COMBINE Behavioral Intervention (CBI)

#### 6.7.2.1 Therapist Qualifications

The recruitment of therapists will be initiated by the CRU Principal investigator. Minimal qualifications will be as follows.

1. Completion of at least a master's degree in psychology, counseling, social work or a closely related mental health field.
2. A minimum of two years of clinical experience after completion of qualifying degree.
3. Experience in conducting behavioral treatment consistent with CBI.
4. Experience in treating alcohol use disorders or closely related problems.
5. A willingness to provide manual-guided treatment and be audio-taped for
supervision and research purposes.
6. Willingness to complete a preliminary battery of confidential questionnaires to provide the project with documentation of therapist attributes.
7. Familiarity and comfortable with the involvement of a SSO in treatment
8. Upon hiring agrees to make a two-year commitment to the study.
9. Demonstration of a high level of skill in accurate empathy (reflective listening).
10. A therapeutic skill level, demonstrated by a taped sample of a therapy session submitted to, and approved by both the site PI and the Training Center.

Applicants for the therapist positions who meet criteria 1-7 and are proposed for hiring by the site P.I. will then submit to a simulated therapy session, conducted with a scripted proxy participant. The session will be audiotaped. The audiotape will be sent to the training center where it will be evaluated for therapist skill level and demonstration of a high level of empathy. Therapists meeting these criteria will be approved by the training center. Therapists failing these criteria will be permitted to submit a second therapy tape that will be independently evaluated. Those who do not meet criteria in either submission will be precluded from filling a therapist position. The results of the tape evaluations will be communicated to the site PI who will then make final selections among those meeting all of the qualifications. In making final selections the site PI may also take into consideration three other desirable characteristics:

1. Specific training and experience in areas covered by the modules.
2. Specific training and experience in motivational interviewing.
3. Prior experience with research protocols.

In order to permit examination of within site therapist variability each site will hire a minimum of two therapists to deliver CBI.

6.7.2.2 Prescreening
Empathic skillfulness has been shown to be an important predictor of treatment outcome in both behavioral (Miller, Taylor & West, 1980, Miller & Baca, 1983) and nonbehavioral therapies (Valle, 1981), and is an essential fundamental skill for the motivational approach that underlies the CBI (Miller & Rollnick, 1991). Empathic skillfulness is a precondition for training and certification in CBI. Prior to acceptance for training, therapists at individual CRUs will provide an audiotaped role-play sample of their ability to use accurate empathic listening, as behaviorally defined by Carl Rogers and his students. The content of the role-play will be standardized across sites, and structured observational criteria will be used to establish a sufficient level of empathic skill to enter CBI training. Dr. Miller will oversee this process, using a coding system that he developed and tested with a group of trainers at the Kaiser Permanente Center for Health Research. All tapes will be double-coded to ensure convergence, and to ascertain inter-rater reliability with this sample. Additional work samples may be required. Therapists must be approved by the Training Center director before attending training.

6.7.2.3 Training
A detailed therapist manual has been developed. The Training Center will be responsible to provide CBI trainers. Initial CBI training occurred at a 3-day trial-wide training meeting held in Albuquerque in May of 1999. Two to three therapists attended from each CRU, along with a designated Lead Therapist (who may be one of the 2-3 therapists). The Lead Therapist will be responsible for on-site monitoring of CBI therapists at their own CRU during training and the main trial. The Training Center plans to prepare one or more CBI training videotapes that can be used both at the May training and at local sites. Another trial-wide CBI training will be held in
September 1999, to accommodate staff from CRUs that were not funded during the first two trial years, as well as additional therapists being hired for the trial.

6.7.2.4 Certification
Before CBI therapists may see randomized participants in the main trial they will be certified by the Training and Monitoring Center. New CBI therapists must pass an empathy prescreen, and then submit complete tapes for at least two post-training cases. A CBI therapist will be certified when the Training Coordinator determines that he or she is adhering closely to treatment procedures as described in the CBI manual. If performance does not meet protocol standards, additional cases may be required prior to approval.

6.7.2.5 Monitoring
The Training and Monitoring Center will be responsible for monitoring trial-wide adherence to the protocol. The local CRUs will be responsible for on-site supervision of CBI therapists. (see section 6.8 on CBI supervision). This means that the local CRU will need to resolve issues or problems arising in maintaining therapist adherence to the CBI protocol. All CBI sessions will be audiotaped and these audiotapes will be retained at the CRU. The Training and Monitoring center will request one audiotape per case for each CBI therapist. The Training Coordinator will notify the CRU designated supervisors of the tapes that are to be copied and sent to the Training and Monitoring Center. Thus, therapists will not know in advance which sessions will be monitored. Adherence checklists will be completed and forwarded electronically to the CRU designated supervisors.

If average adherence slips below criterion level (average of 5 on 7-point Likert scales), a clinician may be “red-lined” (decertified) by the Training Coordinator. The clinician is thereafter prohibited from beginning new study cases until adherence returns to an acceptable level. Improved adherence may be demonstrated with cases that were already in treatment at the time of decertification, or with additional practice cases that will not be included in trial data. The density of session monitoring will be increased during a red-lined period. The Training Coordinator must recertify the clinician as consistently adhering to the CBI protocol (ratings of 5 or higher) before he or she may see new research cases.

A red-line warning is issued by the Training and Monitoring Center as a preliminary step, prior to red-lining. The warning triggers an intensification of monitoring of recent and new sessions. Priority is given to monitoring these sessions, so that a determination can be made expeditiously as to whether to proceed to red-lining. In the interim, the practitioner may continue to see COMBINE patients, including new patients. The Training and Monitoring Center will request specific tapes to review, and role-play sessions may also be required.

6.7.2.6 Documentation
The fidelity of CBI will be documented via global rating scales and more specific therapist adherence checklists completed at the Training Center, identified by therapist number, case number, and session number. This will further allow comparisons of adherence ratings given by the CRU Senior Therapists and by the therapists themselves who complete a parallel checklist during treatment. The inter-rater reliability of adherence ratings will be ascertained by double-coding 5% of rated sessions, selected at random.
6.8 **MM and CBI Case Management and Supervision**

### 6.8.1 Overall Approach

1. To ensure fidelity of treatment models and to resolve ongoing clinical issues, a supervisory structure will be developed for CBI therapists and MM clinicians. Responsibility for implementing the supervisory structure lies within the local CRU.

2. To preserve the independence of the two treatment conditions, MM supervision will be conducted separately from CBI supervision.

3. MM clinicians will address both case management and manual adherence issues in a single supervisory session. These sessions will be held weekly and will last approximately 30-60 minutes.

4. CBI therapists will be required to attend two supervisory sessions a week. The first meeting will deal with ongoing case management concerns and the second will involve issues related to maintaining fidelity to the CBI manual. These two meetings can occur back-to-back or at separate times. The case management meeting should take no more than 60 minutes with the majority of meetings lasting 30 minutes. The fidelity meetings should not go beyond 90 minutes with most meetings lasting about 60 minutes. The total amount of time devoted to these supervisory activities should be no more than 120 minutes.

5. It is expected that the amount of time devoted to supervising manual adherence will be reduced as therapists/clinician become more familiar with the treatment models. A suggested model is to have weekly CBI adherence meetings for the first five cases, biweekly meetings for the second five cases, and monthly meetings for the last 10 cases. The current plan is to review the time demands of supervising therapist/clinician adherence during the first three months of the implementation phase of the trial.

### 6.8.2 MM Supervision

1. Individuals attending the weekly supervisory meeting will include the study physician or individual responsible for prescribing medications, MM clinicians and Project Coordinator. It is important that the study physician or individual responsible for prescribing medications attend these meeting since side effects/safety issues will be discussed.

2. To maintain fidelity to the MM model, efforts will be made to review different components of the MM approach at each meeting. Discussion will be focused on how MM components are being delivered. Information of the MM Adherence Checklist completed at the Training Center will be reviewed by the PC in order to identify problems clinicians are having in applying the various components such as medication noncompliance, participation in mutual self-help groups, and obtaining a commitment to abstinence. Also, attention will be devoted to ensuring that coordination between MM and CBI is flowing smoothly.

3. The Project Coordinator or designated MM monitor (i.e., lead MM clinician or PI) will listen to 1 tape per month for each MM clinician until proficiency/competence (measured in terms of protocol adherence/protocol non-adherence) is demonstrated in the following categories: 2 initial sessions; 4 follow-up sessions which must include all 4 scenarios (drinking and medication compliant; abstinent and medication compliant; drinking and medication noncompliant; abstinent and medication noncompliant). Of these 4 scenarios, 2 cases should include participant(s) randomized to MM-only and 2 cases should
include participant(s) randomized to MM + CBI. A peer supervision model will be employed to review adherence at weekly meetings.

6.8.3 CBI Supervision

6.8.3.1 Case Management Component
1. Attendance at the case management meetings will include the PC, Lead CBI therapist, and other CBI therapists.
2. As in MM supervision, issues pertaining to drinking/drug use, noncompliance (e.g., reviewing inactive status of certain participants), and safety concerns will be addressed. Difficulties occurring in MM and CBI coordination will be discussed. The MM Treatment Coordination Checklist will be reviewed by the PC prior to the meeting to identify immediate and potential case management concerns.

6.8.3.2 Fidelity to Treatment Component
1. Attendance at these fidelity meetings will include Lead CBI therapist and all CBI therapists.
2. To ensure that the CBI modules are implemented in accordance with study requirements, different CBI modules will be reviewed each session. In reviewing a particular module, focus will be placed on the following: (a) review of the core and elective components of the module (i.e., examining overlap and other issues of unclarity); (b) how much exposure of the module (dosage) is sufficient; (c) how to combine this module with others in a single session; (d) and anticipated or current problems that could arise in delivering this module such as participant noncompliance. In general, discussion will be centered on practical issues involved in utilizing the module with a heterogeneous alcohol participant population.
3. Once the module has been delivered by all CBI therapists, a review of an audiotape of the module session will occur. One therapist tape will be reviewed at each meeting. A peer supervision model will be employed in reviewing the audiotapes and the Lead CBI therapist will be responsible for coordinating the peer supervision. This will entail the following: Two CBI therapists will be paired off prior to the meetings; one CBI therapist will be designated as the listener of the others audiotaped session. The designated listener will be responsible for moderating the peer supervision. Again, the discussion will involve issues covered previously in didactic sessions. However, greater emphasis will be placed on linking application problems to supervisory needs of the individual therapist. Such needs may entail therapist bias against using the module due to a lack of familiarity with the approach, difficulties in engaging the SSO in the module and failure to address compliance problems in applying the module. It is expected that such a process will refine or enhance therapist skill in employing CBI modules with different kinds of participants.
4. Feedback on tapes submitted to the Training Center will be examined in the sessions (especially in those cases where therapist ratings fall below criterion level). Additional supervision will be needed in cases where the therapist is "red-lined" (decertified).
CHAPTER 7: Measurements

7.1 Screening Assessments

7.1.1 Quick Screen
The Quick Screen will be used for four primary purposes: (1) To inform potential participants of the basic nature of the study; (2) To obtain basic inclusion/exclusion information to determine individuals’ provisional eligibility (nursing or pregnant women, permanent address, AUDIT Score, medical problems); (3) To ask questions regarding individuals’ willingness to participate in a research study; and (4) To obtain basic sociodemographic information to determine the nature of the population from which the study sample is drawn (age, gender, AUDIT Score).

7.1.2 Eligibility Criteria Checklist
After the completion of the Quick Screen, Pretreatment Assessment and Medical Evaluation sessions, the Project Coordinator will record the information obtained from these Quick interviews onto the Eligibility Criteria Checklist. If the individual is clearly excluded from the study, the Project Coordinator does not need to meet with that person.

7.1.3 Reasons for Participation
It is important to get information about the reasons that potential participants were interested in seeking involvement in COMBINE. This provides an index of the possible extent and locus (e.g., intrinsic or extrinsic) of motivation for treatment and participation in a clinical trial. The Reasons for Participation questionnaire that was developed and used in Project MATCH will be used for COMBINE. Participants are asked to indicate their reasons for wanting to participate from a listing of possible alternatives that are categorized as logistical/practical reasons (e.g., convenient location; free treatment), treatment/program related reasons (e.g., hopes to receive a particular type of COMBINE treatment, treatment likely to be better because its part of a research project), and the influence of others (e.g., spouse/significant other, friends/co-workers).

Similarly, if after screening the individual chooses not to participate in the trial, they are asked to check those items in the logistical/practical reasons (e.g., too much time required, child care problems), treatment/programmatic (e.g., do not want random or “chance” assignment, program too long or too intensive), and influence of others (e.g., spouse/significant others, employer) that reflect the main reasons for not participating.

7.2 Physical, Laboratory, and Physiologic Assessments

7.2.1 History and Physical Exam
The study physician will evaluate each participant to rule out significant medical disorders with a thorough medical history, physical exam, electrocardiogram (as clinically indicated), and the laboratory tests specified below. Potential participants will also be screened to rule out major psychiatric disorders, including current dependence on substances other than nicotine, caffeine and cannabis.

7.2.2 Clinical Institute Withdrawal Assessment for Alcohol - Revised (CIWA-AR)
The Clinical Institute Withdrawal Assessment for Alcohol-Alcohol Revised (CIWA-AR) is a brief 10-item measure used to provide a quantitative index of the severity of the alcohol withdrawal syndrome (Sullivan, et al., 1989). It has been used both in clinical and research applications and has demonstrated both reliability and validity (e.g., Sellers, et al., 1992; Stuppaek, et al., 1994).
7.3 **Laboratory Measurements**

7.3.1 **Electrolytes**

Heavy alcohol use is associated with a number of electrolyte abnormalities that need to be assessed prior to enrolling participants into the trial. The most common electrolytes affected by chronic alcohol use include magnesium, sodium and calcium. The study medications do not appear to effect electrolyte levels. The electrolyte panel will include sodium, potassium, calcium, magnesium, inorganic phosphorus, and bicarbonate (as measured by a CO$_2$ content). Electrolytes will be assessed as part of the chemistry panel that will be obtained at baseline and at weeks 8 and 16. Abnormalities of the tests will be referred to the participant’s physician, as there are multiple causes for changes in electrolytes.

7.3.2 **Uric Acid**

Persons who are alcohol dependent may have higher levels of uric acid. The study medications have not been found to alter uric acid levels. Uric acid is included in the chemistry panel.

7.3.3 **Calcium and Phosphorous**

Calcium and phosphorous will be measured and monitored for several reasons. There is a concern, since acamprosate’s chemical formulation is, in fact, calcium homotaurinate, that individuals may be receiving a larger than normal daily calcium load during the trial. For instance, the minimum daily requirement for calcium is 800 mg in adults and the participants in this trial may be receiving several times the daily requirement.

7.3.4 **CBC with Differential and Platelet Counts**

Persons with alcohol dependence may have a number of abnormalities of the hematopoetic system including iron and folic acid anemias, chronic illness anemias, thrombocytopenias and white cell abnormalities. A CBC with a differential and platelet counts will be assessed at baseline and at the end of treatment (16 weeks). Participants with values outside the normal range will be assessed by their personal physician. Participants with an abnormal CBC may be eligible for the trial depending on the etiology of the hematopoetic abnormality and the overall health of the participant.

7.3.5 **Liver Function Tests**

Liver function is frequently affected by chronic alcohol consumption. In addition naltrexone may have direct toxic effect at high doses (>300 mg per day). The complete LFT panel will be performed at baseline and at weeks 4, 8, 12, 16, 26, and 52. The full LFT panel includes a total bilirubin, alkaline phosphatase, lactic dehydrogenase (LDH), gamma glutamyl transferase (GGT), serum gamma oxalacetic transaminase (SGOT, AST), serum gamma pyruvic transaminase (SGPT, ALT), a total protein and an albumin.

7.3.6 **Carbohydrate Deficient Transferrin (CDT)**

Samples for CDT will be drawn at baseline, weeks 8 and 16, and stored. The samples will be analyzed only on those participants who report no relapse.

7.3.7 **Hepatitis C**

In recent studies of alcoholics with elevated liver enzymes, from 20-33% have been positive for Hepatitis C. Of those who tested positive for Hepatitis C, over half (53%) had elevated liver enzymes (one or both SGPT and SGOT). Therefore, if liver enzyme functions are elevated, Hepatitis C testing will be performed, when clinically indicated.
7.3.8 Pregnancy
A b-HCG (either urine or serum, depending on each institution’s IRB requirements) will be performed during the physical examination prior to randomization. This test will be repeated for reports of missed menses of at least 10 days as indicated by the SAFTEE.

7.3.9 Urinalysis
A routine urinalysis will be performed as part of the physical examination. Abnormalities such as hematuria, proteinuria and casts will be referred to the participant’s physician. Persons with glycosuria will have a fasting blood sugar performed to assess for diabetes. Persons with white cells and or bacteria will be assessed for a urinary tract infection. A urinalysis will be completed at baseline and at the end of treatment.

7.3.10 Electrocardiogram (ECG)
Alcohol has a number of toxic effects on cardiac function that may effect participation in the trial. An electrocardiogram will be obtained as part of the physical exam when clinically indicated. Persons with significant abnormalities such as atrial or ventricular arrhythmia’s, evidence of cardiomegaly or hypertrophy or evidence of ischemia will be referred to their physician for consultation prior to enrolling the participant in the study.

7.3.11 Blood Alcohol Content (BAC)
Blood alcohol levels provide an estimate of recent alcohol use. A hand held breathalyzer provides good approximation of a blood alcohol level. A BAC will be assessed at every visit. If a participant has a positive BAC over 0.005 grams%, the clinician must decide whether to assess the participant at that time, wait until the BAC level drops, or reschedule the clinic visit within 24-48 hours. The participant will be transported home, sent to primary care clinician or sent to detoxification as appropriate.

7.3.12 Urine Drug Screens
A baseline urine drug screen will be used to assess participants for the presence of opioids, cocaine, amphetamines, benzodiazepines, barbiturates and other sedative drugs.

7.3.13 Drug Levels
Drug plasma levels of naltrexone, its major metabolite 6-beta-naltrexol and acamprosate will be assessed at weeks 4 and 12 in order to assess compliance and differences in the metabolism of these medications. These samples will be stored and shipped to outside labs for analysis.

7.4 Adverse Events

7.4.1 Systematic Assessment for Treatment Emergent Events General Inquiry (SAFTEE-GI)
The SAFTEE-GI is a clinician-administered instrument (Levine & Schooler, 1986) designed to assess adverse health events. The short form of this instrument should take less than 7 minutes to administer. It was developed to standardize the collection of adverse events. The GI version of the instrument screens for any health problems over a specified period, uses clinical observations to probe for adverse events, and includes study specific events such as expected side effects from the study medication. The reliability and validity of the instrument in psychiatric populations has demonstrated good interrater reliability (kappa = .95) for the presence of an adverse event (Jacobson, Goldstein, Dominguez, & Steinbook, 1986). The validity of the instrument has been demonstrated in studies of patients taking imipramine,
phenelzine, alprazolam, and placebo (Rabkin & Markowitz, 1986). The version being used was adapted for use in COMBINE. One study specific adaptation is the inclusion of two items to assess sleep quality and disturbance. The SAFTEE will be administered at baseline and every MM session (weeks 1, 2, 4, 6, 8, 10, 12, and 16).

**7.4.2 Concomitant Medications, Medical and Adverse event Management and Reporting**

**7.4.2.1 Concomitant Medications**
Participants will be regularly reminded to report any concomitant medications being taken, including over-the-counter preparations, vitamins, herbals etc.

**7.4.2.2 Serious Adverse Event Report (SAE)**
The Serious Adverse Event Report should be completed whenever a participant experiences a serious adverse event. The FDA 21 CFR312.32 definition of adverse/serious adverse events is described in Section 5.4.1 and 5.4.5.

The report form captures information regarding the date of onset of the serious adverse event, a description of the event, action taken, and whether a relationship between the SAE and drug(s) exists.

If a symptom on the SAFTEE (adverse experience report form) is rated as severe, the investigator should consider whether this constitutes a Serious Adverse Event. If so, a Serious Adverse Event form should be completed and submitted to both the Coordinating Center, and Lipha within 24 hours (fax to CC at 919-962-3265; telephone Lipha at 1-800-547-4299)

**7.5 Treatment Related Expectancies**

**7.5.1 Treatment Experiences and Expectancies Questionnaire (TEE)**
This questionnaire asks participants about prior substance abuse treatment episodes, how helpful they feel their prior treatment was, how strongly they feel a current need for treatment, how helpful they expect the medications and counseling of the present trial to be, and how confident they feel that they will be drinking less or sober/abstinent from alcohol in 16 weeks. Most of these items are rated on 5-point Likert scales (0 - 4), with higher scores reflecting more positive appraisals and expectancies. The TEE will be administered at baseline only.

**7.6 Assessments of Behavioral Outcomes, Predictors, Mediators & Generalizability**

**7.6.1 Alcohol and Drug Use**

**7.6.1.1 Within-Treatment Alcohol-Use: Time-Line Follow-Back Procedure (TLFB)**
The Time-Line Follow-Back (TLFB) procedure will be used to assess drinking behavior during the time between clinical visits (Sobell & Sobell, 1992b, 1995). The TLFB is a semi-structured interview that provides estimates of the daily quantity, frequency, and pattern of alcohol consumption during the time periods. It uses a calendar prompt and a number of other memory aids (e.g., holidays, payday, and other personally relevant dates) to facilitate accurate recall of drinking during the target period. The procedure has been used in a number of clinical and research contexts. It has demonstrated adequate levels of reliability and validity when administered as an in-person interview, over the telephone, and when administered via computer (e.g., Carey, 1997; Sobell, Brown, Leo, & Sobell, 1996; Sobell, Sobell, Leo, & Cancilla, 1988). It is estimated that the TLFB assessment will take from 10-15 minutes to complete.
7.6.1.2 Baseline and Follow-Up Alcohol Use: Form 90 –AIR/ED

Retrospective self-reported day-by-day alcohol use at baseline and across follow-up will be gathered using the Form 90-AIR/ED (Alcohol Intake Revised/Economic Outcome Data). Developed for Project MATCH (Miller & DelBoca, 1994), the Form 90 is a semi-structured interview that inquires about participant general functioning, alcohol use, and illicit drug use. Each of these domains has demonstrated reliability with problematic drinkers and treatment-seeking inpatient and outpatient participants (Tonigan, Miller & Brown, 1997; Westerberg, Tonigan, & Miller, 1998), and the alcohol use section combines state-of-the-art grid (Miller & Marlatt, 1984) and calendar techniques (Sobell & Sobell, 1992b). The economic outcome data covers 4 domains: health care, crime, labor market, and motor vehicle accidents. The cost-effectiveness ancillary study will analyze these data.

The original Form 90-A was shortened considerably to meet the purposes of COMBINE. The General Functioning section measures prior treatment and mutual help experiences, work and education experiences, hospital and incarceration experiences, and use of prescribed medications. The Alcohol Use section solicits a day-by-day account of participant drinking and abstinence. A wide array of treatment outcome measures can be derived from this calendar format, two of which will represent the primary outcome measures of drinking behavior for the trial: (1) percent days abstinent, and (2) number of days to first heavy drinking episode. Also, included in the calendar are codes to represent days of health care utilization and incarceration. The Other Drug Use section of the Form 90-AIR/ED inquires about drug use during the 90 days before the interview. Regarding nicotine use, two items have been included from the Fagerstrom questionnaire (Fagerstrom & Schneider, 1989). The remaining eight categories include the following: Marijuana, Tranquilizers/sedatives, Stimulants, Hallucinogens, Cocaine, Inhalants, Opiates, and Other drugs, e.g., Amyl-butyl nitrates (poppers).

The Form 90-AIR/ED will be administered at baseline and the Form 90- F/ED will be given at all follow-up interviews, (e.g., post recruitment weeks 8, 16, 26, 52, and 68). The abbreviated Form 90 will inquire about alcohol use from the 90 days before the assessment interview, thus providing a continuous daily record of alcohol use from the 90 days before study recruitment to the end of treatment. Assessment of general functioning and drug use will likewise ask about the 90 days prior to the assessment interview. Finally, a reconstruction procedure has been developed to collect data that falls beyond the 90-day assessment period (e.g., during 26-week follow-up intervals or due to noncompliance with earlier assessment interviews). Follow-up interviews at week 52 or later will inquire about the prior 90 days of drinking; the reconstruction technique will be used to estimate alcohol consumption beyond 90 days back to the previous follow-up interview. This procedure will allow estimates of day-by-day drinking across the follow-up period.

7.6.1.3 Alcohol and Drug Involvement

Alcohol use and dependence can be considered complex syndromes with an array of symptom clusters, mediators, and consequences. To assess the full impact of the interventions six secondary indices associated with drinking, drug use, and abstinence will be measured. Three self-report questionnaires, the Drinker Inventory of Consequences (DrInC, Miller, Tonigan, & Longabaugh, 1995), the Alcohol Dependence Scale (ADS, Skinner & Allen, 1982), and Alcohol Abstinence Self Efficacy scale (AASE; DiClemente, Carbonari, Montgomery, & Hughes, 1994) will be administered at baseline. The DrInC will also be used at all follow-up interviews (weeks 8, 16, 26, 52, and 68). The AASE will also be administered at weeks 16 and 26. A fourth measure, Drug Use Index (Clayton & Voss, 1981) yields a global judgment of illicit drug use severity and can be derived from responses to the Form 90 Drug Use section. Thus, the Drug use
index measure will be available for baseline and all follow-up assessments. The fifth measure, SCID-IV Module E, composed of alcohol and non-alcohol use disorders focuses on the assessment of alcohol and drug use, determining the number of diagnostic symptoms endorsed and whether the individual is categorized as having alcohol and/or drug abuse or dependence diagnoses at baseline. The alcohol use disorders section will also be collected at 16, 52, and 68 week follow-ups. The sixth measure, ASI Family History, is included only in the baseline assessment battery; it is the only semi-structured assessment in this assessment block.

Characteristics of these six measures of involvement with alcohol and drugs are provided in the Table 7.1 below. Screening (5 subscales) and diagnosis of alcohol dependence and abuse will be assessed from two perspectives, past 12 and 6 months before study recruitment. Recent alcohol-related consequences - past 90 days - will be measured in five areas: (1) interpersonal, (2) intrapersonal, (3) social responsibilities, (4) physical, and (5) legal. Negative consequences can be rated in each of these areas even if the person has been abstinent during the assessment period (e.g., legal consequences of a DWI received prior to the rating period). Likewise, global rating of severity of illicit drug use will consider past 90 days use. Given the state nature of self-efficacy and temptation to drink, the AASE will measure current participant beliefs in these two domains.

7.6.1.4 Composite Outcome Index

Also included in Table 7.1, as a measure of alcohol involvement is a categorical outcome measure. Categorical measures are used to provide a more clinically-interpretable outcome status of an individual or a group of individuals receiving alcohol treatment based on multiple outcome measures. Cisler & Zweben (1999) developed and validated a measure for use in Project MATCH (Project MATCH Research Group, 1993; 1997a) that drew upon NIAAA guidelines for “at-risk” or “hazardous” drinking and DSM-IV criteria for problems related to alcohol disorders (NIAAA, 1995; American Psychiatric Association, 1994). This composite outcome measure integrates both alcohol consumption and alcohol-related problem variables to classify participants into four categories: abstinent; moderate drinking without problems; heavy drinking or problems; heavy drinking and problems. Data derived using the Form 90 (Miller, 1996) and alcohol-related problems using the Drinker Inventory of Consequences will be used to determine composite outcome status.

Table 7.1 Seven Measures of Alcohol and Drug Involvement

<table>
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<td>Past 90 days</td>
<td>Negative consequences (5 subscales plus total)</td>
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<td>Alcohol dependence screening</td>
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<td>Composite Outcome Measure</td>
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7.6.2 Motivation

Motivation for change is assumed to be a critical variable related to initiation of treatment, participation in treatment, and the modification of the problem behavior. In this trial motivation is related to the stages of change for addictive and health related behaviors (Prochaska, DiClemente, & Norcross, 1992). The stages of change (Precontemplation, Contemplation, Preparation, Action and Maintenance) have been identified and related to participation and outcome for unaided and treatment assisted change of addictive behaviors (DiClemente & Prochaska, 1998). Motivational readiness to change is related to the stages of change. In Project MATCH, baseline motivational readiness emerged as the strongest predictor of drinking outcome for outpatients during the posttreatment period and at the three-year follow-up (Project Match Research Group, 1997a, 1998a). Motivational readiness for change will be assessed at baseline and at posttreatment evaluations in order to evaluate its role as a predictor and moderator of treatment outcome and drinking modification.

7.6.2.1 University of Rhode Island Change Assessment Scale (URICA)

Assessment of motivational readiness to change will use a version of the University of Rhode Island Change Assessment Scale (URICA; McConnaughy, DiClemente, Prochaska & Velicer, 1989) that has been adapted for use in alcoholism treatment. Four subscales are derived, each having six items, each representing precontemplation, contemplation, action and maintenance (resisting relapse). Similar versions of this measure have been used in a number of prior alcoholism treatment studies (DiClemente & Hughes, 1990; Isenhart, 1994; Carney & Kivlahan, 1995). This measure demonstrated solid psychometric properties in Project MATCH with Alpha internal consistency coefficients for the four subscales ranging from .74 to .82 in the aftercare arm and .75 to .86 in the outpatient arm. The 24-item URICA will be administered at baseline only.

7.6.3 Craving

The medications to be used in this trial are considered “anticraving” drugs and the goals of CBI include the reduction of craving. Therefore, measurement of craving during the trial is necessary to examine the effects of treatment on this condition.

7.6.3.1 Obsessive Compulsive Drinking Scale (OCDS)

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, 1996b). The OCDS will be supplemented by two additional questions taken from the 5-item Craving Questionnaire developed by Weiss et al. (1995, 1997). This questionnaire, originally developed to assess craving in cocaine dependent patients, has been shown to have internal consistency and predictive validity in an outpatient population of cocaine dependent patients. 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 both independently and in conjunction with the OCDS to complete the evaluation of craving during the trial. Both measures will be given at baseline, and every research visit thereafter (weeks 0, 1, 2, 4, 6, 8, 10, 12 and 16), as well as at the 26-week follow-up visit.
7.6.4 Psychological Assessment

7.6.4.1 Rationale
There is substantial evidence from previous research to support the inclusion of psychiatric/psychological assessment in an alcohol treatment outcome study. The co-occurrence of psychiatric disorders and alcohol dependence has been well documented in both the general population (Helzer & Pryzbeck, 1988; Kessler et al., 1997; Regier et al., 1990) and among patients seeking treatment for alcohol dependence (Driessen et al., 1998; Hesselbrock et al., 1985; Penick et al., 1994; Rounsaville et al., 1987; Walker et al., 1994). Patients receiving alcohol treatment also exhibit high levels of psychological distress (Benishek et al., 1992; Harvey et al., 1994; Rounsaville et al., 1987; Svanum and McAdoo, 1989) and often relapse in response to negative emotional states (Marlatt & Gordon, 1985b). Personality research informs us that antisocial features may influence the onset and course of drinking behavior (Hesselbrock et al., 1985; Schuckit, 1985) and that “temperament factors” described by a biosocial model (Cloninger et al., 1993) discriminate among alcoholics with and without antisocial features (Howard et al., 1997).

Psychiatric disorders (Rounsaville et al., 1987), levels of psychological distress (Svanum & McAdoo, 1989; Rounsaville et al., 1987), and global psychiatric severity ratings (McLellan et al., 1983) have been shown to have prognostic value for the outcome of alcohol treatment. The specific usefulness of diagnostic assessment is supported by findings that some specific disorders have better prognostic value than others and that this relationship is not the same for men and women (Rounsaville et al., 1987). Whether temperament factors described by Cloninger and his colleagues (Cloninger & Svrakic, 1997; Svrakic et al., 1993) show the same ability to predict response to treatment as antisocial personality features (Powell et al., 1998; Rounsaville et al., 1987; Schuckit, 1985) remains to be determined. Including assessment of each of these domains in COMBINE will allow us to determine whether relationships found in previous research also occur when a combination of pharmacotherapy and behavioral treatments are employed.

7.6.4.2 Goals
The overall goals for including psychiatric/psychological assessment measures in COMBINE are: (a) to verify that participants meet criteria for eligibility, (b) to describe the psychiatric/psychological characteristics of the treatment sample for comparison with other alcohol treatment studies, (c) to determine whether initial psychiatric/psychological characteristics of the sample relate to treatment outcome, and (d) to determine whether changes in psychiatric status and psychological symptoms occur during treatment or follow-up and relate to outcome.

7.6.4.3 Objectives
The specific objectives of psychiatric/psychological assessment in COMBINE are: (1) to describe the incidence of AXIS I psychiatric disorders and Antisocial Personality Disorder in the sample using DSM-IV criteria, (2) to monitor changes in psychological symptoms and mood states during treatment, (3-) to monitor changes in psychiatric diagnoses by the completion of treatment, and (4) to monitor changes in psychological symptomatology during the follow-up period.

7.6.4.4 Methods
The specific methods used to achieve the objectives of the study are as follows. Psychiatric assessment at baseline will include: (1) administration of a structured, computer-assisted, clinical screening interview that is designed to assess current psychiatric disorders on AXIS I (SCID Screen), and (2) self-administration of measures that are designed to assess psychological
symptomatology (Brief Symptom Inventory; BSI), and mood states (Profile of Mood States; POMS), perceived stress (Perceived Stress Scale, PSS). During the active treatment phase, participants will be asked to complete self-report measures that are designed to assess current mood states (POMS) and perceived stress (PSS). These latter measures are thought to be sensitive to the acute effects of medication and treatment. The POMS will be administered at research weeks 0, 1, 2, 4, 8, 12, and 16 and the PSS will be administered at research weeks 0, 1, 2, 4, 6, 10, 12, 16, and 52. The BSI will also be administered at baseline, and weeks 8 and 16 to examine changes in psychological symptomatology during the process of treatment. Participants will also be asked to complete self-report measures designed to measure psychological symptomatology (BSI) throughout the follow-up period at weeks 26, 52, and 68.

7.6.4.5 Psychiatric/Psychological Assessment Instruments

7.6.4.5.1 SCID Screen Patient Questionnaire
The SCID Screen Patient Questionnaire (formerly Mini-SCID for DSM-IV) (First, Gibbon, Williams, & Spitzer, 1996; Raffoul & Lyle, 1993) is a computer administered diagnostic screening interview based on DSM-IV criteria and the Structured Clinical Interview for DSM-IV (Spitzer, Williams, Gibbon, & First, 1992). The SCID Screen covers the following major areas of psychopathology: Mood Disorders, Anxiety Disorders (including Posttraumatic Stress Disorder), Substance Use Disorders, Psychotic Symptoms, Somatoform Disorders, and Eating Disorders. In total, for all the categories, there are approximately 76 questions included in SCID Screen. However, it is possible to choose any one or combination of these categories to be screened. The ability to select the categories to be screened, in addition to an automatic branching program that skips questions if a participant denies certain symptoms, allows the number of items presented participants to be considerably less than 76. The average participant takes under 20 minutes to complete the interview. The SCID Screen generates a listing of symptoms associated with all current psychiatric diagnoses for which the participant meets criteria. The SCID Screen will be used to provide information for each participant on presumed current AXIS I symptoms and diagnoses. The measure is described as an easy-to-use program that can serve as the first stage of a complete diagnostic evaluation or to screen for the presence of Axis I disorder (Raffoul & Lyle, 1993). It will be administered by a research assistant at baseline.

7.6.4.5.2 Brief Symptom Inventory (BSI)
The BSI (Derogatis, 1993) is a 53-item self-report symptom inventory that was designed to reflect psychological symptom patterns. The scale summarizes information across nine primary symptom domains (Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism) and on three global indices (Global Severity Index, Positive Symptom Distress, and Positive Symptom Total). Participants are asked to describe “how much a problem has bothered or distressed them over the -point scale. Evidence for good internal consistency for the nine subscales (.71-.85) and test-retest reliability for the nine subscales (.68-.91) and three global indices (.80-.90) has been provided (Derogatis, 1993). Convergent validity with other continuous measures of psychological symptomatology has also been reported (Derogatis, 1993). Norms based on adult psychiatric outpatients and adult nonpatients are available for comparison. The BSI is sensitive to symptom presentation in patients with alcohol and drug problems and shows sensitivity to symptom change during treatment (Benishek et al., 1992; Harvey et al., 1994). The BSI will be used to describe psychological symptomatology at baseline and to measure changes in symptomatology during treatment and follow-up. It will be self-administered at baseline, during treatment at weeks 8 and 16, and during follow-up at weeks 26, 52, and 68. It takes
approximately eight minutes to complete.

7.6.4.5.3 Profile of Mood States (POMS)
The POMS (McNair, Lorr & Droppleman, 1981) is a 65-item self-report measure that is designed to provide information on fluctuating mood states. A participant is given 65 five-point adjective rating scales and asked to describe how “he or she has been feeling during the past week including today.” The questionnaire yields scores on six factor-analytically derived subscales of mood states, including the following: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment. Evidence for internal consistency across the six subscales (.84-.95), test-retest reliability (.65-.74), and concurrent validity has been provided (McNair et al., 1981). Norms developed on male and female psychiatric outpatients are available for comparison. The POMS has been shown to be sensitive to the acute effects pharmacological interventions (Little, 1989), psychotherapy (Haskell et al., 1969), and substance abuse treatment (McMahon et al., 1986). The Profile of Mood States (POMS) will be used to obtain information on mood states throughout the course of treatment and will be sensitive to the acute effects of medication as well as cognitive-behavioral treatment. The instrument will be self-administered during weeks 0, 1, 2, 4, 8, 12, and 16. It takes approximately 3-5 minutes to complete.

7.6.4.5.4 Perceived Stress Scale (PSS)
The degree of stress experienced or perceived by alcoholics in recovery has been shown to be a significant predictor of relapse (e.g., Brown, Vik, McQuaid, Patterson, et al., 1990; Brown, Vik, Patterson, Grant, et al., 1995). It also appears that drinking to cope with stress and the level of perceived stress are related and mediate drinking behavior (Abbey, Smith, & Scott, 1993). There is also suggestive evidence that pharmacological agents such as naltrexone could potentially reduce the urges to drink and the loss of control over drinking by modifying the links between reward, stress, and craving (Anton, 1995). The Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1983) will be used to assess this 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). Subsequently, a shorter 10-item scale was factor analytically derived and found to have comparable levels of reliability and validity in comparison to the 14-item scale. An even more abbreviated 4-item scale has been developed; while its level of reliability is somewhat lower than the two longer measures, it was judged to be adequate for use in situations requiring a very brief measure of the perception of stress (Cohen & Williamson, 1988). The 4-item measure will be administered at weeks 0, 1, 2, 4, 6, 8, 10, 12, and 16. It will also be administered at the week 52 follow-up visit.

7.6.5 Social Support
The purpose of including measurement of social support in COMBINE is that prior research has shown that a person's social network influences treatment outcomes. This construct is included for two purposes: 1) to control for this factor when testing trial wide hypotheses; and 2) to test whether participants with unsupportive networks who are assigned to CBI have better outcomes than those who are assigned to MM, when controlling for pharmacotherapy condition.

7.6.5.1 Important People Scale (IP)
The Important People and Activities (IPA) instrument was developed to operationalize the construct of network support for drinking. Prior to doing so alcohol-specific support had not been differentiated from general support, with the result that the influence of social support on
drinking outcomes had been inconsistent and diluted (Longabaugh & Beattie, 1985, Beattie & Longabaugh, 1997). This instrument has been used in several RCT’s involving psychosocial treatments. In MATCH, pre-treatment support for drinking was found to significantly predict one year drinking outcomes in both the outpatient and aftercare arms (Project MATCH, 1997a). It was also found to be prognostic of three-year outcomes (Longabaugh et al., 1998). Further, network support for drinking was hypothesized to interact with treatment condition to produce matching effects. At three year follow-up results indicated that, as hypothesized, patients with networks supportive of participant drinking had better drinking outcomes in Twelve Step Facilitation therapy than in Motivational Enhancement (Project MATCH, 1998a). Causal chain analysis identified AA involvement as a partial mediator of this matching effect (Longabaugh et al., 1998). In COMBINE, CBI will take special efforts to involve participants in mutual help programs such as AA. It is anticipated that this involvement will partially mediate drinking outcomes for CBI participants with pre-treatment support of participant drinking.

To accommodate the needs and interests of COMBINE the IPA has been shortened and modified by eliminating the Activities portion of the interview, (reducing the "IPA" to the "IP", which it will be called in COMBINE). This information is not used to provide the summary support score, and thus is not essential.

The IP has been modified to incorporate new questions that will assist in evaluating the influence of network support on important treatment issues: 1) to what extent does the participant's network support participation in the treatment? 2) to what extent does the network support the participant's taking medication for his/her drinking? 3) to what extent does the network support participant participation in mutual help group programs?

Administration time for the IP will be 12 minutes on average, at baseline, 16- and 26-week visits. Scoring of the overall support for drinking measure will be retained from the MATCH study. The new questions asked will be single item variables that will be weighted by a measure of the importance of each network member and summed across the network.

7.6.6 Quality of Life
Alcoholism research has traditionally relied on measures of consumption such as percentage of days of abstinence or drinks per drinking day. These measure alone do not reflect the full range of severity and treatment outcome. Information on an individual’s ability to function in daily life, their degree of well-being, and their satisfaction with their status is also necessary. Work in the last 10 years in numerous biomedical areas has resulted in development of indicators of functional status or quality of life and their widespread use in clinical trials as secondary outcomes. The measurement approaches are varied and may be either global or disease specific and may involve combinations of unidimensional instruments or multi scale measures. Measures may be entirely health related or may include a broader range of life quality issues. Definitive work has not been done in the alcoholism area to systematically define the relevant life function areas that are affected by the disorder and which may be expected to change as a result of treatment. There is by no means a “standard” instrument for this purpose suitable for use in clinical trials.

7.6.6.1 World Health Organization Quality of Life (WHOQOL) Assessment Instrument
The World Health Organization (WHO) has developed a measure of quality of life that has been used with a number of medical disorders in a number of countries (Anderson, et al., 1996; Szabo, 1996). This self-report measure consists of 25 items that are rated on 5-point Likert scales. A number of functional domains are included in the assessment: physical, psychological, level of independence, social relationships, environment, and spirituality/religion/personal beliefs. A number of more specific areas are assessed within each of these domains. For each of these, the
individual is asked to provide information about relatively objective factors (e.g., assessments of his or her behaviors, states, and capacities) and more subjective evaluations of these factors (e.g., satisfaction with or concern about these behaviors, states, or capacities). The measure will be administered at baseline and at weeks 26 and 52.

7.6.6.2 Global Assessment of Functioning (GAF)
The DSM-IV diagnostic system (American Psychiatric Association, 1994) includes the provision for assessing the participant’s level of functioning on a continuum based on psychological, social, and occupational function. The Global Assessment of Functioning (GAF), a clinical rating of global functioning used in Axis V of DSM-IV, was adapted from previous indices that had been used in clinical and research settings (e.g., Endicot, Spitzer, Fleiss, & Cohen, 1976). It is assumed that this global rating ranges along a continuum from 1 to 100. Examples are provided to help anchor the scale at each 10-point increment. There are guidelines to assist clinicians and research personnel to make these ratings, helping to increase their reliability and inter-judge agreement (First, 1998).

7.7 Treatment Compliance and Process Measures

7.7.1 Treatment Compliance
Attendance records will be maintained by all investigators to register participant compliance with psychosocial treatments. A combination of returned medication and a self-report of medication compliance based on time-line follow-back procedures offers a satisfactory and inexpensive means of assessing compliance, with confirmatory drug plasma levels in the active drug conditions.

7.7.1.1 Pill Count Form
The Pill Count Form is completed at every MM visit in order to assess pill compliance. Whether or not the participant returned the blisterpack, pills prescribed, pills taken, and whether there was a change in dosing are documented on the form. In order to assess pill compliance, the form is checked against the medication blisterpack and the participant’s self-report is noted.

7.7.1.2 Medication Non-Compliance Checklist (MNC)
The Medication Non-Compliance Checklist documents whether the participant was medication compliant. If the participant is medication non-compliant, the primary reason(s) for non-compliance is documented. The form outlines responses in terms of whether non-compliance is intentional or unintentional. The checklist is completed at every MM session.

7.7.1.3 Reasons for Premature Treatment Termination
An effort must be made to have all participants prematurely terminating study participation, for whatever reason, undergo an end of treatment evaluation. In designing a multi-center study of the efficacy of combined pharmacotherapy, high rates of discontinuation from treatment or poor medication compliance would be of great concern. Treatment discontinuation can result from a variety of reasons, most often adverse events, poor treatment response, or lack of participant interest.

7.7.1.4 Working Alliance Inventory (WAI)
The Working Alliance Inventory (WAI) is a 36-item questionnaire that provides an assessment of the participant-therapist working relationship along three dimensions: therapeutic interpersonal bond between participant and therapist (Bond), participant and therapist agreement about the goals of therapy and the perceived helpfulness of the therapist in achieving these goals (Goals), and the extent
to which participant and therapist agree on the therapeutic tasks necessary to achieve these goals (Tasks) (Bordin, 1979; Horvath & Greenberg, 1989; Tracey & Kokotovic, 1989). The therapeutic alliance between the therapist and participant, as measured by the WAI, was found in Project MATCH to be predictive of treatment outcome (Connors, et al., 1997).

For the purposes of the present study the 12-item Bond subscale, which reflects the therapeutic interpersonal bond between participant and therapist, will be used. The Bond scale will be filled out by the participant after the third MM contact and the third session of CBI. The staggered administration of the Bond scale represents an attempt to keep clear, in the participant’s mind, which person (MM or CBI therapist) they are evaluating.

7.7.2 Processes of Change

7.7.2.1 Processes of Change Questionnaire (PCQ)

The transtheoretical model of behavior change posits that individuals differ in their readiness to change, and that each stage of readiness involves specific processes of change (DiClemente & Prochaska, 1998; Prochaska, DiClemente, & Norcross, 1992). Information about the stages of change will be derived from the URICA. The Processes of Change questionnaire will be used to assess the processes that participants employ as they go about the change process. The questionnaire, consisting of 65 items, assesses two broad dimensions of change process: experiential processes and behavioral processes. These two dimensions subsume 10 more specific processes (e.g., consciousness raising, self-reevaluation, and stimulus control). The PCQ will be administered at weeks 16 and 26.

7.8 Evaluation Of and Satisfaction With Treatment

Kazdin (1986) noted that the emphasis on outcome measures and symptom domains overlooks many other types of measures that may contribute information about the relative utility and value of alternative treatments. One type of measure to be included in a multidimensional assessment of treatment outcomes involves “participant reactions to treatment,” including indices such as attrition, untoward side effects, adherence to the prescribed regimen, attendance, and participant satisfaction with and acceptability of treatment (Kazdin, 1986). Such measures, although not reflecting the primary focus of treatment, may be important in differentiating among alternative treatments in a comparative study. Whether the outcomes of two opposing treatments are identical, or even if one is less effective than the other, the treatment of choice may be determined by the participant’s preference, with any potential loss in therapeutic effectiveness outweighed by the gain in other benefits (Kazdin & Wilson, 1978). Positive clinical outcomes are often predicated on compliance with treatment that, in turn, is dependent on participant satisfaction; as such, participant satisfaction may be a prerequisite to quality care. Consequently, participant satisfaction has come to be seen as a legitimate and desired outcome in itself, one of a number of desired end products of clinical care (Gaston & Sabourin, 1992) and as one of the core elements of many quality-assurance procedures (Pekarik & Wolff, 1996). The assessment of participant satisfaction provides valuable information about treatments that is only partly subsumed by an evaluation of treatment outcome (Lebow, 1982).

7.8.1 Evaluation of Treatment Questionnaire

The participant satisfaction questionnaire employed in COMBINE was adapted from that used in Project MATCH. It evaluates both global aspects of participant satisfaction and aspects that are more specific to the therapeutic interventions used in COMBINE. The global satisfaction items were modeled after the 8-item Client Satisfaction Questionnaire (Attkinson & Zwick, 1982). The
second section of the questionnaire includes 14 items that deal more specifically with aspects of the participants’ experience in COMBINE. The items ask about the perceived helpfulness of the therapist, the counseling, the medications, receiving feedback about alcohol and its consequences, monitoring alcohol use through breathalyzer tests, learning more about alcohol and its effects, sharing problems and feelings with someone, learning and practicing skills to help keep from drinking, the homework assignments given by the therapist, meetings with family members or significant others, encouragement to get involved with AA or other mutual-help groups, filling out forms and questionnaires, and talking to research staff. Each of these items was rated on a scale from 1 (extremely helpful) to 5 (extremely unhelpful).

Participant satisfaction ratings will be collected at the 16-week follow-up assessment that corresponds with the scheduled conclusion of therapy.

Table 7.2 provides an overview of the measures to be employed in the trial, their content domain, the method of administration (e.g., self-administered or conducted by research assistant), and the estimated time associated with their administration. Tables 7.3 and 7.4, respectfully, provide schedule of assessments and time estimates. Tables 7.2 – 7.4 are given in the Appendix to this protocol.
CHAPTER 8: Schedule of Data Collection

8.1 Introduction

The schedule of data collection for COMBINE has been designed to consider the temporal needs of measuring changes that may result from both behavioral and pharmacological interventions. These may be as different as the measurement of medication adverse effects, which necessarily must be gathered during treatment, or the measurement of helping alliance, which may not be fully gauged until after treatment. Measures that are required for determining the presence of inclusion and exclusion criteria must be obtained prior to randomization, but not too far ahead of that point, as participants’ circumstances are fluid. The timing of outcome measures requires consideration of the sequential manifestations of different outcome categories. Primary outcome measures will be obtained with some redundancy (Form 90 and TLFB) and case report forms will require careful delineation of dates being assessed, so that these sources will be synchronous. Change in alcohol use is an early phenomenon in treatment studies, whereas reduction in medical severity may take longer and improvement in quality of life may be best measured considerably longer after treatment has ended. Putative mediators of treatment may need to be measured both before and within treatment. Some measures require that data be gathered contemporaneously with treatment or in close proximity to an episode.

Where possible, the schedule of measure collections has been distributed so as to minimize the burden of data gathering from participants at any given time point. Hence, the decision to measure personality trait typology after rather than with the baseline assessment battery.

8.2 Data Collection Procedures

There are multiple potential sources of data: self-administration by the participant, the research assistant, the MM provider, the CBI therapist, the admitting physician or addiction psychiatrist, and the laboratory. Each measure is assigned its own designated respondent. These are indicated in Table 7.2.

Measures are scheduled in two time dimensions: by date or session, and by sequence within a given battery. The latter is important in order to preserve or optimize the psychometric properties of certain instruments. For example, the assessment of motivation can be different before vs. after an extensive review of drinking consequence items. Some measures must be completed only after a treatment session. Some measures are only obtained when indicated; this is the “for cause” condition in which Hepatitis C is obtained when the AST is elevated. Others are usually obtained at a set time point, e.g. 16 weeks, but should be obtained sooner if the participant is dropping out of treatment.

When an assessment battery is particularly lengthy, as at baseline, specific instructions are given as to how it should be divided into multiple sessions. These instructions include the maximal number of days over which the battery can be divided.
8.3 Recruitment and eligibility determination

8.3.1 Recruitment
Participants will be recruited through three primary sources: (1) “In house” - from inpatient or outpatient programs at the clinical research unit; (2) External sources - from inpatient or outpatient programs from other clinical sites; and (3) Media sources - from newspaper, television, radio or pamphlet/flyer mechanisms. Regardless of the recruitment source all participants will undergo a two-tier approach to ascertain eligibility and willingness to participate in the main trial: (1) A quick screen; and (2) An eligibility assessment and determination.

8.3.1.1 Tier 1 - Quick Screen
A 10 to 15 minute Quick Screen will be administered to each potential participant regardless of the source of recruitment. This screen is designed to inform participants about the trial, to gather very basic information for provisional eligibility to the study, and to ascertain the nature of the population from which the participants were drawn. Those identified as provisionally eligible and willing to participate in the study will be scheduled for a more thorough assessment interview, including a meeting with the Project Coordinator (see below).

Regardless of the recruitment source, each potential participant will be given the Quick Screen interview in-person or over the telephone. Procedures for randomly screening individuals should be used if participant enrollment exceeds desired goals. The Quick Screen will identify participants who are ineligible to participate based on the study exclusion criteria. It is important that all responses be recorded for respondents who are willing to be screened, even for those who are unlikely to meet inclusion criteria for the study. These data will be used to describe the population of individuals from which the study sample has been drawn. Each individual, whether provisionally eligible or not, should be assigned a participant identification number at this time.

8.3.1.2 Tier 2 - Eligibility Assessment and Determination
If participants are willing and provisionally eligible to participate, they will be scheduled for a two-day comprehensive assessment and medical evaluation for final determination of eligibility and to gather pretreatment baseline information. Day one will consist primarily of a fuller description of the study protocol, expectations of participant involvement, informed consent procedures, a breathalyzer and a clinical interview to rule out psychiatric disorders. Day two will consist primarily of a physical examination, review of laboratory tests and medical history and an ECG if clinically indicated. The eligibility criteria are discussed in Chapter 3. The checklist contains each of the current 24 eligibility criteria with appropriate references to the measures or portions of the assessment and medical evaluation from which this information is drawn. Changes are expected to the inclusion/exclusion criteria as the pilot studies inform the nature of the main study protocol.

The Project Coordinator will be responsible for compiling participant information from the screening, pretreatment assessment and medical evaluation sessions. The Project Coordinator will be able to easily identify some respondents who meet the inclusion or exclusion criteria on the basis of the Quick Screen, Pretreatment Assessment and Medical Evaluation, but some may prove more difficult to identify. With difficult cases, the Project Coordinator will make the final inclusion decision after consulting with site and Coordinating Center investigators.
8.4 Baseline data collection

Based on the Screening Visit evaluation and availability of laboratory results, all potential candidates who fulfill entrance criteria must return to the site at Visit 0 within a time frame adequate to complete study assessments and with no less than 4 consecutive days of abstinence but no more than 21 days of abstinence.

The Baseline Assessment Battery should be divided into at least two consecutive days, and up to three days, when needed, for the participant’s comfort or convenience. It must be completed, however, within 7 calendar days, in order to be valid. This will permit administration over a weekend, and even a long holiday weekend, e.g. Wednesday, Thursday and Tuesday.

8.5 Follow-up Visits

Following baseline assessment, follow-up visits will be conducted by a trained research interviewer at 8 to 16 week intervals during the first year of participant participation.

Each interview is intended to take place at the setting in which the participant received treatment. The interview will be face to face. In the event that the participant is unwilling or unable to meet with the interviewer at the treatment setting, the interview may be conducted over the phone, or as a last resort at the participant's residence or another location mutually convenient.

Interviews conducted at the treatment setting will commence with an update of information obtained for the purpose of locating the participant. Then the participant's physical status will be reviewed, including a laboratory visit to provide samples for biochemical assays. When this information has been collected, the interviewer will proceed with administration of the Form 90, followed by the IP. Following the collection of all information requiring interview administration, the participant will then be asked to complete self-report questionnaires. (See Table 7.2 for a listing of the laboratory tests, interview measures and self report questionnaires that will be administered at each of the follow up visits). When these have been completed, the participant will be thanked for their participation, paid, and their next visit will be scheduled.

If a symptom on the SAFTEE is rated severe, the investigator should consider whether this constitutes a Serious Adverse Event. If so, a Serious Adverse Event form should be completed and submitted to both the Coordinating Center, and Lipha within 24 hours (fax to CC at 919-962-3265; telephone Lipha at 1-800-547-4299)

For participants for whom the interview is conducted over the phone or outside of the treatment facility, measures requiring face to face contact and a laboratory will be rescheduled for a subsequent date. Payment for participation will occur after the participant has provided the complete data set for that time period.

8.6 Monitoring Data Quality

The quality assurance protocol distinguishes between data collected in semi-structured interviews, self-report questionnaires, and computer-assisted assessment. Further, some assessment domains (e.g., motivation for change) are more sensitive than others to assessment reactivity (as opposed to order effects), and, as such, domains sensitive to the effects of assessment will be placed early in the baseline and follow-up assessment batteries.
There will be six components in monitoring data collected through semi-structured interviews: (1) initial interviewer training to criterion, (2) monitoring interviewer performance using coding and video tape exercises as well as pilot participants, (3) audio taping actual of participant interviews and reviewing these for assessment drift, (4) evaluation of completed assessment instruments for errors in recording, scoring/coding, and missing values, (5) monitoring data entry for key punch error, and (6) consistency in responses across assessments.

Monitoring data quality of self-administered questionnaires will require fewer resources, but is equally important to the success of the trial. Order effects associated with large self-administered assessment packets are a major concern. To offset this potential bias, the sequence of self-administered questionnaires within each of the assessment modules will be rotated (order of modules, however, will be held constant). A second concern is participant reading level, and participant ability to understand item content of self-administered questionnaires. To address these concerns, the Slosson reading test will be administered when reading ability is questionable, to indicate when a client needs to have assistance with a measure. Research assistants will be available to answer questions regarding questionnaire instructions and item content. A third concern involves gathering complete data for each questionnaire. To this end, research assistants will review completed questionnaires for missing item responses before the participant has left the clinic. Non-response to items will be identified and reviewed with the participant to ascertain whether the non-response was accidental or intentional.

Monitoring of data quality generated by computer-assisted assessment involves supervision of the validity of participant responses and maintenance of an appropriate data file backup system. It is our experience that computer assisted assessment offers many advantages, and that it can be a useful procedure under controlled circumstances. Validity of participant response will be monitored by first ensuring that users are familiar and comfortable with the task demands of the assessment. If required, research assistants will instruct participants in the use of window-based software. Second, all participants will have the intent of the assessment explained briefly beforehand. One potential disadvantage of computer-assisted assessment is that participants learn quickly that positive responses often lead to additional branching questions. While this is also the case with semi-structured interviews, there is less restraint upon a participant in computer assisted assessment to blindly respond “no” to all questions in order to complete an assessment rapidly. Therefore, participant responses on these assessments early in the trial will be examined to determine whether participants are fully engaged in the assessment tasks.
CHAPTER 9: Adherence, Retention and Drop-out Recovery

9.1 Introduction

Problems and solutions for problems in adherence, retention and drop-out recovery are linked to the three distinct phases of Study 3: a) recruitment (up to randomization); b) medication and psychosocial treatment; and c) post-treatment assessment and follow-up interviews. However, some general principles and guidelines apply to each. This section addresses a and c only, that is before and after treatment. See Chapters 5 and 6 for issues related to b.

Compliance and retention in the study begin with the very first contact with a potential participant. Second, every step of the process must be understood by the participant to ensure commitment by the participant for the entire project. Third, the shifting phases of the study may not be discernible to the participant, yet compliance and retention is a scientific goal across all the phases, with no one phase less or more important. A corollary point is that participants often do not distinguish between different phases of the trial and the personnel in those phases. For example, although the difference between a therapist and a research assistant is clear to us, such distinctions may not be obvious to the participant. Fourth, since the study staff has an understanding of the entire project, the compliance contract between the staff and the participant is more the responsibility of the staff. Fifth, noncompliance is assumed to result from a variety of sources including individual, interactional and contextual sources (Zweben, Project MATCH Monograph Series). An understanding of the sources can decrease noncompliance. Sixth, experience has demonstrated that the majority of participants pose few problems. Those few participants who present problems require a standardized approach to adherence and retention. However, the standardization must allow flexibility in accordance with the fifth point (above). Seventh, although retention in one phase influences retention in another, drop-out from one phase does not always assume drop-out from the other. Participants can be lost, resistant or refusing additional contact. Each type of participant requires standardized decision rules for management. Finally, contact must be maximized across the entire project in order to ensure the scientific and practical use of the data.

In general compliance and retention in the trial is dependent on a contract between the provider and the participant with a greater burden on the study staff especially prior to randomization. Study retention is essential to the internal validity of the study. Since the general principles of adherence, retention and drop-out recovery for the active treatment phase of the project are covered in the treatment manuals, the following sections apply only to the window of time between initial contact with potential participants through initiation of treatment, and then post-treatment assessment and follow-up.

9.2 Approaches to Adherence and Retention

Previous experience has led to a set of some practical strategies that enhance the likelihood that a person will become a participant in a research project and continue in that project until completion. Carty, Rice and Barrett (1998) have listed these and we have very briefly summarized them below. Some are more specific to recruitment than to adherence, but adherence in a study begins at first contact. Every effort to use these practical guidelines across sites must be made.

Proper site selection includes making sure that the site can generate enough eligible participants. Sites that are in transition or unstable are not good candidates. Sites with professional staff of high quality and strong community reputations are desirable. Sites should have easy access for
both participants and staff, yet be secure and safe. Sites where confidentiality issues are not respected will prove undesirable. Sites with comfortable facilities, access to laboratory facilities, in-house child care, ease with English and a warm environment are desirable. Site selection is of primary concern.

Ensuring quality interactions between study staff and site staff is very important. Initial contact with treatment sites should be made by the Principal Investigator. Project Directors need to be available and visible on site as much as possible, and should participate in site staff meetings wherever possible. While study staff are distinct from site staff, positive colleague interactions will facilitate referral to the project, as well as ongoing site support for adherence and retention.

Staff selection and training is very important. Study staff should be socially and professionally skilled so as to increase the folding in of study procedures to existing staffing procedures. Roles for each staff should be clearly defined. Project Directors should be skilled managers capable of providing scientific and clinical supervision.

A tracking system is necessary. Prior to randomization, the tracking system must obtain sufficient information to describe screening failures and assist with identification of participant characteristics that will describe the sample for an evaluation of generalizability. Following treatment, the tracking system needs to be complete enough to ensure participant contact throughout the follow-up period regardless of treatment compliance. Tracking systems should be electronic and can be as simple as spreadsheets.

Possible participants must be educated in a fashion that informs them in a manner that increases willingness to participate. The benefits of participant participation should be highlighted.

Incentives for study participation and retention should be clear at the outset, and must be comparable across sites in order to minimize site differences.

Our participants are the most significant people in the study, without whom there would be no data. Communicating the value of the participant is important in increasing compliance and retention.

Participants can be inadvertently non-compliant with assessment procedures. Alerting participants to these issues can increase adherence and retention.

With all of this in mind, then, some practical tips for what to do when our best efforts still result in non-adherence to the protocol include the following. First of all, define the type of non-adherence, and proceed as described:

Lost Participants: The first step is to locate the participant. Methods of location include contacting locators and collateral informants through the information obtained at baseline. Use of institutional information is appropriate. Department of Motor Vehicles records and internet search engines may be useful.

Resistant Participants: The first step is to engage the participant in a discussion about the problems, with the participant looking for possible solutions.

Refusing Participants: Before accepting the refusal at face value, it is recommended to first try to address the participant's problems with the study so that they may reconsider and continue. This approach is considered prudent in view of the diverse reasons for which a participant may
consciously drop out of the study.

More generally, research assistants and assessment personnel might identify and remove barriers to assessment completion such as:

- Making free parking passes available.
- Reimbursement for cab or bus fare.
- Providing local bus schedules and telephone numbers for taxi service.
- Making home visits an option. (For personal safety reasons, two research assistants should go on home visits.)
- Arranged pre-scheduled child care during assessments.
- Reimbursements for baby-sitting.
- Making early morning and evening appointments available.
- Have weekend appointment slots available.
- Be willing to schedule assessments on holidays.
- Have waiting areas for family that accompany participants.
- Provide cultural sensitivity training to all staff.

The point of all techniques listed here is to keep participants engaged in the study while deviating minimally or not at all from the study protocol. However, there will be those participants who for any number of reasons take measures that will deviate to some degree from study protocol to keep them in the study. A reasonable rule of thumb is that some data are better than no data but this must be balanced by good scientific judgment against the importance of protocol violations (data that should be preferentially collected are those that will be used in calculating primary and secondary study endpoints). Barrett & Morse (1998) list seven adaptive strategies that can be carried out to obtain data from these exceptional cases. They recommend that these be carried out incrementally because each represents a greater deviation from protocol. These steps are:

- offer (increased) financial incentives
- remove aversive elements
- obtain partial data
- delay decision making
- defer decision making to a higher authority
- accept “no” as temporary and situation specific
- when all else fails accept the situation gracefully

General regular contact tips include keeping careful tabs on telephone and mailing procedures:

For the telephone, the RA should document when phone calls were made and the results of the phone calls. If an answering machine is reached, it is a good idea for the RA to attempt another phone call in order to speak to a person. If someone other than the participant answers, request the person’s name and the relationship to the participant, and record the information. This information enables the RA to know what has been done and to determine the feasibility of leaving another message with the same person. It also helps to determine times that may be inconvenient for the participant or may indicate a change in the participant’s schedule. Phone contact will be used to contact participants who fail to appear for study visits.

For the mails, letters can be sent out prior to each study visit as a reminder. Brief letters can be sent out at regular intervals during follow-up to maintain contact with the participant between study visits. Letters should have an easily identifiable logo matching the logo on the business
card. They may also provide study information that may be of interest to the participants and reinforce a sense of belonging with the study. Any mailed information should be designed with care to exclude information that would compromise the participant's confidentiality. When participants fail to show up for their second study visit and phone contact is not possible, registered mail can be used to assist with reaching the participant.

Any mail should include a return address, along with the letters ACRDNF (Address Correction Required, Do Not Forward). This alerts the post office to return the unopened mail with a new address listed if one is available. The post office will forward first class mail for 12 to 18 months provided an address has been given. They will notify the sender of a new address for 1 year. They will forward second class mail for 60 days. If there is no forwarding address available, it will be noted as Moved No Forwarding Address.

One week before follow-up visits, participants will be notified by letter. They will be contacted by phone the day before follow-up. Participants who do not show up for follow-up will receive a phone call that night to determine when the participant can come in for assessment. Locator persons will be contacted in the event that the participant cannot be reached by phone. If the locator person cannot determine the whereabouts of the participant, a registered letter will be mailed to the most recent address of the participant.

9.3 Maintaining Boundaries between the Data Collection and Treatment Arms

Those who collect data for treatment outcome studies need to be trained in the distinction between the treatment and data collection phases of the trial, and be given the skills and resources to understand where these boundaries lay. Research assistants who cross the line into therapeutic relationships with participants not only risk contaminating the data but are not providing good clinical care. A formal training session with “booster” training over the course of the trial is helpful for maintaining these boundaries. Research assistants should be given support in responding humanly and compassionately to participant distress. However, where the participant begins asking for personal advice, detailing situations where advice is needed, or especially showing signs of acute distress, research assistants should gently take this situation to the supervisor or to the project coordinator to be dealt with.

As will be elaborated on in the next section participants should never be regarded as dropping out of the data collection phase of the trial. In treatment outcome research the distinction between the treatment phases and the data collection phases may not be clear to the participant, and there are times when the research assistant may himself or herself feel hard pressed to not cross into therapy. Of course, a human connection between the research assistant and the participant is natural and is to be fostered, but there must be a line between this state and that of providing therapy. Data collection during the course of active therapy allows for an easier division of responsibility between therapy and data collection staff, and serious issues that arise with participants can be easily referred to the trial therapist. This may have to occur at the time of the research interview. After active treatment is over, the situation may become more difficult as the participant has established a rapport with the research staff and the several hours long interaction provides ample time and opportunity to raise personal issues. Furthermore, because active treatment is over the participant may regard data collection as aftercare. It is important for the research assistant to understand the difference between compassion and a human reaction to pain, but to also make the appropriate referral to a trained professional and to note that referral. This is best done by each research assistant going to their supervisor or the project coordinator with the situation and letting the these people deal with the situation.
9.4 Drop-out Recovery

A randomized participant should not be regarded as ever out of the study. Research Assistants need to be trained that regardless of what occurs in the treatment sessions, they must collect the research data. The importance of the separation between the phases is really embodied in the fact that there is different staff to perform these two vital functions. Although a participant may leave treatment, the research assistant must understand and convey to the participant that data collection follow-up sessions will continue throughout the course of the trial. It is, of course, a participant’s choice to terminate all association with the study and that final choice must be respected. However, in most circumstances it is unwise to take the first expression of a participant’s wish to drop out as the final choice. It is also a good idea to attempt to explore the reasons why a participant expresses a desire to drop out. With each contact between the research staff and the participant, information contained in the tracking system should be verified, including address, day and evening telephone numbers, name under which the telephone numbers are listed, time of day the participant is available for contact, and appointments and locators. It is also beneficial to elicit the participant's level of enthusiasm for continuing the study so that decreases in enthusiasm can be addressed.

When a participant sounds as though drop-out is a possibility, every effort to collect as much useful information as possible should be made. Adhere to the idea that some data are better than no data. As mentioned above, the data that should be preferentially collected are those data that are necessary to calculate the primary and secondary endpoints of the study (see chapter 13). However, take advantage of ambivalence on the participant’s part to encourage staying in the study.

Specific windows for contact are delineated in the assessment description; note that some are calibrated to increase retention and diminish drop-out.

The merit of this scientific endeavor rests on collection of the most complete and accurate data possible. Every effort to increase adherence and retention, even to the degree of recovering drop-outs, is a necessity.
CHAPTER 10: Participant Safety

10.1 Introduction

The psychosocial intervention will consist of individual cognitive-behavioral therapy for all participants. The active treatment phase will last sixteen weeks with follow-up for fifty-two weeks post-treatment. The pharmacological intervention will consist of acamprosate and naltrexone, both alone and in combination. The active treatment phase will co-occur with the psychosocial intervention. The experimental treatments for the COMBINE study are not expected to pose any particular risk. Each participating investigator has primary responsibility for the individual participants under his/her care.

10.2 Protocol Review and Study Monitoring

An independent Data and Safety Monitoring Board (DSMB) was appointed by NIAAA and charged with monitoring the progress of the study. The DSMB will review and approve the protocol prior to study initiation. During the study the DSMB will meet periodically to review study progress. These reviews will include evaluation of interim data as well as the monitoring of participant safety and the quality of all aspects of study operations.

Prior to study initiation, the study protocol will be reviewed and approved by each center's Institutional Review Board (IRB).

After enrollment, each individual Principal Investigator will monitor safety issues at his/her site continuously and report any problems to the Coordinating Center, which will inform the NIAAA Project Officer.

10.3 Exclusions

Persons with medical or psychological contraindications to the experimental treatment will not be eligible to be enrolled. Exclusions are detailed in Chapter 3.

10.4 Informed Consent

Informed consent will be obtained from each participant before he or she is enrolled in the study. The consent form will describe the potential risks and benefits of study participation as well as the responsibilities of the participants and the investigators.

10.5 Management of Treatment Failures

See Chapter 5 and Chapter 6 for procedures specific to each intervention.

10.6 Adverse Event Reporting and Discontinuation of Study Treatment

As treatment progresses and at all follow-up visits, possible adverse effects of the experimental treatment will be assessed. If participant assessment indicates an adverse reaction, the study investigator may, at his/her discretion and according to the psychosocial intervention design described in Chapter 5, refer the participant for additional medical follow-up, additional individual therapy sessions, and/or assessment for psychopharmacological intervention. Depending on the situation, the change may be temporary or continue throughout the study term. In rare cases the experimental treatment may need to be discontinued, however the participant would continue to be
followed. A Clinical Care Committee will be appointed to advise the study investigators in possible procedures following an adverse experience. A protocol for this committee is included as Appendix C.

10.7 Protection of Participant Privacy

Privacy in the context of this study includes confidentiality of data and personal information at the Clinical Center and in the handling and reporting of data by the Coordinating Center. It also includes discretion on the part of the clinical center staff and arrangements for physical privacy during interviews and examinations. Each Clinical Center will be responsible for ensuring physical privacy of participants and ensuring that data are stored in a secured area accessible only to COMBINE staff. These provisions will be monitored during periodic site visits from the Coordinating Center.

In addition to the above protection of privacy, a certificate of confidentiality will be held at each participating site. This will protect against involuntary disclosure of the identities of research participants.

10.8 Data Security and Confidentiality

The original paper data collection forms will be retained at the clinical centers. They should be stored using the confidentiality procedures provided for other medical records at the institution.

All data transferred to the Coordinating Center will be stored, processed, and analyzed within the Coordinating Center office suite. At the Coordinating Center, all access to office space containing data is controlled through manned reception areas. Visitors are screened by the receptionists and cannot move about without an escort. All office space is locked after working hours. Access to computer data files is controlled by passwords released only to those Coordinating Center personnel who use the files. In addition, critical data files are encrypted.

A backup of the database will be made daily to a second disk drive on the Coordinating Center local area network. Automatic magnetic tape backups of the database also will be made daily. Once a month, the current backup tape will be removed from the cycle and permanently archived at the Coordinating Center's off-site data storage facility.

Output mailed to clinical center staff will identify participants only by ID number. No individually identifiable information will be distributed to clinical centers. When printed material containing confidential information is to be discarded, it is loaded, transported, and stored under supervision (using a chain of custody control process) until the material can be recycled into paper pulp.

All Coordinating Center staff are required to complete a confidentiality certification procedure upon employment. Policies regarding the confidential nature of the data collected, processed, and stored at the Coordinating Center, are explained to all personnel, who must then sign a "confidentiality certification," before being allowed access to confidential information. In addition to this initial training, the Coordinating Center reinforces the need for careful and confidential handling of data at staff meetings.
CHAPTER 11: Close-out Procedures

11.1 Objectives

The COMBINE trial may terminate on schedule or at an earlier date if circumstances warrant. Regardless of the circumstances, the objectives of study close-out are:

♦ To complete data collection and processing quickly, while maximizing data quality and completeness.
♦ To fulfill our ethical obligations to trial participants.
♦ To ensure the maximum possible analysis and dissemination of the information from the trial.

11.2 Endpoint Ascertainment

The co-primary endpoints of the trial are percent days abstinent, and time to relapse of heavy drinking. On a routine basis, these endpoints will be ascertained by participant interview at scheduled follow-up visits, from follow-up contacts for missed visits, or by participant (or confidante) telephone report between visits. As the trial progresses, some participants will be lost to follow-up. Thus at any point during follow-up, several months will have elapsed since most participants were last screened for potential endpoints. As the end of each participants individual follow-up period approaches, it is essential to make special efforts to collect information to document endpoints through the 68th week of follow-up on all participants. Absolute verification of final drinking status for all participants is critical for the validity of the statistical analysis of the co-primary endpoints (see Chapter 13).

11.3 Data Clean-up and Closure

The routine data processing and data closure activities described in Chapter 12 will also be accelerated as the end of follow-up approaches. Data closure checks will be generated more frequently, with tighter windows between scheduled collection and query for missing forms. In extreme cases, coordinating center staff may need to schedule site visits of clinical centers to help address significant data management backlogs or volumes of outstanding data closure problems.

11.4 Unmask the Investigators to the Study Results

As the end of follow-up approaches, a small writing committee will be formed to draft the primary results manuscript, before follow-up is complete. This would include the Chair of the Steering Committee, the Principal Investigator of the Coordinating Center, the Project Officer, and a small number of other Investigators. Of necessity, this group is unblinded to the preliminary trial results several months prior to the meeting at which the results will be presented to the Steering Committee. Once data collection is complete, a closed Steering Committee meeting will be held to present the results to the Investigators and to provide them with an opportunity to review the draft manuscript and provide comments to shape the revision for final submission.

11.5 Complete the Primary Results Manuscript

As soon as those components of the database necessary for the primary manuscript have been closed, the statistical analyses will be re-run on the finalized database, and the manuscript submitted to the journal for publication.
11.6 **Inform Participants of the Study Results**

Each participant will be informed of the major results of the study, and counseled concerning the implications of the trial for their future care. Participants will be encouraged to schedule an appointment with their primary care physicians to discuss their post-trial management.

11.7 **Close-out Clinical Center Activities**

The coordinating center will work with each clinical center to finalize all data transfer and clean-up. Clinical centers will arrange for archival storage of participant data and other study materials in line with their institutional requirements for retention of research data.
CHAPTER 12: Data Management

12.1 Introduction

This study will involve a variety of data sources, including review of laboratory reports and/or medical records, participant interviews by case managers and therapists, and self-administered questionnaires. The data management system must be flexible enough to mesh with the variety of institutional facilities, and operational procedures likely to be in use at the participating centers, while still providing the necessary standardization and quality assurance in data collection and processing.

12.2 Data Collection

The data collection methodologies used in COMBINE are:

♦ Recording data by clinic staff on paper forms.
♦ Participant self-completion of paper forms.
♦ Recording of data on electronic forms by clinic staff by keying on PCs / laptops during interviews.
♦ Participant self-completion of electronic forms by keying on PCs.

12.3 Data Entry

For data collected directly onto electronic forms, there is no separate data entry process; the electronic record is the primary data collection document. However, for data collected by manually printing on paper forms key entry will be required. Keying will be done remotely, at the Clinical Centers using software provided by the Coordinating Center. The data entry system will display data entry screens that closely resemble the paper data collection forms. The system will be menu driven, with context-sensitive help available at any time. Each data value will be validated (edited) during entry, as described below.

In our experience, complete double entry is not necessary in distributed systems, provided that the data is keyed by protocol-knowledgeable individuals (e.g., data collectors or study coordinators). Entry by such staff provides a level of human review during entry that reduces errors to an acceptable level (Neaton 1990, Mullooly 1990). Instead, we recommend a data entry quality control system, with a sample of forms re-keyed at the Coordinating Center to monitor and control data entry error rates at the Clinical Centers. However, should data entry by done centrally at the Coordinating Center, or should the Clinical Centers opt to have data entered by clerical data entry staff, complete re-key verification will probably be required (Blumenstein 1993, Reynolds-Haertle 1992).

12.4 Data Transfer

With the distributed entry model, data is transferred from the Clinical Centers to the Coordinating Center by modem or via the internet using a commercially available communications program. Frequency of data transfer could be weekly, or twice a month. An alternative method of transfer supported by the software would be to mail diskettes to the Coordinating Center. Given the relatively large volume of data per center and the need for timely reports on participant screening and recruitment, we would suggest weekly electronic transfer.
An additional type of data transfer that will be needed is the shipment of samples (e.g., urine or blood plasma samples for assay) to the central lab and the transfer of results from those agencies to the Coordinating Center. Specific procedures for labeling, packing, and shipping samples are part of the central laboratory manual of operations. These procedures were pilot tested in each Clinical Center before the initiation of the trial protocol.

The central laboratory data management system will provide for inventorying samples as they are collected, and generate packaging lists for inclusion in each shipment (as an electronic file or on paper if the laboratory/reading center prefers). This information will be transferred to the Coordinating Center along with other study data, allowing the completeness and timeliness of sample collection, and shipping to be monitored. Procedures have been developed for transfer of data from central agencies to the Coordinating Center.

12.5 **Data Validation**

Each data field will be edited during entry. The data management system will flag each data value with a "status character" documenting the current validation status of the item (empty, skipped, questionable, clean, confirmed, etc.).

With electronic collection or distributed entry, values that fail a validation routine will cause a message to be displayed. The person entering data will then have 3 options:

- To correct the value, in which case the new value will be validated as was the previous entry.
- To flag the value as questionable, in which case the system will generate a printed form to document the question, and for use in recording a resolution.
- To confirm the value as known to be correct, overriding the validation routine.

12.6 **Database Closure**

Before each major analysis, the database will go through a series of closure checks to insure the completeness and correctness of data collection and processing. These checks will be performed on a "frozen" version of the database defined by a specific time cut point. The classes of checks done at closure include:

- Determining the status (excluded, ongoing, completed, withdrawn, etc.) of each participant entered.
- Assuring all expected forms have been received.
- Assuring all received forms have been processed.
- Assuring all queries generated have been resolved.

12.7 **Data Retrieval and Statistical Computing**

Data will be retrieved from the study database and converted into SAS files on a monthly schedule tied to the production of the study status report and data closure checks. Additional retrievals will be done as needed for the production of other reports. These retrieval files will be stored as SAS datasets within a SAS data library. The SAS database created for each report will be permanently archived on magnetic tape cartridge or CD-ROM.

All statistical computing will be done using the SAS system, BMDP, or other validated statistical software. All computing will be documented using the Coordinating Center's statistical computing request system. This system requires the responsible Coordinating Center statistician
to produce a written specification of each analysis to be done. The specification, the resulting
analysis program, and the output produced are all catalogued and archived (in both paper and
electronic format) to provide complete documentation of each computing task. All computing
requests whose output is distributed outside the Coordinating Center (e.g., to the study
investigators or Project Officer) are independently reviewed by a second programmer for
accuracy.

12.8 Data Security and Confidentiality

The original paper data collection forms will be retained at the Clinical Centers. They should be
stored using the same confidentiality procedures provided for other medical records at the
institution.

In the distributed data management system being used, each user of the data management
systems at the Clinical Centers will need an individual user ID and password to access the local
database. Individually identifying fields within the database will be encrypted, and decrypted
only for display on-screen. Only electronic records of study data will be transferred to the
Coordinating Center as described above. These transfer files will be encrypted when created by
the Clinical Center data management system.

All data transferred to the Coordinating Center will be stored, processed, and analyzed within the
Coordinating Center office suite. At the Coordinating Center, all access to office space
containing data is controlled through manned reception areas. Visitors are screened by the
receptionists and cannot move about without a Coordinating Center escort. All office space is
locked after working hours. Access to computer data files is controlled by passwords released
only to those Coordinating Center personnel who use the files. In addition, critical data files are
encrypted.

A backup of the database will be made daily to a second disk drive on the Coordinating Center
local area network. Automated magnetic tape backups of the database will also be made daily.
Once a month, the current backup tape will be removed from the cycle and permanently archived
at the Coordinating Center's off-site data storage facility.

Output mailed to Clinical Center staff will identify participants only by ID number. No
individually identifiable information will be distributed to Clinical Centers. When printed
material containing confidential information is to be discarded, it is loaded, transported, and
stored under supervision (using a chain of custody control process) until the material can be
recycled into paper pulp.

All Coordinating Center staff are required to complete the Coordinating Center's confidentiality
certification procedure upon employment. Policies regarding the confidential nature of the data
collected, processed, and stored at the Coordinating Center, are explained to all personnel, who
must then sign a "confidentiality certification," before being allowed access to confidential
information. In addition to this initial training, the Coordinating Center reinforces the need for
careful and confidential handling of data at staff meetings. A Certificate of Confidentiality will
be applied for from the appropriate NIH agency to further protect participant information housed
at the Coordinating Center.
CHAPTER 13: Statistical Analysis

13.1 Overview of Study Design

COMBINE is a multi-center, randomized clinical trial, evaluating three interventions and their combinations for the treatment of alcohol dependence. The two pharmacological treatments (naltrexone and acamprosate) will be delivered in a double-blind, double-dummy fashion. 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. Assignment to levels of this factor is unblinded, but outcome assessment will be blinded. 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.

![Figure 1. COMBINE Treatment Combinations](image)

<table>
<thead>
<tr>
<th>Medical Management</th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Management + Psychotherapy</th>
<th>Placebo</th>
<th>Acamprosate</th>
<th>No Pills</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>No Pills</td>
<td></td>
<td></td>
<td>9</td>
</tr>
</tbody>
</table>

Eleven clinical centers will recruit and randomize a total of 1,375 participants over 30 months. Randomized participants will receive sixteen weeks of therapy, with subsequent long-term follow-up assessments. All participants will be followed for a total of 68 weeks (1 year post treatment). All participants will have follow-up assessments at weeks 8, 16, 26, 52, and 68.

13.2 Primary Outcome Measures

The efficacy of the therapies will be evaluated with two co-primary outcome measures: percent days abstinent and time to relapse to heavy drinking.

13.2.1 Percent days abstinent

Percent days abstinent (PDA) will be evaluated using a revised version of the Form 90-A interview developed by Project MATCH, the Form 90-AIR/ED, described in Section 7.6.1.

13.2.2 Time to relapse to heavy drinking

Drinks consumed per day will be evaluated using Form 90-AIR/ED. Heavy drinking will be defined as consumption of 5 or more drinks per day for males and 4 or more for females.
13.3 **Primary Hypotheses**

The primary hypotheses will be the traditional main-effect and interaction ANOVA contrasts, based on the eight cells in the 2x2x2 factorial design. These are presented below, in terms of the numbering of treatment combinations (cells) presented in Figure 1. For simplicity, the definitions below ignore the repeated time measurements and covariate adjustments.

**Figure 2. COMBINE Design in 2 x 2 x 2 factorial layout**

<table>
<thead>
<tr>
<th>Medication Management</th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medication Management + Psychotherapy</th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

The full 2 x 2 x 2 factorial model with all interactions can be defined as:

\[ \mu_{anp} = \mu + \alpha_a + \nu_n + \psi_p + \alpha \nu an + \alpha \psi ap + \nu \psi np + \alpha \nu \psi anp \]

where:
- \( \alpha_a \): main effects of acamprosate, placebo
- \( \nu_n \): main effects of naltrexone, placebo
- \( \psi_p \): main effects of psychotherapy + MM, MM

The interaction effects are identified by the pairwise and three-way combinations of the same symbols and subscripts.

Primary hypotheses 1-3 are the main effects of acamprosate, naltrexone, and psychotherapy. For example the main effect of acamprosate is evaluated by testing:

**Ho:** \( \alpha_a = 0 \)

In terms of the cell means above, we can express the hypothesis as:

**Ho:** \( (2 + 4 + 6 + 8) / 4 = (1 + 3 + 5 + 7) / 4 \)

This tests whether, averaged over the two other factors, there is a mean difference between acamprosate and placebo.

Primary hypothesis 2, the main effect of naltrexone, and primary hypothesis 3, the main effect of psychotherapy, have analogous definitions.
Primary hypothesis 4 is the 2-way acamprosate by psychotherapy interaction:

\[ H_0: \alpha\psi_{ap} = 0 \]

In terms of the cell means above:

\[ H_0: (1 + 3 + 6 + 8) / 4 = (2 + 4 + 5 + 7) / 4 \]

This tests whether the effect of adding psychotherapy to MM is the same when combined with acamprosate as when combined with placebo (both averaged over naltrexone or placebo). Equivalently, it tests whether the effect of acamprosate is the same when combined with medication management as when combined with psychotherapy + MM (both averaged over naltrexone or placebo).

Primary hypothesis 5, the naltrexone by psychotherapy interaction, and primary hypothesis 6, the acamprosate by naltrexone interaction, have analogous definitions.

Primary hypothesis 7 evaluates the 3-way acamprosate by naltrexone by psychotherapy interaction:

\[ H_0: \alpha\nu\psi_{anp} = 0 \]

In terms of the cell means above, we can express the hypothesis as:

\[ H_0: (1 + 4 + 6 + 7) / 4 = (2 + 3 + 5 + 8) / 4 \]

13.4 Statistical Methods for Primary Analyses

The primary analyses will evaluate outcomes for the sixteen-week period following randomization. Analyses will be based on the principle of intention-to-treat.

13.4.1 Percent days abstinent

Percent days abstinent will be computed monthly. A mixed-effect general linear model will be used to evaluate the primary hypotheses. The three treatments will be fixed effects. Standard ANOVA main effects and interactions will be fit, as defined above. The main effect of clinical center will be included as a fixed effect. Time (month since randomization) will be treated as a random effect. A baseline measure of PDA will be computed using the 30 days prior to the participant’s last drink; this will be used as a covariate in the model.

13.4.2 Time to relapse to heavy drinking

Time to relapse to heavy drinking will be analyzed using proportional hazards models. Standard ANOVA main effect and interaction parameters will be fit, as defined above. The main effect of clinical center will be included. Participants who are lost to follow-up will be assumed to have relapsed to heavy drinking on the day after their last study contact.
13.4.3 Type I error control
The traditional ANOVA approach of family-wise error control will be used (testing each main effect and interaction at a .two-tailed 05 level). A Bonferroni correction will be used to adjust for the two co-primary endpoints. Thus each primary hypotheses will be evaluated at a two-tailed .025 level (.05/2).

13.5 Secondary Analyses for the Primary Outcome Paper

In addition to the primary analyses, two sets of secondary analyses are felt to be fundamental to interpreting the main outcome of the trial. These are described below

13.5.1 Secondary Analyses of Post-Treatment Outcomes
While treatment effects during the sixteen-week active treatment period have been selected as the primary measure of treatment efficacy, post-treatment outcomes are key secondary analyses that will also be reported in the primary results paper. The hypotheses and analysis methods will parallel those in sections 13.3 and 13.4, but the dependent measures will be based on the post-treatment assessments (months 4-36).

13.5.2 Secondary Analyses of Placebo Effects
The inclusion of cell 9 (CBI with no pills or medication management) allows an evaluation of the magnitude (and direction) of placebo effects on CBI. This comparison is of interest to psychotherapy practitioners with concerns about medication detracting from psychosocial treatment benefits (e.g., attributional negative placebo effects).

13.6 Other Preplanned Secondary Analyses

Understandably, the primary analyses cannot begin to test all of the important questions of the study. Proposed secondary analyses are therefore considered an important adjunct to the primary analyses, and this section offers a strategy for identifying and integrating the wide array of purposes of the secondary analyses. Temporally, secondary analyses may precede the primary analyses (e.g., psychometric analyses of baseline measures) or follow primary analyses (e.g., use of alternative outcome measures to confirm findings derived using primary outcome measures). Secondary analyses also may be used to inform the conduct of primary analyses (e.g., examination of site effects) as well as be intended as stand alone analyses leading to a publication.

13.6.1 Analyses of baseline data
Generally, analyses in this category will examine the psychometric properties of instruments. In addition, distributional characteristics of the primary dependent measures and potential site effects may be examined.

13.6.2 Process analyses
We anticipate a wide array of analyses in this category including but not limited to predictors of therapeutic and medication compliance, therapist effects, predictors of treatment engagement and use of extra-treatment resources, and exploration of treatment fidelity.

13.6.3 Secondary outcome analyses
There will be substantial interest in determining whether findings based on primary outcome measures are confirmed using other measures of participant functioning. Secondary outcome measures may be modifications of the primary measures (e.g., defining of heavy drinking using
different criteria, duration of abstinence) or may be distinct from the primary outcome measures.

For evaluating the impact of the interventions, quality of life is a particularly important secondary outcome. As described in Section 7.6.7, the WHO quality of life instrument and the DSM-IV-based global assessment of functioning will be used to evaluate both global quality of life and more specific functional domains.

13.6.4 Prognostic analyses

These analyses will examine the main effect of participant attributes on primary and secondary outcome measures controlling for treatment interventions.

13.6.5 Treatment-participant matching

Several proposals identified a priori participant-treatment matching hypotheses. In addition to profiling optimal treatment responders, this category will include site specific matching hypotheses.

13.6.6 Causal chain analyses

This wave of analyses will examine whether the proposed active ingredients of the interventions operated as hypothesized (e.g., is medication compliance negatively related with alcohol craving?). In addition, analyses in this category will examine the associations between participant post-treatment functioning and non-manipulated variables (e.g., mutual-help participation).

13.7 Study Power

Estimating the power of the study requires specifying both the size and the pattern of the departure of the mean vector from the null hypothesis. There are no published data to suggest the likely effect sizes of combinations of the study treatments. Therefore, we will estimate power based on relatively simple, uniform patterns of effects.

13.7.1 Percent days abstinent

Data from the outpatient arm of Project MATCH were used to estimate the variance / covariance matrix in percent days abstinent for months 1-6. To adjust for the planned use of baseline PDA as a covariate, the residual variance / covariance matrix was computed, adjusting for baseline PDA. The estimated residual correlation matrix is presented in figure 3, below. The pooled within-cell estimate of the standard deviation of PDA is 28%.

Figure 3. Correlation of PDA by month of follow-up, adjusted for baseline PDA

<table>
<thead>
<tr>
<th>Month</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>.8</td>
<td>.7</td>
<td>.6</td>
<td>.5</td>
<td>.4</td>
</tr>
<tr>
<td>2</td>
<td>.8</td>
<td>1.0</td>
<td>.8</td>
<td>.7</td>
<td>.6</td>
<td>.5</td>
</tr>
<tr>
<td>3</td>
<td>.7</td>
<td>.8</td>
<td>1.0</td>
<td>.8</td>
<td>.7</td>
<td>.6</td>
</tr>
<tr>
<td>4</td>
<td>.6</td>
<td>.7</td>
<td>.8</td>
<td>1.0</td>
<td>.8</td>
<td>.7</td>
</tr>
<tr>
<td>5</td>
<td>.5</td>
<td>.6</td>
<td>.7</td>
<td>.8</td>
<td>1.0</td>
<td>.8</td>
</tr>
<tr>
<td>6</td>
<td>.4</td>
<td>.6</td>
<td>.7</td>
<td>.8</td>
<td>1.0</td>
<td>.7</td>
</tr>
</tbody>
</table>

We will assume an average PDA in the control group (medication management, and both placebos) of 70%. This level is essentially arbitrary; the power calculations are only affected by the between group differences and are invariant to the overall average level. Assume 153 participants per cell (a total of 1,375 for 9 cells).
Case 1: two main effects, no interaction.

Based on published reports of the effect of monotherapy with acamprosate or naltrexone, we will assume a “true” treatment effect, in complying participants, of 10%. We will assume 25% of participants are treatment dropouts or have inadequate compliance, and that the treatment effect in this group is zero. Thus the observed efficacy, adjusted for non-compliance, will be 7.5%. This leads to a pattern of means like that shown in figure 4, which assumes main effects of each drug and no effect of psychotherapy.

Figure 4. Model with Two Main Effects

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>70</td>
<td>77.5</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>77.5</td>
<td>85</td>
</tr>
</tbody>
</table>

For this alternative, power to detect each main effect is .98. Since there is no interaction, “power” in this case is .025, the type I error rate.

Case 2: two main effects, two-way positive interaction.

Again, assume the observed main effects, adjusted for non-compliance, will be 7.5%. Assume an observed interactive effect half the size of the main effects (3.75). This leads to a pattern of means like that shown in figure 5, which assumes main effects of each drug and no effect of psychotherapy.

Figure 5. Model with Two Main Effects and Positive Interaction

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>70</td>
<td>77.5</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>77.5</td>
<td>88.75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>70</td>
<td>77.5</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>77.5</td>
<td>88.75</td>
</tr>
</tbody>
</table>

Again, power to detect each main effect is greater than .99. Power to detect the interaction is only .08.
Case 3: two main effects, two-way negative interaction.

Assume the observed main effects, adjusted for non-compliance, will be 7.5%. Assume an observed negative interactive effect half the size of the main effects (3.75), meaning the combined effect of the two drugs is less than the sum of the individual effects. This leads to a pattern of means like that shown in figure 6, which assumes main effects of each drug and no effect of psychotherapy.

Figure 6. Model with Two Main Effects

<table>
<thead>
<tr>
<th>Medical Management</th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>70</td>
<td>77.5</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>77.5</td>
<td>81.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Management + Psychotherapy</th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>70</td>
<td>77.5</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>77.5</td>
<td>81.25</td>
</tr>
</tbody>
</table>

Power to detect each main effect is .84. Power to detect the interaction is again only .08.

13.7.2 Time to relapse to heavy drinking

As before, we assume 153 participants per cell. In contrast to the linear models, power for the survival analyses is effected by the assumed event (relapse) rate in the placebo group, in addition to the size of the treatment effect. Based on published reports, we have assumed an average 12-month relapse rate of 70% in the cells receiving both medication placebos. The published survival data consistently show a hazard rate that is not constant, but rather declines over time. We have approximated this by basing the calculations on a Weibull model with a shape parameter of .6. In contrast, the exponential distribution is a Weibull with a shape parameter of 1. The difference in shape of the hazard functions is illustrated in Figure 7 below, which tabulates the percentage of events in each 90 day interval predicted from the two distributions:

Figure 7. Effect of Shape Parameter on Percentage of Events per Quarter

<table>
<thead>
<tr>
<th>Shape</th>
<th>Days 1-90</th>
<th>Days 91-180</th>
<th>Days 181-270</th>
<th>Days 271-360</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.6</td>
<td>41</td>
<td>14</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>1.0</td>
<td>26</td>
<td>19</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>

We evaluate power for a treatment effect (difference in hazard) that would produce a 10% difference in cumulative 6-month relapse rates (i.e., 55% versus 45%). We assume all participants will be followed for 6 months. In practice, a few patients may be lost to follow-up, but the numbers will be too small to affect the power.

Power calculations for survival analyses in complex designs currently require simulation methods, rather than closed-form calculations. The estimates below are based on software recently published by Natarajan, Turnbull, Slate, and Clark (1996). This software only provides power estimates for type one error rates of .01 and .05. Power calculations are presented below for both levels; the power using the planned alpha of .025 will be bounded by those presented here.
Case 1: two main effects, no interaction.

This leads to a pattern of 6-month relapse rates like that shown in figure 8, which assumes main effects of each drug and no effect of psychotherapy.

Figure 8. Percent Relapsing in 6 months with Two Main Effects

<table>
<thead>
<tr>
<th>Medical Management</th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>45</td>
<td>37</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Management + Psychotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Naltrexone</td>
</tr>
</tbody>
</table>

For this alternative, power to detect each main effect is .91 / .80, with alpha = .05 / .01, respectively.

Power to detect differences between individual pairs of cells is presented in Figure 9, below:

Figure 9. Power for Pairwise Comparisons with Alpha = .05 / .01

<table>
<thead>
<tr>
<th>6-month Relapse Rate</th>
<th>45%</th>
<th>37%</th>
</tr>
</thead>
<tbody>
<tr>
<td>55%</td>
<td>.45 / .25</td>
<td>.92 / .80</td>
</tr>
<tr>
<td>45%</td>
<td></td>
<td>.40 / .20</td>
</tr>
</tbody>
</table>

The power of the study to detect a main effect is very good, while a pairwise difference must be approximately twice as large for good power.
Case 2: two main effects, two-way positive interaction.

Assume an observed interactive effect half the size of the main effects. This leads to a pattern of relapse rates like that shown in figure 10, which assumes main effects of each drug and no effect of psychotherapy.

Figure 10. Percent Relapsing in 6-months with Two Main Effects and Positive Interaction

<table>
<thead>
<tr>
<th>Medical Management</th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>45</td>
<td>33</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical Management + Psychotherapy</th>
<th>Placebo</th>
<th>Acamprosate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>45</td>
<td>33</td>
</tr>
</tbody>
</table>

For this alternative, power to detect each main effect is greater than .95, for both alpha = .05 and .01. Power to detect the interaction is is.15 / .05, with alpha = .05 / .01, respectively.

Power to detect differences between individual pairs of cells is presented in Figure 11, below:

Figure 11. Power for Pairwise Comparisons with Alpha = .05 / .01

<table>
<thead>
<tr>
<th>6-month Relapse Rate</th>
<th>45%</th>
<th>33%</th>
</tr>
</thead>
<tbody>
<tr>
<td>55%</td>
<td>.45 / .25</td>
<td>.98 / .94</td>
</tr>
<tr>
<td>45%</td>
<td></td>
<td>.68 / .44</td>
</tr>
</tbody>
</table>

As with PDA, the power of the study to detect a main effect is very good, while power to detect interactions of this magnitude is low. Again, a pairwise difference must be approximately twice as large as the assumed main effect for good power.

The results for case 3 (two main effects and a negative interaction) are essentially identical to case 2.
CHAPTER 14: Interim Data Monitoring

14.1 Steering Committee Reports

To assist in the operation of the study, the Coordinating Center prepares routine reports for the Steering Committee. These reports cover 1) recruitment, 2) participant adherence, 3) clinician adherence to the intervention protocol, and 4) quality control. Special attention is given to that the inclusion and exclusion criteria are being applied consistently. Data on screening and recruitment are forwarded to the Coordinating Center at least weekly, and a weekly recruiting report is produced. Reports will include summaries for each clinical center. No endpoints or safety data will be included in the Steering Committee reports.

14.2 Data and Safety Monitoring Board (DSMB) Reports

The Data Safety Monitoring Board Reports will be prepared twice a year (or as specified by the DSMB). Although the DSMB determines the format of the report, each report consists of seven sections: 1) recruitment, 2) treatment efficacy, 3) adverse effects of therapies 4) participant adherence, 5) clinician adherence to protocols, 6) data quality, and 7) ancillary sub-studies. The recruitment section compares overall recruitment with the pre-specified targets. The treatment efficacy section contains a comparison of the co-primary endpoints (percent days abstinent and time to relapse to heavy drinking) across the treatment combinations. The section on adverse effects of the treatments reports any adverse outcomes associated with individual treatments or with treatment combinations. Participant adherence data will summarize participant attendance at therapy sessions and monitoring of consumption of medication. The section on clinician adherence to the protocol will describe the efforts at each clinical site to ensure that the designed intervention is administered. The quality control sections will include summaries of the quality control data collected by the Coordinating Center to monitor and correct operational data collection. Any ancillary sub-studies will be monitored to ensure that they do not adversely effect recruitment or adherence.

Approximately six weeks prior to the scheduled meeting of the DSMB, an edited data file is created by the Coordinating Center. A random sample of the records on the file is compared to the original data sources to check that participant records have not been altered or processing errors have occurred. Key data fields are checked to ensure that invalid values have not been entered. A report based on the data file is sent to members of the DSMB two weeks prior to the meeting. Steps taken to ensure security and confidentiality include distribution by certified mail and enactment of a return policy of all reports. Tables comparing the co-primary endpoints and other major outcomes are updated the week before the DSMB meeting to provide the committee with the most up-to-date data.

The Coordinating Center will provide analyses to assist judgments about whether the study should be terminated early because of either:

- efficacy, that is, by the time of an interim analysis one (or more than one) treatment combination is clearly superior or inferior to the other combinations; or
- futility, that is, the results obtained at an interim analysis suggest that it is highly unlikely that a significant result will be obtained if the study continues to the planned completion date.

The primary measures of efficacy are percent days abstinent (PDA) and time to relapse to heavy drinking. A number of methods for the repeated analysis of accumulating data have been proposed (O'Brien and Fleming, 1979; Lan and DeMets, 1983). The procedures are well-
established for trials in which the treatment arms do not overlap. For trials evaluating combinations of treatments such as in the factorial design in COMBINE, the development of procedures is still in its infancy. We propose the procedure below for interim monitoring for efficacy.

The study is scheduled to run for 46 months with new participants being randomized to treatment combinations in the first 30 months. Interim analyses will be conducted at 18, 24 and 30 months after the first participant is randomized. Having the first interim analysis no earlier than 18 months means that participants randomized within the first 6 months of the study will have been followed for at least 12 months at the time of this randomization. For these participants we shall then have outcome data for the 6 months while they are under treatment as well as for at least 6 months post-treatment. Having sufficient data on the post-treatment period is essential. One treatment combination may be superior while the treatments are being applied whereas a different treatment combination may have superior long-term benefits.

At each interim analysis the appropriate O’Brien-Fleming p-value will be used. If for either of the primary effect measures the p-value for simultaneous test of the contrasts of interest is larger than the corresponding O’Brien-Fleming p-value the study will continue as planned. If both p-values are smaller than the O’Brien-Fleming limits, consideration will be given to terminating either the whole trial or some of the treatment combinations. The 9 treatment combinations will be ranked on the basis of each of the outcome measures and the Tukey method (Miller, 1981) for simultaneous comparisons (using the appropriate O’Brien-Fleming p-value) will be used to determine whether there are some treatment combinations which are clearly superior or inferior to others. If one treatment combination is clearly superior to all the others consideration will be given to terminating the whole study. If there is no clearly superior treatment combination but some combinations are clearly inferior consideration will be given to dropping the inferior combinations but continuing with the other combinations.

For early termination because of futility, Halperin, et al., 1982, proposed a method to guide judgments about whether interim data is sufficient to determine that the treatment effect is likely to be 1) too small to be of practical importance or 2) so small that it cannot be demonstrated with a trial of the currently planned size. The Halperin procedure needs to be modified somewhat to accommodate the complexity of this study. At each interim analysis, the following procedure will be applied for each of the three individual treatments (naltrexone, acamprosate, and behavioral therapy) separately. The best treatment combination containing that treatment will be identified. This treatment combination will then be compared with the placebo/placebo/medication management “treatment” and the Halperin method will be used to determine whether it is worthwhile continuing with this treatment. As an extreme example, suppose that in order to achieve a significant result by the end of the study one group would have to have an average PDA of 102% from the time of the interim analysis to the end of the study. As PDA cannot exceed 100% it would be futile to continue to the planned end. If it is regarded as being futile to continue with the best combination containing that treatment then it will also be regarded as futile to continue with any other combination containing that treatment. This proposed procedure will be very conservative. For instance, consider the extreme case where treatment A is very effective but B and C have no effect at all. When investigating the futility of B, the “best” combination containing B will be one that also contains A. The effectiveness of A means that it is unlikely that continuing with B will be regarded as being futile. However, if A is so clearly superior then the procedure for early stopping because of demonstrated efficacy may detect this superiority.
Although the Coordinating Center has proposed methods for monitoring the progress of the trial and will provide data management and statistical computing to support the monitoring, the actual recommendation concerning the termination or continuation of the trial will be made by the DSMB to the NIAAA.
CHAPTER 15: Study Organization

15.1 Steering Committee

The Steering Committee is composed of the Principal Investigator of each of the Clinical Research Units, the Principal Investigator of the Coordinating Center and the NIAAA Staff Collaborator. Each will have one vote, when a vote of the Steering Committee is necessary to make a decision. The Chair is elected by the Steering Committee from among the non-NIAAA members, and serves a fixed term of one year. There is no limit on the number of terms an individual may serve as Chair. The Steering Committee oversees all aspects of the design, execution, and publication of the study. The Steering Committee met six times in year 1 and will meet four times yearly in subsequent years to monitor the progress of the study. The Steering Committee has established subcommittees to develop and monitor aspects of the study, reporting recommendations to the Steering Committee for approval.

15.2 Operations Committee

The Operations Committee manages the day-to-day operations of the study between Steering Committee meetings. Two of its functions are to develop the agendas for and prepare recommendations for the Steering Committee meetings, and to monitor interim progress of subcommittee’s tasks and participant recruitment. The Steering Committee Chair, Coordinating Center Principal Investigator, NIAAA Staff Collaborator, and Chairs of each Subcommittee are members of this committee. The Operations Committee meets weekly by conference call. The agenda and minutes of the Operations Committee conference calls are distributed by email to the Steering Committee for their review.

15.3 Subcommittees

The Steering Committee established subcommittees, to develop and monitor various aspects of the study. Subcommittee members include Investigators and staff of the Clinical Centers, Coordinating Center, and Project Office, as appropriate. Additional representatives of NIAAA’s Treatment Research Branch may participate as members of subcommittees. The subcommittee Chairs are elected by the subcommittees, subject to Steering Committee review and approval. Subcommittees develop recommendations and proposals for Steering Committee review and decision. The following subcommittees have been established:

♦ Treatment
♦ Research Protocol
♦ Project Coordinator
♦ Publications and Analysis

15.4 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is an independent group of experts in the relevant biomedical and behavioral fields, biostatistics, and bioethics, appointed by NIAAA. The primary role of the DSMB is to advise NIAAA on scientific, safety, ethical and other policy issues relating to the study. The DSMB will meet at least twice a year. The NIAAA Staff Collaborator, Steering Committee Chair, and Coordinating Center Principal Investigator will also participate in DSMB meetings as non-voting members. The DSMB will review and approve the
protocol prior to study initiation and approve the progression from one phase of the trial to the next. During the execution of the study, the DSMB will monitor study progress and review interim analyses of accumulating study data. Its primary function is to review all issues pertinent to participant safety and study integrity. As appropriate, it will make recommendations to the Institute and Steering Committee concerning changes in study conduct.

15.5 Study Centers

The Principal Investigator and location of each COMBINE study center are provided below.

Clinical Centers:  
Raymond F. Anton, MD  
Medical University of South Carolina  
Charleston, SC  
Domenic A. Ciraulo, MD  
Boston University  
Boston, MA  
Dennis M. Donovan, PhD  
University of Washington  
Seattle, WA  
Bankole A. Johnson, MD, PhD  
University of Texas Health Science Center  
San Antonio, TX  
Robert Swift, MD, PhD  
Brown University  
Providence, RI  
Barbara J. Mason, PhD  
University of Miami  
Miami, FL  
William R. Miller, PhD  
University of New Mexico  
Albuquerque, NM  
Stephanie O’Malley, PhD  
Yale University  
New Haven, CT  
Helen M. Pettinati, PhD  
University of Pennsylvania  
Philadelphia, PA  
Roger D. Weiss, MD  
Harvard University  
Belmont, MA
Allen Zweben, DSW
University of Wisconsin-Milwaukee
Milwaukee, WI

Coordinating Center: James D. Hosking, PhD
University of North Carolina
Chapel Hill, NC

Project Office: Margaret Mattson, PhD
National Institute on Alcohol Abuse and Alcoholism
Bethesda, MD
16.1 **Purpose**

The purpose of these guidelines is to structure an internal peer review process for Project COMBINE that will: a) facilitate the production of high quality manuscripts submitted to journal editors, book publishers, and conference organizers; b) facilitate open access by trial researchers to publication opportunities and prevent disputes concerning authorship credits; c) prevent the occurrence of duplicate or overlapping publications that may create copyright problems or conflicts with editors.

These guidelines apply to all abstracts, manuscripts and presentations developed under the support of the trial. The policy is the same for investigators, other CRU or CC scientific staff, NIAAA staff, and consultants or other collaborators from outside the trial.

16.2 **Definition Of A “Publication”**

The following kinds of publications, presentations and other products are covered by this policy:

A. Data-based articles, methodological papers, reviews, and book chapters to be published in scientific journals and other scholarly literature.

B. Presentations at scientific meetings (oral and posters)

C. Publications in the popular press and presentations to lay audiences (e.g., books, monographs, training manuals, therapist manuals, summaries of study protocol and trial progress reports).

D. Press releases

E. Other products of the trial including methodology and other know-how or information regardless of the form in which it is recorded (e.g., research instruments, computer software, video and audio taped materials) produced in the performance and preparation of the study.

16.3 **Categories Of Data**

A. “Trial wide data” is defined as protocol-required data pooled across all centers. It includes primary outcome data, secondary outcome data, and process data. The main results of the study will be presented in a series of corporate and commissioned papers releasing findings in a sequenced and timely fashion. Subsequent papers involving trial wide data by individual investigators will be guided by a data sharing and access policy established by the Steering Committee. (To be developed.)

B. “CRU-specific data” is defined as protocol-required data from a single center.

C. “Ancillary studies data” are derived from supplementary data collection efforts that use trial participants but are not a part of the main trial protocol. (See Chapter 17)
16.4 Types Of Authorship

Three types of authorship for abstracts, presentations and publications are defined:

16.4.1 Corporate publications
Corporate publications use trial wide data from all centers and present overall conclusions on major aspects of the trial. Such publications are few in number and are overseen by the Steering Committee. Authorship on corporate papers is attributed to “The Project COMBINE Research Group.”

For all corporate papers, the Steering Committee will appoint one individual to take the lead on preparation of the publication, and may appoint additional individuals to assist. The contributions of such individuals will be acknowledged in an author footnote. The authorship byline, however, will contain only: “The Project COMBINE Research Group.”

In the first corporate publication introducing the trial, the full membership of the Project COMBINE Research Group will be listed, along with a listing of Collaborating investigators and participating sites. In further corporate publications, this listing may or may not be reproduced, at the discretion of the Steering Committee. The Coordinating Center will maintain an up-to-date listing of the Project COMBINE Research Group for use in publications. This list will include three elements: (1) the official members of the Project COMBINE Research Group itself; (2) the names of collaborating investigators from each site; and (3) the names of clinical facilities participating in the trial.

16.4.2 Commissioned publications
Commissioned publications likewise present major aspects of the trial, but more clearly reflect the work of a subgroup of investigators. Publications are identified as “commissioned” by the Steering Committee, which also appoints an individual to take the lead on preparation of the publication. Additional authors for commissioned papers are identified and approved by the Steering Committee, in consultation with the lead author and the Publication Committee. In commissioned publications, the byline contains the names of the approved authors in order of their contributions to the publication, or in alphabetical order where contributions are judged equal, but always beginning with the name of the individual designated by the Steering Committee as lead author. The byline will also contain the designation, “In Collaboration with the Project COMBINE Research Group.” A full listing of the Project COMBINE Research Group is not necessary in commissioned publications.

16.4.3 Investigator-initiated publications
Investigator-initiated publications may use any of the three categories of data specified above. These are analysis and publication projects initiated by a specific individual or group. The intention to develop such a project must be announced to the entire Steering Committee, by procedures outlined below, in a manner that permits interested individuals to initiate collaboration. Final authorship of all such publications is based on actual contributions to the manuscript, discussion among the main author and secondary authors, and, as necessary the Publications Committee. The byline in investigator-initiated publications will list authors in the order of respective contributions to the publication, or in alphabetical order where contributions are judged to be equal. The byline may include the designation “In Collaboration with the Project COMBINE Research Group.” It is not necessary to list the Project COMBINE Research Group in investigator-initiated publications.
All publications, presentations and abstracts must be reviewed and approved by the Publication Committee prior to submission, and must have the trial name or acronym as part of the authorship, title, or abstract body.

16.4.4 Acknowledgement
Proper acknowledgment of the funding agency is also required in all publications. Appropriate forms for this acknowledgment are as follows.

16.4.4.1 When no author is a government employee:
This publication was supported by a series of grants from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), as part of the Cooperative Agreement on Combining Medications and Behavioral Therapy. [List grantee institutions and grant numbers.] Its contents are solely the responsibility of the authors and do not necessarily represent the official views of NIAAA.

16.4.4.2 When one or more authors are government employees, not supported by grant funds:
Dr. [state names of non-government authors] were supported by a series of grants from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), as part of the Cooperative Agreement on Combining Medications and Behavioral Therapy. [List grantee institutions and grant numbers.] The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of NIAAA. Note: In the latter case, government (e.g., NIAAA) employees are not included in the acknowledgment because they are not supported by directly by grant funds.

Publications prepared by trial investigators or consultants who relate in any way to the trial should be screened by the Publication Committee. If determined to be trial-related, they will be processed through normal Publication Committee review. If determined to be exempt, the authors will be given approval to proceed without further review.

16.5 Criteria For Determining Authorship
Guidelines from other studies have been reviewed to address various authorship issues and provide the basis for a rational procedure for authorship assignment. At least three criteria can be used to evaluate the assignment of authorship credit. These are: major contribution, effort, and follow-through.

16.5.1 Major contribution
Major contribution involves the independent development or interpretation of ideas that are critical or essential to the advancement of a scientific study. All persons making major contributions should receive authorship credit. Examples of major contributions are: (1) design of the study, (2) recruitment of participants and conduct of the study, (3) statistical analysis, (4) writing of the paper, including interpretation of results and integration with existing information.

16.5.2 Effort and Follow-through
In considering the relative importance of major contributions, two additional factors must be taken into account. These factors are effort and follow-through. “Effort” pertains to the amount of time spent on the particular contribution. “Follow-through” involves active participation at various stages, throughout the project. For example, if a person has participated in a study in a minor way, or has made a major contribution that involves minimal effort and/or follow-through,
this does not necessarily entitle the individual to authorship if other persons have made greater contributions with respect to effort and follow-through.

Evaluation and negotiation of authorship credits should be an ongoing process, beginning with the establishment of a set of expectations concerning authorship credit at the onset of the collaboration. Clear communication about these matters among all concerned and development of criteria for authorship credit is essential during the planning, as is periodic reassessment of the contributions of the research team throughout the study. If it is found that previous expectations are not being met, then assignment of authorship credit should be modified, based on the actual contribution following completion of the study.

Under usual circumstances non-substantive considerations should not determine the order of authorship or whether or not to include an individual as an author. Such non-substantive criteria may include such factors as rank or status, PI designation, need for publication credits to justify advancement, involvement in the project as consequence of normal duties for which the individual is paid, or ability to provide access to experimental participants.

Finally, members of the research team recognize that simply by virtue of their participation in a multi-center collaborative research study, individuals will be expected to contribute to projects in a collegial fashion without necessarily receiving credits in all publications.

16.6 Procedures For Approval Of Publications

The following procedures apply only to the review and approval of proposed publication projects. All projects requiring use of Project COMBINE data must also receive separate approval for data access and analysis, according to project guidelines for data sharing (N.B. to be developed by the Steering Committee.)

16.6.1 Stage 1: Initial Notification

Potential publications may be identified by the Steering Committee or Publication Committee, or by individuals or groups of collaborating investigators. Notification of interest to initiate a project is made to the Operations and Publication Committees by specifying the title, a brief description, and authors, of the proposed work. Such initial notification will be appended to the weekly minutes of the Operations Committee to inform the Steering Committee and to allow for open discussion and collaboration. Members are encouraged to contact other with similar interests and discuss publication options.

16.6.2 Stage 2: Detailed Notification and

16.6.3 Stage 3: Approved Proposal

At Stage 2, a more detailed plan is submitted to the Publications Committee by the author team. The plan consists of information on hypothesis, data analysis plan, publication outlet, target dates etc.. After review and any discussion necessary to clarify issues such as overlap and data availability, the author is notified of approval (Stage 3) or other outcome.

In the case of corporate and commissioned papers, the members of the writing group and the target dates will be designated by the Steering Committee. The Publication Committee will be responsible for monitoring the timetable and may recommend replacing the chairperson or any other member of the writing group if the target dates are not met.
16.6.4 Stage 4: Complete Manuscript Submitted for Committee Review

Upon completion of the paper, it is submitted to the Publication Committee. The Chair designates two individuals to serve as reviewers. The primary reviewer will be from the Publication Subcommittee. The secondary reviewers will be from the investigator pool and may or may not be a member of the Publication Committee. The reviewers will submit written recommendations to Chair, who in turn will distribute them to the entire Publication Committee and to the submitting author. Although the intention of the review is to focus on accurate representation of trial results and adherence to trial policies, reviewers may choose to make other nonbinding suggestions (e.g., style, completeness of literature review) deemed to be helpful to the authors.

Following all reviews, the paper is deemed acceptable or unacceptable. The three possible avenues for action following the review are as follows:

1. Acceptable "as is" - distributed to the Steering Committee for their information
2. Acceptable with revisions - author(s) asked to make suggested revisions; revised paper reviewed; distributed to Steering Committee for informational purposes when revisions are approved.
3. Unacceptable - returned to author(s) with comment.

When serious objections are raised by the reviewers concerning the manuscript, the Steering Committee can be asked to resolve disputes or recommend modification.

Informational copies of all publications will be distributed by the Coordinating Center to the Steering Committee once they have appeared in print.

16.6.5 Stage 5: Manuscript Submitted for Publication

16.6.6 Stage 6: Publication in Print

The Coordinating Center will maintain updated lists of all notifications (Stage 1) and all subsequent steps for all proposed manuscripts or presentations. The listing will be distributed at each Steering Committee meeting.

16.7 Procedures For Abstracts And Presentations

16.7.1 Approval

Abstracts and presentations must be approved by the Publication Committee before being submitted to any outside source. Abstracts or presentations submitted that are not approved will be withdrawn upon request. It is not necessary to submit for review abstracts or presentations dealing with material previously published. However, such items should be sent to the Coordinating Center and the Publication Committee Chair for archival purposes.

16.7.2 Submission

In order for abstracts to be considered by the Publication Committee, requests must be submitted in writing to the Chair prior to the author’s submission deadline. To assist in this process, the Publications Committee will prepare, on a yearly basis, a calendar of relevant meetings with submission deadlines. A date will be specified for each meeting by which the proposed abstract needs to be submitted to the Publications committee for review, generally about 2-3 weeks prior to the conference submission date. The chair will review the proposal and refer it to another Committee member who will serve as primary reviewer. It will be the Chair's responsibility to have a mechanism for an alternate from the Committee to perform this function during periods
when he/she is unavailable.

16.7.3 Reviews
A committee member will act as primary reviewer of every abstract or presentation. The member may assign another individual to assist with the review in special cases, or refer the abstract to the whole Publication committee for review.

The entire Publication Committee will receive a copy of each abstract/presentation and may submit opinions or comments to the reviewer. Due to the tight deadlines on abstracts, the absence of a comment by a Committee member to the reviewer by the due date will be considered implicit approval by that member.

Upon receipt of the primary reviewer's comments, the chair will then notify both the author and the Publication Committee of the decision.

16.7.4 Archiving and Distribution
When an abstract or presentation has been approved by the Publication Committee, the author does not need to submit a script if he/she uses the information only for a presentation. If the abstract or presentation results in a publication, then the manuscript must be submitted to the Publication Committee. Any summaries, publications, etc. which result from the abstract are to be submitted to the Coordinating Center and Publication Committee Chair for archival purposes.

Informational copies of accepted abstracts and presentations will be distributed by the author to all members of the Steering Committee.

16.8 Press Releases
A standard public information release regarding the trial will be maintained and updated by the Publication Committee. This information may be provided to representatives of the press without prior approval to provide an overview of the trial, as may copies of publications that have appeared in print.

Press releases and interviews involve presentations or discussions relative to the trial with representatives of the lay press; i.e., newspapers, magazines and other periodicals not listed in Index Medicus. Information presented on such occasions must be limited to items described in the RFA, the above-mentioned model press release, or official trial publications and presentations. Copies of press releases must be sent to the NIAAA Project Officer, and the Coordinating Center.

16.9 Publications By Those Outside The Steering Committee
If a researcher from an institution which is not a participating center proposes to participate in analysis of and produce a publication from Protect COMBINE data, she/he will submit a request in writing to the Publication Committee describing the project proposed. The Publication Committee will consult the Steering Committee and decide whether, and on what conditions, the information can be released for that purpose.

Publication or presentation projects related to trial data may also be proposed by investigators who are not members of the Steering Committee, but who are part of institutions participating in Project COMBINE. Such projects are proposed through the same Publication Committee
channels described above. In such cases, at least one member of the Steering Committee would normally participate in the collaborating research team.

16.10 **Disclaimers**

When conclusions in a publication are expected to be particularly important, controversial, or at variance with those in any previous report of the study, whether such previous report is in draft or already published form, the Center or associated researcher concerned will keep the Publication Committee informed in detail and will provide it, and any collaborating center, upon request, the opportunity for consultation during the preparation stage of such papers.

If a paper prepared for publication or presentation at a scientific meeting contains statements concerning NIAAA, the study, a Participating Center or Collaborating Investigator that are considered by the Steering Committee to be unacceptable for political, moral or legal reasons, it will notify the Center or researcher concerned. Such statements will be either:

1. deleted or modified so as to remove the reasons for notification, or

2. subject to a footnote, the text of which is to be cleared with NIAAA, indicating that NIAAA and, if applicable, other Participating Centers and Collaborating Investigators expressly disassociated themselves from the statement.

16.11 **Implementation Of The Publications Policy**

The three main responsibilities of the Publications Subcommittee are:

A. Planning and solicitation of publication proposals.

B. Review of proposals to initiate an analysis project presentation or other scientific communication.

C. Review of completed manuscripts and abstracts prior to submission to a journal.

In order to carry out these responsibilities, the Subcommittee will:

A. Promote timely dissemination to the scientific community of results and methods from the trial, as well as related research and clinical information from other sources. This includes proposing topics for publications to the Steering Committee, seeking publication and presentation opportunities for the trial, and monitoring progress on commissioned papers.

B. Review proposed and completed data analysis projects, presentations, manuscripts and other products proposed for publication in terms of their scientific quality, adherence to trial policy, and impact on the trial.

C. Encourage the maximum participation of all collaborating investigators in scientific communications and assure that publications and authorship reasonably reflect contribution to the trial and to the analysis of its data.
D. Report regularly on the status of all proposed and ongoing trial publications to the Steering Committee and other trial investigators. Keep accurate minutes of all meetings of the Publications Subcommittee and distribute copies to members of the Steering Committee. These activities are intended to keep all participants in the trial aware of how trial data is being used and to promote opportunities for collaborations among those having similar interests. The Subcommittee will point out areas of overlap between planned projects so that duplicated effort is avoided and possibilities for joint publication are evident.

E. Propose changes to the Steering Committee in publications policy and procedures as needed as the trial evolves.

16.12 Structure Of The Publications Committee

Nominees for the Publication Committee are submitted to the Steering Committee, which will review and select a roster of nominees. The Committee Chairperson is nominated by the Steering Committee in consultation with the Project Officer. Final approval of the membership of the committee and appointment of the chairperson is by vote of the Steering Committee.

Committee members will be appointed for a specified period of time on a rotating basis. At the time the committee is originally established, two members will be appointed for a two-year period. The other three members will be appointed for one-year periods. The chairperson will serve for a two-year term. After the first year, replacement nominations will be required each year. The rotating time periods will ensure that at least two committee members remain on the committee during the transition to new members, so that there is continuity in the decision-making process.

To ensure equitable representation of all centers and of all categories of participants (e.g. PIs, project directors), the following procedures are suggested: (1) no more than one person from a participating center (CRU), the Coordinating Center, or NIAAA may serve on the Committee at any given time; (2) membership is open to all personnel supported by the trial’s budget; (3) the Committee will at all times have one member representing NIAAA, one member representing the Coordinating Center, and the remaining members representing the CRUs.
CHAPTER 17: Ancillary Studies

17.1 Introduction

COMBINE Investigators can propose ancillary studies to be conducted in collaboration with the main protocol. An Ancillary Study uses supplementary data that are collected on participants who are screened for entry into, or enrolled in COMBINE, over and above the data collection required by the COMBINE protocol. Ancillary Studies are funded from sources other than the COMBINE budget.

Investigators wishing to develop an ancillary study will submit a proposal for the planned study describing the study rational, objectives, participant sample, data collection procedures and burden, timeline and planned analyses. The proposal will be reviewed by the COMBINE Steering Committee.

All publications from ancillary studies will be controlled by the COMBINE publication policy and must follow standard study procedures.

Ancillary studies must have sufficient funding to support data collection, management and analysis.

17.2 Independent Studies

Independent studies of concern to the COMBINE Study are studies conducted in participants with alcohol abuse/dependence who enter the COMBINE Study Clinical Unit but are not enrolled in the COMBINE Study.

It is understood that each Clinical Unit is free to conduct any study in participants they screen who do not meet criteria for enrollment into the COMBINE Study. Independent studies of participants who meet the COMBINE eligibility criteria but are not enrolled in COMBINE must be reviewed by the COMBINE Operations Committee. COMBINE Study Investigators will ensure that any independent study they initiate in participants who meet the COMBINE eligibility criteria does not interfere with achieving their recruitment commitments to COMBINE.

17.3 Preparation of Proposals for Ancillary Studies

Each proposal for an Ancillary Study should contain a brief description of the study objectives, significance of the study, methods, data management and analysis plans, and proposed collaborators. All required data collection procedures should be described. The extent of additional participant burden should be described.

The proposal must include a budget, describing the level of funding to be provided to the clinical centers, coordinating center, and any other relevant agencies for personnel effort and other required costs. The level of funding must be sufficient to support the additional data collection, management, and analysis required by the ancillary study. In particular, funding of a grant proposal for an ancillary study at a reduced level from that proposed will likely require corresponding modifications to the workscope of the ancillary study. The SC will review the proposed modifications before final approval is granted. Investigators planning an ancillary study are encouraged to consult with the Operations Committee during development of the proposal to ensure consensus on the resources required for the project.
17.4 Submission and Review of Proposals

The proposal should be submitted to the Coordinating Center for inventory and transmission to the Operations Committee. The Operations Committee will briefly review the proposal to ensure that it adequately addresses the issues listed in section 17.3, above. The proposal will then be forwarded to the Steering Committee for review. The Steering Committee may, at its discretion, seek the advice of outside reviewers in regard to the technical merit and feasibility of the proposal. The primary focus of the review is to evaluate the benefits to be gained from the additional data collection in comparison with the impact on the conduct of the main protocol. Highest priority will be given to ancillary studies which:

♦ Have the highest scientific merit
♦ Do not interfere with the main study objectives
♦ Produce the least burden on participants
♦ Have objectives directly related to the main study
♦ Require the unique characteristics of the study participants.

The Coordinating Center will notify the Investigator when the project is approved, disapproved or additional information is needed before a decision can be made.

Investigators are cautioned to account for the time required for Steering Committee review and approval in planning for grant submission. The Steering Committee will attempt to reach a decision within 3 weeks of receipt of a complete, reviewable proposal.

17.5 Publications and Presentations

All publications and presentations from Ancillary Studies will follow the COMBINE publication procedures described in Chapter 16. In planning ancillary studies, it is important to account for the fact that publications from any ancillary studies will not be allowed to precede the relevant COMBINE corporate publications. Thus publications reporting the baseline data from an ancillary study will only be approved following the publication of the main COMBINE baseline manuscript. Similarly, publications based on outcome data will follow the primary COMBINE outcome manuscript.

Publications and presentations from independent studies are not subject to the COMBINE publications policy.
References


### A. Screening Assessments (Prior to Baseline)

<table>
<thead>
<tr>
<th>Assessment &amp; Source</th>
<th>Construct/ Purpose</th>
<th>Adm.</th>
<th>Pre - BL</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. COMBINE Quick Screen Including the AUDIT, Alcohol Use Disorders Identification Test (WHO, 1995)</td>
<td>Inclusion/ exclusion criteria</td>
<td>RA</td>
<td>10</td>
<td><em>In-person or by phone. Also to obtain data re generalizability, following a statement of duration &amp; consent.</em></td>
</tr>
<tr>
<td></td>
<td>Screen for hazardous drinkers &amp; alcohol abuse/ dependence</td>
<td>SA</td>
<td>5</td>
<td><em>In-person or by phone</em></td>
</tr>
<tr>
<td>2. Determinants of participation or non-participation (rev. from Project MATCH)</td>
<td>Reasons for study participation</td>
<td>SA</td>
<td>1</td>
<td><em>In-person. To include reasons for choosing either to participate or not</em></td>
</tr>
</tbody>
</table>

Total minutes screening (Self & Interview) = 16

### B. History / Physical, Physiologic and Laboratory Assessments (Includes questions for contraindicated Rxs, excluded OTCs & "natural" agents)

<table>
<thead>
<tr>
<th>Assessment &amp; Source</th>
<th>Construct/ Purpose</th>
<th>Adm</th>
<th>BL</th>
<th>Wk 8</th>
<th>Wk 16</th>
<th>Wk 26 Mo 6</th>
<th>Wk 52 Mo 12</th>
<th>Wk 68 Mo 16</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| **a. History / Physical, Physiologic Assessments**
| 1. Demographics | SA | 3 | | | | | | |
| 2. History and physical exam | Health screen | MM | 15 | 15 | History at BL only |
| 3. Psychiatric History | MM | | | | BL only |
| 4. Blood pressure | WD measure | MM | 3 | 3 | 3 | 3 | 3 | 3 |
| 5. Heart rate | WD measure | MM | 1 | 1 | 1 | 1 | 1 | 1 |
| 6. Weight & Height | Body mass | MM | 2 | 2 | 2 | 2 | 2 | 2 | Wt. only after baseline. |
| 7. CIWA-Ar -- Clinical Institute Withdrawal Assessment for Alcohol (Sullivan et al., 1989) | WD measure | MM | 5 | | | | | | |
| **b. Laboratory Measurements**
| 8. Electrolytes, BUN & Glucose | lab | * | * | * | |
| 9. CBC | lab | * | * | | |
| 10. Liver Function Tests (AST, GGT, Bili T & D) | prn if elevated GGT | lab | * | * | * | * | | | |
| 11. beta-HCG | lab | * | | | | | | | prn with missed menses by 10 or more days or high risk behavior |
| 12. Urinalysis | Health screen | MM | * | * | | | | | |
| 13. ECG | Safety | lab | | | | | | | Done only if clinically indicated |
| 14. BAC (breathalyzer) | RA | 2 | 2 | 2 | 2 | 2 | 2 | Admin. at every visit. |
| 15. Urine toxicology screen | RA | 5 | | | | | | Screening only. |
| 16. beta-naltrexol levels | lab | | | | | | | | wks 4 and 12 (not for participants in CBI-only) |
| 17. Acamprosate levels | lab | | | | | | | | wks 4 and 12 (not for participants in CBI-only) |
| 18. CDT | lab | * | * | * | | | | | BL, wks 8 and 16 |
| **c. Adverse Events**
| 19. SAFTEE short form Side Effects Checklist | Toxicity | MM | 7 | 7 | 7 | | | | Includes items for sleep: appetite (incl. CHO craving). Admin. at every MM session. (not for participants in CBI-only) |
| 20. Concurrent Medication | MM | 3 | 3 | 3 | 3 | 3 | 3 | | Asked at every session |
| 21. SAE-Serious Adverse Event Form | Safety | | | | | | | | Completed when event meets FDA definition of serious or the investigator feels that a “severe” rating on the SAFTEE constitutes filling out the SAE form. |
| 22. Inactive Status Form | RA/ MM/ CBI | | | | | | | | Completed if participant withdraws or is withdrawn from the study after randomization. |

**CODES for Administration:** RA (research assistant); SA (self-administered); MM (physician or nurse practitioner); na (not administered, i.e. calculated)

1. Estimated time for administration.
2. Committee recommendations for measures within treatment are listed in the Comments section.
### C. Treatment Related Expectancies

<table>
<thead>
<tr>
<th>#</th>
<th>Assessment &amp; Source</th>
<th>Construct/ Purpose</th>
<th>Adm</th>
<th>BL</th>
<th>Wk 8</th>
<th>Wk 16</th>
<th>Wk 26</th>
<th>Wk 52</th>
<th>Wk 68</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TEE-Treatment Experiences and Expectancies Questionnaire (Donovan)</td>
<td>Expectancies concerning treatment effectiveness</td>
<td>SA</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### D. Assessments of Behavioral Outcomes, Predictors, Mediators & Generalizability

#### a. Alcohol Consumption

<table>
<thead>
<tr>
<th>#</th>
<th>Assessment &amp; Source</th>
<th>Construct/ Purpose</th>
<th>Adm</th>
<th>BL</th>
<th>Wk 8</th>
<th>Wk 16</th>
<th>Wk 26</th>
<th>Wk 52</th>
<th>Wk 68</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Time-line Follow-Back Procedure (Sobell &amp; Sobell, 1995)</td>
<td>Primary within-treatment measure of daily alcohol use and patterns</td>
<td>RA</td>
<td>15</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>At each of the scheduled appointments to determine drinking between visits.</td>
</tr>
<tr>
<td>2</td>
<td>Form 90-AIR/ED Form 90-F/ED Form 90-A² (Project MATCH, 1996)</td>
<td>Primary outcome; comprehensive, daily alcohol use, patterns &amp; Tx; Economic outcome data</td>
<td>RA</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>Use long version at BL for prior treatment Hx. Collect non-consumption data only unless the time frame between visits is ≥ 6 weeks. Complete entire FED at weeks 26, 52, and 68 (and an additional 20 months for economic ancillary study).</td>
<td></td>
</tr>
</tbody>
</table>

#### b. Alcohol & Drug Involvement

<table>
<thead>
<tr>
<th>#</th>
<th>Assessment &amp; Source</th>
<th>Construct/ Purpose</th>
<th>Adm</th>
<th>BL</th>
<th>Wk 8</th>
<th>Wk 16</th>
<th>Wk 26</th>
<th>Wk 52</th>
<th>Wk 68</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DrInC Drinker Inventory of Consequences (Miller et al., 1995)</td>
<td>Consequences of drinking since last DRF was administered</td>
<td>SA</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>BL and wks 8, 16, 26, 52, and 68. Complete DB again if time frame between baseline screening and the day of randomization exceeds 30 days.</td>
</tr>
<tr>
<td>2</td>
<td>Alcohol Dependence Scale ADS (Skinner)</td>
<td>Alcohol Dependence</td>
<td>SA</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SCID-IV Module E (Spitzer, et al., 1992)</td>
<td>Alcohol and Drug abuse &amp; dependence</td>
<td>RA</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>Entire module is given at baseline. Alcohol use disorders section given at follow-up visits.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Drug Use Index (Clayton &amp; Voss, 1981)</td>
<td>Scoring algorithm, yields a global drug use score</td>
<td>(na)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Derived from responses to Form-90.</td>
</tr>
<tr>
<td>5</td>
<td>ASI Family History Chart (McLellan et al., 1992)</td>
<td>Predictor Mediator</td>
<td>RA</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A FH+ assessment for alcoholism &amp; drug problems only, to complement genetic testing.</td>
</tr>
<tr>
<td>6</td>
<td>AASE Alcohol Abstinence Self Efficacy (DiClemente, Carbonari, Montgomery &amp; Hughes 1994)</td>
<td>Self-efficacy &amp; temptation Prognostic Mediator</td>
<td>SA</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>Not required at last visit since only prognostic.</td>
</tr>
<tr>
<td>7</td>
<td>Composite Outcome Index (Cisler &amp; Zweben, 1999)</td>
<td>Composite measure of drinking and negative consequences</td>
<td>(na)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Derived from responses to Form-90 and DrInC.</td>
</tr>
</tbody>
</table>

#### c. Motivation

<table>
<thead>
<tr>
<th>#</th>
<th>Assessment &amp; Source</th>
<th>Construct/ Purpose</th>
<th>Adm</th>
<th>BL</th>
<th>Wk 8</th>
<th>Wk 16</th>
<th>Wk 26</th>
<th>Wk 52</th>
<th>Wk 68</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>URICA—Short Form Readiness to Change (alcohol)</td>
<td>Stage of change Prognostic Mediator</td>
<td>SA</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

#### d. Craving

<table>
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<tr>
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<th>Construct/ Purpose</th>
<th>Adm</th>
<th>BL</th>
<th>Wk 8</th>
<th>Wk 16</th>
<th>Wk 26</th>
<th>Wk 52</th>
<th>Wk 68</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OCDS Obsessive-Compulsive Drinking Scale (Anton et al., 1995)</td>
<td>Mediator</td>
<td>SA</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
<td>Admin. at BL and again on the day of randomization. Also collected at all within treatment research visits and week 26.</td>
</tr>
<tr>
<td>2</td>
<td>Relapse questions (Weiss)</td>
<td>SA</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>Admin at BL and again on the day of randomization. Also collected at all within treatment research visits and week 26.</td>
</tr>
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</table>
## D. Assessments of Behavioral Outcomes, Predictors, Mediators & Generalizability cont.

### e. Psychological / Psychiatric Assessment

<table>
<thead>
<tr>
<th>#</th>
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<th>Construct/ Purpose</th>
<th>Adm</th>
<th>BL</th>
<th>Wk 8</th>
<th>Wk 16</th>
<th>Wk 26</th>
<th>Wk 52</th>
<th>Wk 68</th>
<th>Mo 6</th>
<th>Mo 12</th>
<th>Mo 16</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>SCID Screen Patient Questionnaire (formerly Mini-SCID for DSM-IV (First, et al., 1995)</td>
<td>Screen for various Axis I disorders.</td>
<td>RA</td>
<td>20</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>BSI Brief Symptom Inventory (Derogatis 1993) adapted from SCL-90</td>
<td>Symptoms of anxiety, depression, etc.</td>
<td>SA</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>wks 0, 1, 2, 4, 8, 12, and 16</td>
</tr>
<tr>
<td>3.</td>
<td>POMS short Profile of Mood States</td>
<td>Serial measure of mood &amp; treatment response</td>
<td>SA</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Perceived Stress Scale (PSS) (Cohen, et al., 1983)</td>
<td>Serial measure of stress</td>
<td>SA</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4-item scale administered wks 0, 1, 2, 4, 6, 8, 10, 12, 16 and 52</td>
</tr>
</tbody>
</table>

### f. Social Support

<table>
<thead>
<tr>
<th></th>
<th>Assessment</th>
<th>Measures support for drinking vs. abstinence in patient's social network &amp; importance of network to patient.</th>
<th>RA</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>BL week 16 and 26. If not obtained at wk 26, then obtain at wk 52.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>IP Important People Instrument – revised (Longabaugh &amp; Zywiak)</td>
<td></td>
<td>RA</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### g. Quality of Life

<table>
<thead>
<tr>
<th></th>
<th>Assessment</th>
<th>Clinical rating of global functioning used in Axis V of DSMIV; Outcome</th>
<th>(na)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Algorithm will be used to provide GAF rating based on items derived from other assessment instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>GAF Global Assessment of Functioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>WHO Quality of Life Assessment</td>
<td>Life functioning &amp; satisfaction with physical &amp; mental health; Health status &amp; outcome</td>
<td>SA</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Admin at BL and at 6-month follow-up intervals thereafter (wks 26 and 52).</td>
</tr>
</tbody>
</table>

### h. Therapy Compliance and Process Measures

<table>
<thead>
<tr>
<th></th>
<th>Assessment</th>
<th>Perceived therapeutic alliance</th>
<th>SA</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Administered after third MM contact and third session of CBI (if in CBI condition) to help client know which clinician is being rated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Pill Count Form</td>
<td></td>
<td>RA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completed at every MM visit</td>
</tr>
<tr>
<td>2.</td>
<td>MNC-Medication Noncompliance Checklist</td>
<td>Reasons for med noncompliance</td>
<td>MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completed at every MM visit (even if compliant)</td>
</tr>
<tr>
<td>3.</td>
<td>ISF – Inactive Status Form</td>
<td>Reasons for dropping out of study</td>
<td>SA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Complete for participants that are inactive in CBI, MM, or the medication portion of the trial. If a participant discontinues, section B (reasons) should be completed. If the patient is unwilling/unable to complete the form and the RA or PC is aware of the reason, s/he can complete section B.</td>
</tr>
<tr>
<td>4.</td>
<td>WAI-Working Alliance Inventory– Bond subscale</td>
<td>Perceived therapeutic alliance</td>
<td>SA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Administered after third MM contact and third session of CBI (if in CBI condition) to help client know which clinician is being rated.</td>
</tr>
<tr>
<td>5.</td>
<td>PCQ - Processes of Change Questionnaire (Prochaska et al., 1988)</td>
<td>Processes of change Prognostic mediator</td>
<td>SA</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stages of change derived from the URICA</td>
</tr>
<tr>
<td>6.</td>
<td>EOT-Evaluation Of and Satisfaction With Treatment (adapted from Project MATCH)</td>
<td>Client satisfaction and perceived helpfulness of treatment components</td>
<td>SA</td>
<td>(na)</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time to collect this information is included in Form-90 estimates given above</td>
</tr>
</tbody>
</table>

Subtotal (minutes): 187 66 129 81 60 48 Assessments only; excludes labs. 

Total (hours) for assessments: 3.1 *4.06 *including 1 hour (labs, consent and logistical down time)
### Table 7.3 Test Administration Schedule

#### A. Screening Assessments

<table>
<thead>
<tr>
<th>Weeks</th>
<th>BL</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>16</th>
<th>26</th>
<th>52</th>
<th>68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>6</td>
<td>12</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **COMBINE Quick Screen**
  - Including the AUDIT, X
- **Determinants of participation or non-participation**
  - X

#### B. History / Physical, Physiologic and Laboratory Assessments

<table>
<thead>
<tr>
<th>Weeks</th>
<th>BL</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>16</th>
<th>26</th>
<th>52</th>
<th>68</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>6</td>
<td>12</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

##### a. History / Physical, Physiologic Assessments

- **Demographics**
  - X
- **History**
  - X
- **Physical Exam**
  - X
- **Psychiatric History**
  - X
- **Blood pressure**
  - X X X X X X X X X X X X X X X X
- **Heart rate**
  - X X X X X X X X X X X X X X X X
- **Weight & Height**
  - X
- **CIWA-A -- Withdrawal Assessment for Alcohol**
  - X

##### b. Laboratory Measurements

- **Electrolytes, BUN & Glucose**
  - X
- **CBC**
  - X
- **Liver Function Tests -- (AST, GGT, Bili T & D)**
  - X X X X X X X X X X
- **Carbohydrate Deficient Transferrin (CDT)**
  - X X
- **beta-HCG**
  - X
  - Repeated only if menses is 10 or more days overdue
- **Urinalysis**
  - X
- **ECG**
  - Only as clinically indicated
- **BAC (breathalyzer)**
  - X X X X X X X X X X X X X X X X
- **Urine toxicology screen**
  - X
- **beta-naltrexol levels**
  - X
- **Acamprosate levels**
  - X
- **CDT**
  - X

##### c. Adverse Events

- **SAFTEE**
  - X X X X X X X X X X X X X X X X
- **Concurrent Medications**
  - X X X X X X X X X X X X X X X X
- **Serious Adverse Event Report**
  - As needed
- **Inactive Status Form**
  - As needed
### C. Treatment Related Expectancies

<table>
<thead>
<tr>
<th>Weeks</th>
<th>BL</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>16</th>
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</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td>6</td>
<td>12</td>
<td>16</td>
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</tbody>
</table>

- **TEE-Treatment Experiences and Expectancies Questionnaire**: X

### D. Assessments of Behavioral Outcomes, Predictors, Mediators & Generalizability

<table>
<thead>
<tr>
<th>Weeks</th>
<th>BL</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>16</th>
<th>26</th>
<th>52</th>
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<tbody>
<tr>
<td>Months</td>
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<td>12</td>
<td>16</td>
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</tbody>
</table>

#### a. Alcohol Consumption

- **TLFB-Time-line Follow-Back Procedure**: X X X X X X X X X
- **Form 90-AIR/ED**: X
- **Form 90-F/ED (drinking data)**: X
- **Form 90-F/ED (non-consumption data)**: X

#### b. Alcohol & Drug Involvement

- **DrInC – Drinker Inventory of Consequences**: X
- **ADS-Alcohol Dependence Scale**: X
- **SCID-IV Module E (drug & alc)**: X
  - Alcohol use disorders section only: X
- **Drug Use Index**: Derived from Form-90
- **ASI Family History Chart**: X
- **AASE**: X X
- **Alcohol Abstinence Self Efficacy**: X X X X X X X X X
- **Composite Outcome Index**: Derived from DrInC and Form-90

#### c. Motivation

- **URICA – Short Form Readiness to Change (alcohol)**: X

#### d. Craving

- **OCDS -- Obsessive-Compulsive Drinking Scale**: X X X X X X X X X X X X
- **Drinking Questionnaire**: X X X X X X X X X X X

*FED (drinking data) collected at week 8 and 16 if the time frame between visits ≥ 6 weeks.*
D. Assessments of Behavioral Outcomes, Predictors, Mediators & Generalizability (continued)

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
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<th>26</th>
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<tbody>
<tr>
<td></td>
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<td>Months</td>
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<td>12</td>
<td>16</td>
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<td>e. Psychological / Psychiatric</td>
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<td>SCID Screen Patient Questionnaire</td>
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<td></td>
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</tr>
<tr>
<td>BSI -- Brief Symptom Inventory</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POMS -- Profile of Mood States (short form)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS - Perceived Stress Scale 4-item</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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</tr>
<tr>
<td>f. Social Support</td>
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<td>g. Quality of Life</td>
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<td>GAF - Global Assessment of Functioning</td>
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<td>WAI-Working Alliance Inventory– Bond subscale</td>
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WAI-after the 3rd MM contact and 3rd CBI session
Table 7.4 Estimated Time for Assessments at Baseline, Within Treatment, and at Major Follow-up Points

A. Assessments at Baseline and Major Follow-up Points

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<td><strong>Total Time -- Minutes</strong></td>
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<td><strong>-- Hours</strong></td>
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B. Within-Treatment Assessments

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<td>ADS-Alcohol Dependence Scale</td>
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<td>OCDS-Obsessive Compulsive Drinking Scale</td>
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<td>IP-Important People</td>
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<td><strong>Total Time - Minutes</strong></td>
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Note: Times for Baseline, 8-, and 16-week follow-up assessments have been included in time estimates for the major follow-up points.
Appendix A1: Patient Instructions for Managing Side Effects

COMBINE Protocol Ver. 8.0
COMBINE
Patient Instructions for Managing Side Effects

Most persons do not experience side effects from the medication you are taking. Occasionally, some people experience symptoms related to giving up drinking, which can be confused with side effects from the medication. These symptoms usually are not serious and they usually get better within a few days. Do not stop your medication until you have called your study healthcare provider. If you are concerned about any symptoms you are having, you can call your study healthcare provider as follows:

During clinic hours:  (Name)___________________(Phone)__________________
After clinic hours:    (Name)___________________(Phone)__________________

Nausea
- Take your medication with food.
- Take Pepto-Bismol® according to package instructions, or as prescribed by your study healthcare provider.

Vomiting
- Call your study healthcare provider.

Diarrhea
- Take Pepto-Bismol® according to package instructions, or as prescribed by your study healthcare provider.
- If diarrhea persists drink plenty of non-alcoholic fluids and call your study healthcare provider.

Significant or persistent abdominal pain
- Call your study healthcare provider.

Headache
- Use non-prescription headache medications according to package instructions. "It is important to avoid alcohol when taking headache medications."
- If headache persists call your study healthcare provider.

Dizziness, Nervousness, Anxiety, Insomnia
- If dizziness, nervousness, anxiety, or insomnia is significant or persistent call your study healthcare provider.

Herbal over-the-counter or prescribed medications should not be started on the study without first discussing their use with your study healthcare provider.
Appendix A2: Medical Management Therapist Guidelines for Managing Side Effect Complaints

COMBINE
Medical Management Therapist Guidelines for Managing Side Effect Complaints

1. Listen to patient complaints seriously.
2. Rule out any serious concomitant medical disorder.
3. Rule out serious drug-related adverse experiences as evidenced by, e.g., yellow eyes, white stools, dark urine, or severe abdominal pain.
4. Ask about recency of any alcohol or drug use. Rule out alcohol, opiate, or other drug use and/or withdrawal as contributors to presenting complaints. Refer to Appendix C-8 of the MM manual for patient instructions on managing side effects.
5. Ascertain what strategies the patient has used to manage the presenting symptom(s) and the degree of relief obtained, if any.
6. Provide reassurance that adverse drug experiences tend to be transient and resolve within 12 - 72 hours.
7. Note that hydroxyzine (Vistaril) is used as a treatment for a number of the side effects that patients may experience. Hydroxyzine can be prescribed for a maximum of 10 days dosage. If Vistaril is discontinued and side effects continue, Vistaril can be prescribed again. However, the patient must be off Vistaril for at least three days before taking it again.
8. In general, the first step in dealing with adverse experiences should be either taking an over the counter medication such as Pepto Bismol® (for GI side effects) or acetaminophen (e.g., for headache) and/or adjusting the time of the dosing (e.g., taking naltrexone at night) and/or taking the medication with meals. If this is unsuccessful or insufficient, the second step should be the dose reduction strategy as detailed under "Procedure for Reducing Dosage." The third step, if necessary, should be the use of prescription medication, i.e., hydroxyzine, if appropriate.

Procedure for Reducing Dosage
1. Tell the patient that you will be reducing the dose of one medication initially, and if this is not sufficient, you will reduce the dose of the other medication.
2. Ask the patient to take only one acamprosate in the morning and one in the afternoon, rather than taking two in the morning and two at noon.
3. Call the patient three days after making the dose reduction. If the patient is doing better, have the patient stay with this dosage regimen. If the patient is still symptomatic, tell the patient to take only one naltrexone in the morning rather than two. If the patient cannot be maintained on the 50 mg dose of naltrexone, the dose can be reduced to 25 mg. Instruct the patient to break one of the naltrexone pills in half.
4. At the next MM visit, encourage the patient to increase the medication dosage, using your clinical judgment as to whether the patient would agree to this. If the patient agrees, the patient should first increase the naltrexone dose. If the patient is able to tolerate it, he or she should then increase the acamprosate dose three days later. If the patient is unable to tolerate the second dose increase, the patient should be told to go back to the reduced dose level.

Note, the naltrexone dose can be reduced prior to the acamprosate dose if bilirubin levels increase by 50% over baseline values but still remain within the normal range, rather than run the risk that the bilirubin will continue to rise and meet the threshold for withdrawal from the study medications altogether. If, after reducing the naltrexone dosage, the patient cannot be maintained on the 50 mg dose, the dosage can be reduced to 25 mg. However, if the patient cannot tolerate the 25 mg dose of naltrexone, all study medications must be discontinued.
Although the dosage reduction procedure is described in detail for nausea and vomiting, the same procedure would apply to other side effects, i.e., diarrhea, dizziness, nervousness, anxiety, insomnia.

**Procedure for Retitratation**

Subjects who have been off study medication for four or more weeks may be retitrated at the discretion of the physician. Subjects who have been off study medication for less than four weeks likely do not need retitratation, but retitratation could be used.

If retitratation is used, the patient would be instructed to take 50mg of naltrexone (1 pill) for 2 days, and then resume 100 mg of naltrexone a day (acamprosate will not be titrated). This will occur at the discretion of the study physician. If a patient did not experience side effects while taking the study medication previously, the physician may decide not to retitrat. If the patient is not tolerating the study medication, s/he could be retitrated on 25mg of naltrexone (half of a pill) at the discretion of the study physician.

**Nausea**

(a.) Suggest that the patient take Pepto-Bismol® if he/she has not already done so. If this does not work in 1-2 days, proceed to (b.)

(b.) Reduce the dose of study medication as per “Dosage Reduction Protocol”.

(c.) If (b.) is not successful and the patient continues to experience nausea for 3 days after the doses of both medications have been reduced, offer a prescription of hydroxyzine pamoate (Vistaril) 25 mg to 50 mg after checking for allergies; instruct the patient to take Vistaril 30 minutes before taking the next dose of the study medication. Patients can take up to 50 mg of Vistaril per day; this can be given either all in the am, all in the pm, or half in the am and half in the pm. Some patients will do better taking the Vistaril in the am because they may experience more nausea in the am. However, Vistaril can be sedating in some individuals, so these two considerations should be balanced in deciding about the timing of the Vistaril dosing. **Please remember to include on the Concurrent Medication form if you have prescribed Vistaril.**

(d.) If (a)-(c) are not successful, hold all doses of study medication, and proceed with steps under vomiting.

**Vomiting**

(a.) Discontinue study medication until the patient is no longer nauseous.

(b.) When the patient has a morning with no nausea prescribe Vistaril 25mg or 50mg, to be taken 30 minutes prior to the morning dose of study medication (see above for further details about Vistaril dosing), after checking allergies.

(c.) When the patient resumes taking the medication, the patient should initially take only 1 acamprosate in the morning and 1 in the afternoon (rather than two in the morning and two in the afternoon). Moreover, the patient should take only 1 naltrexone in the morning rather than two. If the patient is able to tolerate this reduced dosage for three days, encourage the person to return to the full medication regimen, using your clinical judgment as to whether the patient would agree to this. If the patient agrees to try to return to the full dose, the patient should first increase the naltrexone dose. If the patient is then able to tolerate it, he or she should then increase the acamprosate dose three days later. If the patient is unable to tolerate the dose increase, the patient should be told to go back to the reduced dosage level.

**Dizziness, Nervousness, Anxiety, Insomnia**

(a.) Follow instructions for dose reduction. If this is not sufficient, prescribe Vistaril 25mg or 50mg.

**Headaches**

(a) Recommend over the counter medications such as aspirin, acetaminophen or ibuprofin.
**Dermatologic Symptoms**

a) Localized rash or pruritis, no intervention required and other etiology to be explored.

b) Generalized erythema and/or macular or maculopapular rash and/or pruritis, without other etiologic explanation:
   1) Discontinue vitamin B supplements;
   2) Symptomatic treatment with oral antihistamines (e.g., hydroxyzine hydrochloride [Atarax®], 25 mg t.i.d.) and topical corticosteroids (e.g., triamcinolone acetonide cream) for up to one week:
      (i) If rash/pruritis improves or disappears, study drug may be continued;
      (ii) If rash/pruritis worsens, study drug is to be discontinued (code as Adverse Experience on SAFTEE) and refer participant to dermatologist for evaluation and possible biopsy. (NOTE: Written report of such a consultation must be incorporated into CRF).

c) If rash is atypical (i.e., other than maculopapular) or if rash is urticarial or if there is mucous membrane involvement, in the absence of another etiologic explanation, study drug is to be discontinued (code as Adverse Experience on SAFTEE) and refer participant to dermatologist for evaluation and possible biopsy. (NOTE: Written report of such a consultation must be incorporated into CRF).
Appendix B: Allowed and Disallowed Concomitant Medications

Drugs not allowed as concomitant medications

- Cis-retinoic acid (Accutane®)
- Alphamethyl Dopa (Aldomet®)
- Anorexics (e.g., over the counter, amphetamines, phenylpropanolamine, Dexatrim®)
- Antiarrhythmics: e.g., quinidine; digoxin (Lanoxin®); disopyramide (Norpace®)
- Anticoagulants: e.g., coumadin (Warfarin®)
- Anticonvulsants: e.g., valproic acid (Depakote®); gabapentin (Neurontin®); phenytoin(Dilantin®); carbamazepine (Tegretol®)
- Antidepressants: e.g., fluoxetine (Prozac®); sertraline (Zoloft®); paroxetine (Paxil®); trazodone (Desyrl®); desipramine (Norpramin®)
- Antipsychotics: e.g., haloperidol (Haldol®); risperidone (Risperdal®); olanzepine (Zyprexa®); fluphenazine (Prolixin®); perphenazine (Trilifon®)
- Antiretrovirals (Combivir, Epivir, Norvir, Retrovir)
- Buprenorphine (Buprenex®)
- Bupropion (e.g., Wellbutrin®, Zyban®)
- Buspirone (Buspar®)
- Chemotherapeutic agents for cancer
- Cholestyramine
- Disulfiram (Antabuse®)
- Duradrin
- Flexeril
- Herbal supplements with GABA properties (e.g., Kava, GABA or DHEA) or antidepressant properties (e.g., St. John’s Wort, L-Tryptophan or 5-HTP).
- Herbal supplements containing ephedra
- Methotrexate
- Monoamine oxidase inhibitors: e.g., pheneleazine (Nardil®); tranylcypromine (Parnate®)
- Mood stabilizers: e.g., lithium (Eskalith®, Lithobid®)
- Opioid analgesics: e.g., morphine, codeine, oxycodone (Percodan®, Percocet®); hydrocodone (Vicodan); propoxyphene (Darvon); tramadol (Ultram®)
- Ondansetron (Zofran®)
- Oral corticosteroids (e.g., prednisone; dexamethasone)
- Psychostimulants: e.g., amphetamines (Dexadrine®); methylphenidate (Ritalin®)
- Reserpine
- Robaxin
- Sedatives (antihistamines are ok) e.g., barbiturates; benzodiazepines; hypnotics (Ambien®)
Drugs allowed as concomitant medications

- Acyclovir
- Allopurinol
- Antiasthma agents (e.g., inhalers, B-agonists, theophylline)
- Antibiotics
- Anti-inflammatory drugs: e.g., aspirin; ibuprofen (Motrin®, Advil®), naproxen (Naprosyn®, Aleve®)
- Aspirin (81 mg/day regimen for cardiac disease)
- Colchicine
- Inhaled steroids
- Lipitor: permitted if on a stable dose (3 months). Lipitor should not be started and the dose should not be changed during the trial.
- Melatonin
- Nicotine replacement therapy: e.g., gum, inhaler or patch (No Zyban®)
- Proton pump inhibitors (pantoprazole)
- Sildenafil

Drugs allowed as concomitant medications for chronic use only (consistent use for 1 month prior to randomization and dose stabilized, or if the medication is started post-randomization)

- Antianginal agents: nitrates
- Antihypertensives: e.g., doxazosin (Cardura®); terazosin (Hytrin®); Tenormin®; diltiazem (Cardizem®); lisinopril (Zestril®), enalapril (Vasotec®); metoprolol Lopressor®
- Calcium channel blockers; e.g., nifedipine; verapamil; nimodipine
- Clonidine (Catapres®)
- Diuretics: e.g., hydrochlorothiazide(Diuril®; Dyazide®), spironolactone (Aldactone®)
- H2 Blockers; e.g., ranitidine (Zantac®) (No cimetidine)
- Hormones and oral contraceptives: e.g., estrogen (Premarin®); progesterone
- Insulin
- Oral hypoglycemic agents
- Thyroid supplements

Drugs allowed as concomitant medications for episodic use only

- Analgesics, non-narcotic: e.g., aspirin, acetaminophen (Tylenol®); ibuprofen (Motrin®, Advil®)
- Antacids: e.g., magnesium hydroxide-aluminum hydroxide (Maalox®, Mylanta®), calcium (Tums®)
- Antidiarrheal preparations (No opioid-based, e.g., Imodium® or Lomotil®)
- Antihistamines: e.g., diphenhydramine (Benadryl®); hydroxyzine (Vistaril®); Claritin®, cetirizine (Zyrtec®)
- Antimigraine: (Imitrex®; no Fiorinal®)
- Antinausea agents
• Cough/cold preparations (non-narcotic cough suppressants)
• Laxatives

Clinical Care Committee: Overview

General: The Clinical Care Committee is established to assist study sites in determining whether a subject should be discontinued from either taking study medication or from study participation. The Clinical Care Committee is an advisory committee—it does not make decisions that would alter protocol design but seeks to interpret how best to manage subjects within protocol guidelines. General questions about the protocol, study design, behavioral therapies, or medication will be directed to an Operations Committee representative.

Flow of Communication: All queries concerning whether a subject should stay on medication or stay in the trial will first be directed to the Coordinating Center. The Coordinating Center will provide triage and determine whether queries should be forwarded to the Clinical Care Committee or to the appropriate Operations Committee representative. Medical related questions will be directed to the appropriate M.D. site representative and non-medical questions will be directed to the appropriate Ph.D. site representative. Dr. Swift will be available for consultation to Clinical Care Committee site members as needed.

Documentation: The Coordinating Center will maintain a record of queries from sites. In those instances where a subject is discontinued from medication or from the trial the Inactive Status form will be completed and forwarded to the Coordinating Center. A Serious Adverse Event form may also need to be completed.

Committee Membership: Clinical Care Committee members will consist of physicians and other doctoral level scientists and clinicians who are actively involved in Project Combine. It is recommended that at least one member of the Operations Committee be assigned to the Clinical Care Committee. Two members of the Clinical Care Committee, one M.D. and one Ph.D., will be assigned to each treatment site and will have primary responsibility for addressing queries from that site. No member will be assigned to their own treatment site.
Appendix C: Clinical Care Committee

Guidelines for Discontinuation of Subjects from Study Treatment
For reasons of ecological validity, guidelines for discontinuation of subjects from study treatment will be somewhat flexible. Given the duration of the treatment period (sixteen weeks), there will be greater opportunity to resolve clinical problems that might otherwise be more difficult to address in a briefer intervention period (i.e., less than three months). Consequently, drinking and drug use that might require detoxification, or inpatient/partial hospitalization during the 16-week study period should not routinely constitute grounds for removal of subjects from the protocol. However, subjects who are incarcerated for criminal activity will be discontinued from the study during their incarceration. Decisions concerning the withdrawal of hospitalized or incarcerated clients from study treatment will be made on a case-by-case basis and in general, every effort will be made to safely manage subjects in the protocol.

Since this is an intention-to-treat study, individuals will not be required to complete a finite number of sessions or adhere to the medication regime (after random assignment) to be considered a participant in the protocol. Within this context, individuals failing to appear for scheduled appointments, those refusing medication, or evidencing other compliance problems (e.g., failing to return blister pack) will be allowed to remain in the clinical protocol. Subjects who have been absent from the protocol for four or more weeks will need to be rescreened prior to going back on study medication. Full laboratory tests will be performed including a urine drug screen and a pregnancy test. These matters will be addressed by therapists/counselors utilizing procedures and strategies developed in the MM and CBI manuals and clinical supervision.

However, it is anticipated that there will be some cases that cannot be safely managed in the clinical protocol. These cases include, but are not limited to, the following categories:

1. Acute psychosis (hallucinations, impaired reality testing, paranoid ideation, etc.) requiring medication and/or hospitalization or intensive outpatient intervention;
2. Suicidal or homicidal ideation that results in a credible threat of violence directed at oneself or others.
3. Hospitalization for psychiatric symptoms

Subjects requiring more intensive treatment resulting from acute psychosis or suicidal/homicidal behavior will be referred to local treatment centers, but will not be provided with medication or psychotherapy by study staff. It should be noted that these guidelines are meant for non-emergency situations. It is expected that the local clinical staff will deal with emergency situations. In cases where it is unclear whether the subject should be discontinued from study treatment, e.g. transient suicidal ideation in the context of acute intoxication, sites are encouraged to contact a Clinical Care Committee representative for consultation. Subjects will be permitted one medical detoxification and still be allowed to continue in the study. Subjects who are started on antidepressants or other psychotropics will be discontinued from study medication but will be allowed to continue in the protocol. The PI and the Coordinating Center must be notified in all cases involving the removal of subjects from the protocol or from taking medication.
Guidelines for Discontinuing Study Medications

♦ Pregnancy. Subjects who become pregnant during the course of the treatment will be discontinued from the study medication.

♦ Elevated liver enzymes. Individuals whose ALT/AST is greater than 5X normal will need to have ALT/AST repeated within 1-2 weeks and if still greater than 5X normal the subject’s medication will be stopped. If the repeat values are less than 5X normal but still elevated, the subject should be monitored using clinical judgment. Individuals whose total bilirubin is above 50% baseline level but within the normal range will be evaluated by a study physician to determine whether study medication should be discontinued. Procedures for reducing the dosage is outlined in Appendix A2. Individuals whose total bilirubin is greater than 10% above ULN will be taken off the study medication immediately.

♦ Renal insufficiency. Individuals whose serum creatinine level is 1.3 or 1.4 will be evaluated by study physician to ascertain whether study medication should be discontinued. However, a creatinine cut-off of 1.5 should be cause for removal from the study medication.

♦ Opioid medication. The study medication will be stopped if an individual needs opioid medication while participating in the study. There will be a 10-day delay after the last dose of opioid medication before the study medication is restarted (There will be an exception if the individual has been on methadone). Before the study medication is reintroduced the individual will need to produce a negative urine. The study medication may need to be retitrated when it is restarted. Retitration will occur according to the instructions provided in the Medical Management Treatment Manual. Also, the individual will need to be warned about not resuming opioid medication while on the study medication and the risks of having a severe withdrawal if they were to take naltrexone while taking opiates.

♦ Physical illness. Subjects will need to be removed from medication if they have a disabling condition that precludes them from taking the study medication. The MM clinician is responsible for referring the individual to a physician if a previously untreated or new medical problem is identified during the MM sessions.

♦ Psychotropic Medications. Subjects who require psychotropic medication will be discontinued from study medication. Subjects may receive one medical detoxification and remain on study medication. Subjects may receive hydroxyzine (Vistaril®) for anxiety, nausea, dizziness, nervousness or insomnia, as outlined in the MM Treatment Manual, and remain on study medication.

The decision about whether to discontinue a subject temporarily or permanently from the study medications will be made by local medical management staff. Subjects who improve to the degree that their illness or other reason for withdrawing from the medication resolves, and who have no medical contraindication for being rechallenged with study medication, will be encouraged to resume the medication by study staff. Study medication may be retitrated in subjects at the discretion of the treating physician according to the MM Treatment Manual recommendations, but it is suggested that subjects who have been off medication for less than four weeks not be retitrated.

All subjects must be managed clinically. This means that individuals who suffer adverse experiences related to the study medication will be referred to the local medical management staff. The medical staff will utilize guidelines included in the MM manual related to handling adverse effects of study medications and concomitant medications (see Appendices A1, A2 and B for list of procedures to be
employed in managing side effects.) The medical staff may reduce study drug dose and/or provide prescriptions or over-the-counter medications to reduce symptoms as outlined in the MM Treatment Manual. If this is not successful, study drug medication may be held completely until the physician believes study medication can be restarted.

**Clinical Care Subcommittee**

For purposes of quality assurance and monitoring of clinical care, a Clinical Care Committee will be formed and two members of the Committee, to include one M.D. and one Ph.D., will be assigned to each site. In most cases, staff will draw upon procedures in the MM and CBI manuals along with clinical supervision for managing clients in the clinical protocol. Consultation may be requested from the Clinical Care Committee if further assistance is necessary. A site will need to contact the Coordinating Center to initiate a consultation. The Committee will review cases of clinical deterioration and provide guidance when it is unclear whether clients could be managed within the COMBINE protocol or should be withdrawn from the clinical arm of the study and referred for more intensive intervention. This is expected to promote the consistency of application of trial-wide criteria for retention (or removal) of subjects in the clinical arm of the trial. However, the final decision to remove deteriorated subjects from the treatment arm will be made at each site by a joint decision of the project coordinator, therapist and principal investigator. Reports of withdrawals due to clinical deterioration will be forwarded to the Coordinating Center for review of consistency and frequency of, and reason for, removal across sites and treatments. These data will be compiled and forwarded regularly to the data monitoring board for ongoing review of safety of the trial and study treatments. Clients who are removed from the clinical protocol will remain in the research sample and will be followed up and included in the analyses.

**Implementation**

**Goals.** The overall goal of the Committee is to safely manage subjects in the clinical protocol. Another purpose is to attend to issues involving subject removal and possible reintroduction to the study medications. In addition, the Committee will provide consultation dealing with the removal of deteriorated subjects. This will entail (1) further defining and operationalizing adverse consequences occurring during the course of treatment that would constitute cause for removal of subjects from the treatment protocol (2) providing consultation in determining whether or not a client can be managed within the assigned COMBINE treatment (3) assisting the CRUs in safely managing subjects in the clinical protocol and (4) assisting in dealing with the withdrawal of subjects from the protocol if deemed necessary.

**Procedures.** In most instances the decision about whether or not to retain an individual in the protocol treatment can, and will be made by the PIs/PC and therapist based upon case material. In "gray areas", the Clinical Care Committee will be consulted. The first task is to evaluate the behaviors that constitute cause for removal from the treatment protocol (e.g., impairment of mental health) and the potential risks of maintaining the subject in a COMBINE treatment. The second is to assist PIs/PCs and therapists in developing a plan for stabilizing the client so that he or she can remain in the study treatments. The third is to assist in the handling of the removal of subjects from the study and providing recommendations for appropriate levels of treatment.

Two members of the Clinical Care Committee will be assigned to a CRU(s) to act as consultants in decisions involving the retention of subjects. The PC will contact the Coordinating Center to determine the appropriate representative to review a case and to make recommendations about whether an individual should be maintained in the clinical protocol. If there appears to be a consensus about the appropriateness of the client, a plan will be developed for stabilizing the condition of the client so that he or she can remain in the protocol. Committee members will
determine whether the issue can be resolved with the parties involved or whether the case warrants a conference call with the full Committee, a representative of the Operations Committee, the PI/Co-PI/PC and therapist of the local CRU. The final decision about retention will be made jointly by the local PI/Co-PI/PC and therapist after consultation.