DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DRUG ABUSE ADVISORY COMMITTEE

DESIGNING CLINICAL TRIALS FOR DRUGS

TO TREAT ALCOHOL USE DISORDERS

OPEN SESSION

Tuesday, April 20, 1999

8:40 a.m.

CDER/ACS Conference Room
5630 Fishers Lane
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C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. STRAIN: I am Eric Strain. I am the Chairman of the Drug Abuse Advisory Committee. I would like to call this meeting to order and begin by asking members of the committee and consultants and visitors to introduce themselves. Maybe we could start with Dr. Somers.

Introduction of Committee

DR. TEMPLETON-SOMERS: I am Karen Somers. I am the Executive Secretary to the committee, FDA.

DR. LLOYD: I am Llyn Lloyd, Executive Director of the Arizona State Board of Pharmacy, a member of the committee.

MS. YAROMA: I am Delores Yaroma, registered nurse, Second Genesis, Long-term Alcohol and Drug Treatment.

DR. JARVIK: I am Murray Jarvik. I am Professor of Psychiatry at UCLA.

DR. SIMPSON: I am Pippa Simpson. I am Director of Biostatistics at the Children's Hospital Arkansas.

DR. ANDORN: I am Anne Andorn, Professor and Chairman of Psychiatry at University of North Texas Health Science Center.

DR. McCORMICK: Cynthia McCormick, Director of Anesthetics, Critical Care, and Addiction Products, FDA.

DR. WINCHELL: Celia Winchell, Medical Team Leader

for Addiction Drug Products at FDA.

DR. LONGMIRE: Jack Longmire, Medical Review Officer, FDA.

DR. WANG: Sue-Jane Wang, FDA statistician.

DR. O'MALLEY: I am Stephanie O'Malley, Associate Professor of Psychiatry at Yale University, School of Medicine.

DR. MASON: Barbara Mason, University of Miami, School of Medicine.

DR. KRANZLER: Henry Kranzler, Department of Psychiatry, University of Connecticut Health Center.

DR. FULLER: Richard Fuller. I am at the National Institute of Alcohol Abuse and Alcoholism.

DR. de WIT: I am Harriet de Wit from the University of Chicago.

DR. FRANKLIN: I am John Franklin, Associate Professor at Northwestern University.

MS. FALKOWSKI: I am Carol Falkowski from the Research Department at Hazelden Foundation in Center City, Minnesota.

DR. STRAIN: I am Eric Strain from Johns Hopkins in Baltimore.

Next, I would like Dr. Somers to read the conflict of interest statement.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Henry Kranzler would like to disclose for the record that Dupont Pharmaceuticals is providing medication for a study of early problem drinkers. Dr. Stephanie O'Malley reports that she is a principal investigator in a naltrexone trial. Dr. O'Malley has also served as a speaker for Dupont Pharmaceuticals.

In addition, Dr. Barbara Mason reports that she serves as a principal investigator on NIH-funded trials. Dupont Pharmaceuticals is providing the medication and matched placebo under study for these trials.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvements with any firm whose products they may wish to comment upon.

Thank you.

Public Hearing

DR. STRAIN: For the open public hearing, we have one speaker, Dr. Raymond Anton from the Medical University of South Carolina, and a letter from the Hazelden Foundation.

We will begin with Dr. Anton.

DR. ANTON: Thank you, Dr. Strain. I appreciate the opportunity to be here to talk to this esteemed group of experts, both the standing committee and also the consultants, a number of whom have been colleagues of mine throughout the years.

As part of the conflict of interest statement, I should say that I also have received medication and do receive medication from Dupont Pharmaceuticals to understand the use of naltrexone, and some of the data I will be presenting today will be coming from a trial that was

supported by NIAAA and Dupont's sharing of medication.

I am also on a speaker bureau for Dupont. In addition, my travel today has been supported by Contral Pharma, a company that is interested in products for alcoholism pharmacotherapy.

I wanted to take this opportunity and really do appreciate the opportunity to be here to share with the committee some thoughts that I have regarding the development of medications to treat alcoholism.

I am a Professor of Psychiatry at the Medical University of South Carolina, and I am director of the Center for Drug and Alcohol Programs there and co-scientific director of our alcohol center funded by NIAAA.

[Slide.]

Before I get into some substantive material, I wanted to establish my level of expertise. I have been involved with alcoholism pharmacotherapy trials for approximately 12 to 15 years.

This is a partial list of the trials that I have been involved with including collaborative trials supported by the VA, a study in lithium. You can see the rest of the trials. A number of the trials are in alcohol withdrawal, but I have also been involved with trials involved with the prevention of relapse and the treatment of dual diagnosis individuals.

In addition, I have been part of the Project MATCH NIAAA cooperative study that didn't involve medication, but involved three types of well-structured psychosocial interventions to treat alcoholism.

Today, I will be talking to you about data as an example from the naltrexone and cognitive behavior therapy trial, which was completed last year, and is currently in the last stages of review for publication.

[Slide.]

This is a continuing list of trials that either I have been involved with or ongoing. The last trial on this list is a trial which the committee will hear about in closed session this afternoon, I believe.

[Slide.]

In your handout, you will have the same information that I will be presenting on the slides, and I hope to take about maybe 10 or 15 minutes of your time to go through this quickly.

I may be wrong, but I perceive this as a pivotal time for the United States and for the FDA in particular for my colleagues who have been involved with research in this area for many years.

There is a growing interest in the pharmaceutical industry for the development of compounds to treat alcoholism, and I think we need to personally embrace this

development to understand it and to use what we have learned to improve the quality of trials, and to give all of the benefit of finding efficacious compounds to act either by themselves or cojointly with psychosocial interventions to treat this incredibly devastating illness of alcoholism.

[Slide.]

These are the key issues that I think need to be attended to in trials of alcohol pharmacotherapy. I apologize to some of my colleagues who know this data quite well and have their own data to add to this, and I think it is important to have a number of different perspectives.

Population and study retention is quite crucial to not only the treatment of alcoholism, but every medical disorder.

[Slide.]

This is a metric that I devised that I think should help and people should keep in mind in designing trials. My experience over the years in participating in a number of trials is that it is much easier to make a Type II error in this field than to make a Type I error.

In fact, most of the studies in the pharmacotherapy of alcoholism have been negative except for the few studies in naltrexone in this country and a number of studies of acamprosate in Europe, but in general, one can make a Type II error in two different directions.

On the bottom here you can see a list of variables, such as if the person is severe or chronic versus mild or early alcoholism, and there is a range of alcohol dependence. Not everybody is severe. Although many of the people seen in medical situations are quite severe, there are a number of mild or more moderate types of alcohol-dependent individuals in our overall community, in our businesses, in our health care professions, and our churches around the country, and these people far outnumber the number of severe people that we see in medical settings.

Socially unstable versus socially stable, concomitant psychopathology, such as depression and anxiety disorders, no psychopathology, and whether a person receives any sort of psychosocial ancillary therapy or not could determine whether one makes a Type II error in the trial.

If somebody is chronically severe, socially unstable, has concomitant psychopathology, and you don't give any other psychosocial therapy, it is very likely that you are not going to see a medication work because of the dropout rate, lack of compliance, or perhaps the powerfulness of the medication. So, you can have a Type II error rate here.

If somebody is not severe enough, too socially stable, has no concomitant psychopathology, and you give them very intensive ancillary therapy, you might make a Type

II error on the other side of the equation.

So, generally, we like to try to shoot for this middle ground here where the Type II error rate is low. So, it is the idea of matching the type of ancillary therapy with the patient characteristics, which turns out to be a little bit more of an art than a science.

As more studies are published, we can fill in the points along this continuum and have a better idea of where we should be.

[Slide.]

Now, here is another metric that might be useful. In my mind, these two issues of the level of severity of the alcohol dependence and the motivation of the individual to do something about it interact.

If you just bear with this a minute, if severity is going up in this direction, and motivation is going up in this direction, that there should be some area up in here where the level of severity matches the level of motivation, and in general, the medication-placebo difference or the effect size that one would find in trials can be maximized by trying to get the right level of motivation match with the level of severity, and in particular to the matching with the appropriate type of ancillary therapy.

Obviously, the more severe an individual, the more ancillary therapy or psychosocial therapy is needed to

retain somebody in the trial to allow for greater compliance and potentially see a medication effect.

On the other hand, if somebody is not so severe and not so motivated, you still might be able to find a difference, but if you are very motivated and not very severe, you might have a Type II similar to what I suggested on the last slide, because people will get better and respond to placebo.

So, the idea is to try to use whatever skill is available communally to try to figure out what type of individual should be placed in the trial.

Now, there is a corollary of this in that at this stage of development I would urge the committee not to expect overwhelming success of the medications that are being developed across the broad band of alcohol dependence, that it may not be that we can prove that these medications are useful for the most severe individuals or that the generalizability of the medications to all levels of psychopathology, concomitant substance abuse, et cetera, should be attempted during the first trials, and there is a tendency I think for a society to want to be aggressive in that direction, to try to treat everybody as generally as possible, but in order to prove the efficacy of the pharmacology, that one might have to be restrictive during the initial trials.

[Slide.]

In order to show you some data, this actually came from a buspirone trial in anxious alcoholics that we published some years ago, and basically this shows that if you take number of prior treatments as a surrogate for severity, that study retention, almost similar to a pharmacologic dose type of pattern, seems to decrease depending on how many prior treatments one has.

This was a 26-week trial, and you can see that people that had no prior treatments stayed in the trial for about 40 weeks, where people that had two or more treatments had about half as much retention in the trial.

This again bespeaks to the interaction between severity, compliance, and retention, and the ability to not make a Type II error, and, in fact give a medication as much chance as possible to show its pharmacologic effectiveness.

Now, if one thinks about medication compliance for a minute, and all of substance abuse and alcoholism is no different, compliance is crucial to determining whether a medication has efficacy.

It is sort of like in real estate where location, location, location is important, and alcoholism and substance abuse is compliance, compliance, compliance, so we need to do everything to enhance the compliance of individuals in the trial in order to minimize the Type II

error rate.

[Slide.]

Now, to exemplify this, this is some data from the naltrexone and cognitive behavior trial, double-blind trial that we recently completed. We used riboflavin as a marker, and in an attempt to look at compliance of riboflavin as a marker versus pill counts, we counted the number of people that were 75 percent compliant with pill counts over the course of the trial, and people that were 75 percent compliant by urinary riboflavin measurements of at least 1,500 micrograms per milliliter.

You can see here the agreement scores between people that were complaint and non-compliant with medication based on pill count or urinary riboflavin.

First of all, you can see that the agreement, which would be these two boxes here, is approximately 73 percent, and there is a 27 percent disagreement rate, which would be going in that direction.

Several things are evident about this, is that, first of all, you can expect a significant rate of noncompliance in the trial, and these people were very highly motivated, no previous treatment, mild to moderately dependent, outpatient alcoholics, so these people would be deemed, I think, as being some of the more compliant individuals and they were getting a solid psychosocial

intervention.

So, generally, one can expect possibly on the order of 30 to 40 percent non-medication compliance over a 12-week trial.

Data from our cooperative lithium and alcohol trial done in the VA a number of years ago suggested that if you go out to six month, based on lithium levels, that the lithium levels drop markedly between three months and six months, suggesting that compliance diminishes over time, which would not be unexpected and concordant with other medication trials in other medical conditions.

[Slide.]

Finally, I want to mention something about outcome measurement in just two slides. I am not going to talk about ancillary outcome measurements, such as craving, psychosocial improvement, et cetera.

I think it is very germane for this committee to focus on drinking data as the primary outcome measure, and until proven otherwise, it is likely to be the primary outcome measure that is important, not to denigrate the other potential outcomes measures, such as craving and psychosocial intervention.

[Slide.]

This is the data from our naltrexone trial. It looks very similar in many ways to the data published by the

Penn group and by Dr. O'Malley, one of the consultants today from Yale. This is the naltrexone-treated people and the placebo-treated people.

Now, all of these people got concomitant and cognitive behavior therapy, so they were randomized to naltrexone and placebo. You will see in your packet there is actually a line here a day 84. That distinguishes the during treatment period and the posttreatment period.

Several points I wanted to make about this. First of all, this data replicates, at least if you look at the placebo line, data sets that have occurred in many other conditions, both psychosocial conditions such as Project MATCH, or in other pharmacotherapy conditions, that this sort of survival relapse always looks like this in the sense that within the first 90 days of treatment -- and it is interesting that Alcoholics Anonymous says 90 meetings in 90 days, I think there is a message there implicit in maybe how the brain adapts over 90 days -- but you can get as much information out of 90 days from a statistical point of view than if you can go out longer in treatment.

Now one might want to go longer in treatment because it is important to understand how people will do over the long term, but from a pharmacology point of view, I contend that you can get as much information at three months as you can at six months or at a year, and, if anything, you

get decreased compliance after three months, so you actually add noise in the pharmacology point of view.

So, I would urge the committee to consider three months' trials as an appropriate first step in understanding whether a medication has true efficacy or not. After that, it behooves people in a psychosocial community and all people treating addictive individuals to use whatever behavioral or psychosocial repertoires are at their command to encourage people to stay on medication longer and to interact with the behavioral interactions to show continued improvement.

This also shows that once naltrexone is stopped, which is right about here, that there is a general tendency for a convergence of the medication group and the placebo group, so the effect size is not as big here.

This is actually the p-value using the total data from baseline, and this is the p-value using just the within-treatment data showing that you lose some effectiveness once the medication is stopped, implying that some people need to take medication for a longer period of time, that the psychosocial intervention does not hold them past the end of the treatment trial.

[Slide.]

Finally, this is a new way of looking at the data, and this is using a piecewise random regression model. This

was done by a statistician that works with me, Jim Roberts. This is the same data from the same naltrexone trial looked at in a different way - mean number of heavy drinking days per study week of the trial.

This is basically using linear modeling type techniques and looking at individual slopes of progression of drinking, and you can see in the naltrexone group -- which is in the red -- the slope is relatively flat with maybe a slight upward bias, where in the placebo group you can see the slope or the progression of heavy drinking per week is rising steadily.

This line demarcates the end of the medication, and this is the follow-up period. So, one neat thing that one can do with this type of analysis is look at a group by slope difference during the treatment, and look at the change of slope between the treatment period and the follow-up period.

Basically, you can see here at least at trend level that there is actually a change in slope between the naltrexone and the placebo group. The placebo group almost look like they level out in their heavy drinking days per week, but once the medication is stopped in the medication group, there is a progression with the extension perhaps outwards at follow-up that these lines might actually intersect at sometime in the future, again implying that

there may be some individuals that need continued medication use and that cognitive behavior therapy may not be enough given during this period to hold people into the future.

I think future studies should examine that, but again I want to emphasize that one can get the type of pharmacologic data that ensures or could potentially prove efficacy during 12 weeks of treatment, and one does not have to go out further than that to see a drug minus placebo difference.

With that, I will stop. I appreciate the opportunity to address you all and to share some ideas that you might want to consider during your deliberations in this very important area.

Thank you.

DR. STRAIN: Thank you, Dr. Anton.

Are there any other speakers who wish to speak during the open public hearing?

[No response.]

DR. STRAIN: Let's go to then the letter from the Hazelden Foundation.

Before we do that, the final member of our committee has joined us. Dr. Meyer, would you like to introduce yourself.

DR. MEYER: Dr. Roger Meyer.

DR. STRAIN: Thank you.

DR. TEMPLETON-SOMERS: This is a letter from the Hazelden Foundation that was written by Patricia Owen, who is the Vice President of Research and Development.

They are suggesting a plan for clinical trials for drugs to treat alcohol use disorders. Patient samples should be representative of current patient populations treated in both public and private treatment programs in the U.S.

This treatment sample should be representative of the larger population based on gender, age, race, education, employment, comorbid psychiatric disorders, and alcohol/drug use severity/history.

It will be important to use a standardized diagnostic interview to accurately measure the level of alcohol use problem severity and to classify patients with alcohol abuse versus alcohol dependence. It is extremely important to differentiate between people who are dependent versus those who are simply abusers, as the outcome expectations for treatment are different.

An acceptable outcome for alcohol abuse treatment is reduced alcohol consumption to two or less drinks a day with improved quality of life. The goal for alcohol dependence treatment is continuous abstinence with improved quality of life.

Because alcohol dependence, as a disease, behaves

much as other diseases, complete lifetime remission may not be obtainable for all cases. For these cases, other measures should be used to reflect improvement in their clinical picture, such as length of time to first drink or survival analysis, length of longest abstinence, length of relapse. To a lesser extent, overall percent of abstinent days and drinks per drinking day are useful measures. These measures are less than ideal as they are generally reported for the sample as an aggregate, obscuring clinically significant variations in outcomes.

Outcome should be measured with reliable and valid outcome instruments designed for alcoholism treatment. In terms of comparing the results with other studies, it would be helpful to use comparable instruments as have been used in such important national studies as MATCH from the Project MATCH Research Group, and DATOS from Simpson & Curry, both in 1997.

Since alcoholism typically disrupts the patient's social and vocational functioning, treatment outcome is best measured by a multidimensional assessment system administered at pretreatment, posttreatment, and follow-up intervals.

Dimensions in this assessment battery should alcohol use problem severity, comorbid psychiatric disorders, vocational/educational functioning,

marital/family relations, criminal activity, peer and social relations, and health care utilization.

Some studies suffer from high attrition, which limits the generalizability of the results to the populations for which the treatment is intended. One goal of the research methods should be to reduce attrition both during the active treatment period and over the course of follow-up. A typical follow-up response rate goal is to obtain 90 percent of the sample at each follow-up assessment. This is a high standard, but it improves confidence in the results.

Statistical analysis should address both statistically significant and clinically significant change. Clinically significant change shows how many subjects improved, how many did not change, and how many deteriorated. Other types of statistical analyses have proven useful as well, such as survival analysis.

Some research subjects may participate in therapeutic services following the clinical trial and this needs to be noted since this may confound the results of the pharmacological agent when assessing over extended follow-up intervals such as a year.

An approach proposed by Jacobson and Truax looks at clinically significant change. Clients must demonstrate a change in behavior, such as test scores, where the client

moves from the clinical or dysfunctional range of behavior to the normative or functional range of behavior as measured on the standardized scale.

This approach allows for the examination of change in individual clients, and allows the researcher to identify who got better, who did not change, and who got worse. This type of treatment outcome methodology has the following advantages: (a) it measures change from pretreatment to posttreatment, which is superior to reporting posttreatment abstinence rates alone; and (b) it provides outcome results for individual clients.

To consider an outcome as successful, at a minimum, there needs to be a clinically significant reduction in alcohol consumption and alcohol-related problem severity, and improvement in social and vocational functioning. For subjects who are dependent on alcohol as opposed to abusers, treatment outcome is best reflected by continuous abstinence.

I am going to put both these slides from Dr. Anton's presentation and a copy of this letter at the desk outside the door to the conference room for anybody from the public who would like to have a closer look.

Thank you.

DR. STRAIN: Thank you, Dr. Somers.

That then ends the open public hearing portion of

the meeting, and we will next turn to a Welcome from Dr. McCormick.

Welcome

DR. McCORMICK: Thank you. Chairman Strain, advisers, distinguished guests, representatives of private industry, members of the public, and FDA staff, welcome to the April 20th meeting of the Drug Abuse Advisory Committee.

Unlike many FDA advisory committees which are primarily called in to assist in making recommendations about specific actions that are pending, for example, when an NDA is pending and there are specific efficacy or safety issues that a division is grappling with, this committee has frequently been asked to comment on overall approaches to studying addiction medications, recently nicotine and cocaine dependence, for example.

We have asked you to come today to advise the FDA on some of the important issues that have been brought before us in the Division of Anesthetics, Critical Care and Addiction Drug Products regarding the design of clinical trials for pharmacotherapies to treat alcohol disorders.

As we evaluate the armamentarium for treating alcohol disorders, we find that we have very little precedent to draw from, for there are fewer than a handful of drug products approved for the treatment of alcoholism.

Psychotherapy seems to have been the mainstay for

treatment, and the goals of psychotherapy, as one might expect, have probably influenced the design of clinical drug trials in terms of populations studied, the outcomes expected, and the duration of trials. The precedent has been to explore abstinence as an endpoint, to study drugs in known alcoholics, and trials have lasted several months.

Recently, a prospective sponsor brought us a proposal at a pre-IND meeting to evaluate a pharmacotherapy that they wished to study, not in recidivistic alcoholics, but rather in excessive users of alcohol with the emphasis on heavy users who are not yet severely dependent.

The treatment goal proposed was not complete cessation, but rather reduction in use. Because this approach was one that was somewhat inconsistent with what the agency's approach has been towards alcoholism and other addictions in the past, and because there has been so little precedent to draw from in this area, we proposed this meeting.

The sponsor will be presenting its protocol this afternoon in closed session.

During the morning session, we would like the committee and invited guests and ad-hoc members to consider what the precedents are in this field - that therapeutic endpoint can be achieved without medication, which we know it can under certain circumstances, is there even a role for

medication; if there is, what should the goal of that medication be.

The FDA staff and Dr. Fuller from the National Institute of Alcohol Abuse and Alcoholism will set the stage for what we know will be a very useful discussion about appropriate populations to study, clinical or laboratory endpoints, outcome measures, duration of treatment, and even statistical tools for analysis, that will then continue into the afternoon as we focus on a specific proposal.

It is our hope and our expectation that the discussions from this meeting will assist us in better evaluating the sponsor's approach.

I would now like to turn the FDA portion of this morning's meeting over to Dr. Celia Winchell, the team leader for Addiction Products. Before I do, however, I would like to recognize her effort in planning and organizing and researching this meeting, developing the briefing materials that you received, planning a list of consultants and questions that will guide your discussions and the agenda.

Dr. Winchell.

DR. STRAIN: Thank you, Dr. McCormick.

Introductory Remarks

DR. WINCHELL: We are very glad you are all here today because as Dr. McCormick mentioned, we have a

challenging problem which we cannot resolve without your help.

[Slide.]

We have had some interest from both academic and commercial researchers who would like to test both existing and experimental medications for the treatment of alcohol use disorders, but with an approach which departs from our experience.

Although the medications available for the treatment of alcohol problems have been tested in patients who meet criteria for alcohol dependence, people are interested in using these medications in non-dependent drinkers.

Some are interested in seeing whether heavy drinkers can reduce but not stop their drinking. We know that there has been research in the non-pharmacologic areas, looking at how non-dependent drinkers can be taught to moderate their drinking.

We are also aware of the long controversy over whether it is ever appropriate to advise who are alcohol dependent to attempt to moderate their drinking rather than to abstain.

We find ourselves with a conundrum - if alcohol dependent individuals should always be advised to abstain, then, a medication for alcohol reduction is not for them,

but if someone needs a medication to reduce his drinking, perhaps he is alcohol dependent. On the other hand, if we do not test a drug to see if it can help alcoholics moderate their drinking, we might miss finding a treatment that makes the impossible possible. We have brought you here today to grapple with these questions.

[Slide.]

In considering how to test a medication that will help drinkers reduce or moderate their drinking, we need to know the treatment goal, what the treatment should aim to do. We need to address defining the population, which drinkers should be studied and how we will identify them, and we need to talk about what results are clinically meaningful. This will help us know how to define success, which helps us choose our outcome measures and our analysis methods.

[Slide.]

Before we talk about such things as treatment goals and outcome measures, I want to define my terms. These are definitions included, so you can follow what I am talking about. You are welcome to use your own terms as long as you make sure we all know what you are talking about.

By "treatment goal," I mean the result we hope the therapy will accomplish - relief of pain, cure of cancer are

examples.

"Outcome measures" are what we do in a clinical trial to see if we are accomplishing the goal - visual analog scale, amount of rescue medication, tumor measurement.

A "success" definition is a clinically meaningful improvement we have decided in advance would be good enough for us to say that this is treatment works. We don't require pain-free patients in the treatment group. They just have to have less pain than the placebo group, and we have some idea in advance how much less we think would be significant. A cancer drug can be called effective if it reduces tumor burden.

Finally, "analysis methods" refers to how we look at the data we collect to see whether or not we have succeeded - do we average the pain scores or pick the highest one or calculate an area under the curve. There are many things you can do with the same collection of measurements. Ideally, the method is chosen to capture a clinically significant effect.

[Slide.]

The first question is the treatment goal. All previous studies of addiction treatments have had abstinence as the treatment goal, that is, all the ones that have come to FDA.

There have been many definitions of success that acknowledge that many people who attempt abstinence don't achieve it, but abstinence has always been the goal of treatment.

So, we ask: Is it ever appropriate to choose reduction of drinking as a treatment goal? We think we know the answer to this because we know that clinicians are instructed to advise people who drink too much, but aren't alcoholics, to reduce their drinking to low risk levels, but those aren't alcoholics.

We need to ask whether that treatment goal is appropriate only for non-alcoholic heavy drinkers or whether it might be acceptable to pursue a goal of reduction or moderation in people who might otherwise be counseled to abstain.

If there were a medication which could help alcoholics moderate their drinking, would we want to know about it or is abstinence such an important message that we should not do violence to it through promoting investigations of this type?

[Slide.]

Well, if we decide that the research should not be pursued, then, we can all go home, but assuming that that does not occur, we will need to decide whether there is a population that would be suitable candidates for a

pharmacotherapy that helps reduce or moderate heavy drinking.

One important issue here is that this is not a theoretical question. We need to be able to identify these people quite concretely. First, we need to ask whether there is a set of inclusion and exclusion criteria that could be used in clinical trials that would reliably identify people for whom attempting moderation or reduction is appropriate.

The criteria should reliably exclude people who might be harmed by a non-abstinence goal and should also exclude people who really don't need treatment because that would make it hard for the treatment to be placebo.

Moreover, we need to look ahead at how the drug will be used once it is marketed. Finding the right patient for the drug needs to be something a clinician can do easily, practically, and reliably, or the drug will be erroneously used both in people who should be advised to abstain and in people who should be attempting to reduce their drinking without pharmacotherapeutic intervention. Since no drug is benign, we do want to avoid giving medications to people who don't need them.

[Slide.]

There are many, many specific outcome measures of drinking behavior and consequences that can be used, but

before one chooses an instrument for measuring outcome, we should decide what is important to measure.

We need to address how we go about defining reduction or moderation of drinking - should comparisons be made to an individual baseline, should you or even can you try to collect baseline run-in data, or is a self-reported historical baseline acceptable, how much reduction is clinically meaningful, are we looking for some percentage change or is there a particular pattern of drinking behavior all subjects must achieve regardless of baseline behavior in order to be called successful, and what is that? Absence of heavy drinking days, low risk drinking levels? Or should we be looking at alcohol consumption levels alone or at all, or should we be looking at drinking consequences?

[Slide.]

Even if we can reach agreement on what to measure, we will need to discuss how to measure it. There are many different instruments available, such as those listed on this slide and many, many more published in a very thick book by the NIAAA.

There are various biological indicators of alcohol use that may be useful, such as hepatic enzymes, carbohydrate deficient transfer, and the utility of these measures varies depending on whether or not the so-called window they over actually looks out on the outcome we are

interested in.

There are also various measures of drinking behavior using self-report or interview, including the volume frequency approaches and the more detailed time line follow back method. Then, there are instruments that examine aspects of the drinking problem other than the level of consumption, such as the ASI and the Comprehensive Drinker Profile.

These instruments, and dozens of others, have been used in research and in treatment for some time. There is no regulatory standard here, like the HAM-D that is used in the development of antidepressants.

It will be helpful to try to get some guidance on which instruments will be most helpful in delineating clinically relevant changes that would demonstrate a drug's efficacy.

[Slide.]

Finally, we will need to discuss what we should do with the data once it is collected. Studies of medications for alcoholism often include a panoply of interrelated survival analyses, like time to first drink, time to first heavy drinking day, time to relapse, as well as analyses of how many patients did or did not drink during the trial.

Studies also look at cumulative abstinence time, percent days abstinent, drinks per drinking day, and so on.

It would be helpful if we could get some ideas about what analyses are most important. When confronted with various analyses producing mixed results, it is difficult to interpret a study. We would be very troubled if there were a drug that worked, but the analysis somehow failed to show it.

If a drug has an effect on how alcohol is experienced or on modifying the abstinence violation effect or on some other aspect of drinking behavior, it may not always make sense to expect a drug to delay the first drink or the first heavy drinking day, but we need to think about what it might do.

We also need to think about what clinical situations might be represented by various statistics. For example, a subject who drinks every weekend and a subject who abstains for five weeks and then drinks every day for two weeks have the same percent days abstinent and the same cumulative abstinence time.

A patient who drinks four times the first month, twice the second month, and once the third, has the same number of drinking days as the patient who spends the last week of the trial drunk - are they the same, which is preferable, and do we need to be able to distinguish among them?

[Slide.]

So, these are some of the issues we hope to resolve today.

To set the stage for these discussions, we will hear first from Dr. Richard Fuller. Dr. Fuller is the Director of the Division of Clinical and Prevention Research at the National Institute on Alcohol Abuse and Alcoholism. Prior to coming to NIAAA in 1988, he held faculty positions at Case Western and at the Cleveland VA.

During his distinguished career, Dr. Fuller has conducted research evaluating treatments for alcoholism and for alcohol-related diseases, and has devoted substantial attention to the methodologic issues in clinical trials and treatment outcome research in the field of alcohol abuse and alcoholism.

Dr. Fuller will give us an expert overview of alcoholism treatment research, describing the approaches that have been taken in previous clinical trials.

Then, Dr. Sue-Jane Wang, a statistician in our division, will review the analytic methods used in the clinical trials for Revia, and will describe some other techniques which can capture additional information.

Finally, Dr. Jack Longmire, primary medical officer in our division, will review the way moderation of alcohol drinking is handled in primary care because we think that primary care physicians would be major prescribers of a

drug for alcohol abuse of alcoholism.

Then, we hope to have a fruitful discussion that will help answer the questions that you have on the handout before you, as well as others that the speakers will raise.

Thank you.

DR. STRAIN: Thank you, Dr. Winchell.

Next, we will hear from Dr. Fuller, who will provide the Expert Overview.

Expert Overview

DR. FULLER: Thank you, and I want to thank Dr. Winchell for those very kind comments about myself.

I am somewhat embarrassed by the phrase "expert overview." I do consider myself an expert, but I am a big intimidated with several other experts that are here in the audience. However, that will be useful I think in the discussion session because any errors of omission or commission that I make, there will be a self-correcting process in the discussion.

Now, I was asked to speak on the definition of alcoholism. I am going to speak on the diagnosis and also on outcome variables that have been used in alcoholism treatment studies.

[Slide.]

In alcoholism treatment research, there is a considerable consistency at this point, and almost all

studies use the diagnostic criteria that are depicted on this slide that have been developed by the American Psychiatric Association. The American Psychiatric Association puts on a diagnostic manual, a diagnostic and statistical manual, the DSM, and this manual is now in its fourth edition, so the current version is the DSM-IV, and if you go through I think the last 15 years, the previous edition, the DSM-III(r) revised and the DSM-IV have been consistently used in alcoholism treatment research, so there is good consistency there, and it allows comparison among studies.

Now, these, if you will, are the symptoms for alcoholism or dependence in the DSM-IV. Tolerance refers to the ability in a sense to have to drink more to get a desired effect. Anecdotally, many alcoholics will report that they had more tolerance than their friends or peers early in their drinking careers when they began drinking.

From a more scientific viewpoint, Dr. Schuckit in San Diego has done interesting studies. He began by studying sons of alcoholics because there might be a genetic influence there, and he studied tolerance in these young men when they were in late adolescence.

He has followed them now for 10 or more years, and many of them have gone on to develop alcohol dependence or alcoholism. Those sons of alcoholics who exhibited

tolerance to the ingestion of alcohol were much more likely to become an alcoholic during the subsequent 10 years to meet some of these criteria than those who did not exhibit tolerance.

I should mention that you have to have three of these symptoms to be considered alcohol dependent, and while they are listed in this order, I don't believe they are listed in order of priority, and there is debate among those who are interested in this issue, which are the more important symptoms.

Withdrawal refers obviously to the alcohol withdrawal state which, in its mildest form, consists of tremulousness and nausea several hours after stopping the ingestion of drinking, and in its most severe form, consists of delirium tremens.

Now, impaired control, as it is listed in the DSM-IV, says that drinking more than intended or drinking longer than intended. While that is a true statement, it is not quite as vivid as what many alcoholics report, but once they begin drinking, they are just unable to stop their drinking, control their drinking until they are intoxicated, and there are some who consider this one of the most important symptoms.

Now, neglect of activities, of family, job, even giving up leisure activities that at one time were important

to the person is another symptom, and one's life begins to revolve around alcohol and excessive time is spent obtaining alcohol drinking and recovering from the effects. The alcoholic begins to devote time to planning to have a sufficient supply of alcohol at all times, and then lastly, continued drinking despite knowing that the drinking is causing either physical problems or psychological problems.

Now, these are the criteria for alcohol dependence or alcoholism in the DSM-IV. The definition for alcohol abuse is where alcohol is interfering with one's life, causing social problems, psychological problems, for example, legal problems or problems at work, but not meeting the criteria for alcoholism.

So, these criteria at least in alcoholism treatment research, I would contend have become standard.

Now, when it comes to criteria for measuring success of treatment in alcoholism treatment, I am going to present data I think which illustrates that there is no universally accepted definition of success in clinical trials of alcoholism, and this at times leads to difficulty comparing studies.

[Slide.]

Now, I want to distinguish that from the goal of treatment. In the United States, the goal of almost all treatment programs, I would say 98 percent of treatment

programs, is abstinence, and I think the goal for the treatment programs is based on the experience of many people that without abstinence, long-term recovery from alcoholism is unlikely.

I think this is analogous to smoking where abstinence from smoking is the goal. But when it comes to the research, there is no widely accepted definition of success or, the obverse, relapse.

[Slide.]

These are a list of variables that have been used to define success or, the obverse, relapse. I think over the past 20, 25 years, certainly abstinence has been the most commonly used variable, and I think this reflects the emphasis put on it in treatment programs. I am going to show some examples of most of these.

[Slide.]

This data is actually from a VA cooperative study of disulfiram or antabuse. This study was done in the early to mid-1980s, and people were treated for one year, and they were judged to be abstinent if they reported that they had not had a single drink, cohabiting relatives reported the same, and all alcohol specimens were negative, and there was a full-dose disulfiram group and two control groups. One received an ineffective dose and one did not receive disulfiram.

Now, the yellow bar shows the proportion of people that had sustained abstinence for one year, and this was a common way of presenting this data as a categorical measure. These are people who did not fulfill those criteria for sustained abstinence, and some people were lost to treatment, and approximately 7 to 9 percent it was not possible to make that determination.

[Slide.]

Another variation, this is a categorical measure, another variation of abstinence is time to first drink. Dr. Anton has already showed a survival curve, and survival curve analysis has become much more popular in alcoholism treatment research, and this shows the data from the same study showing time to first drink.

In that particular study, they also measured time to fifth drink and time to 10th drink, and did not find any significant difference among the three treatment groups.

Abstinence can be a very stringent criteria because depending on how it is defined, but as little as one drink can knock you from the category of success to the category of failure, and for that reason people have argued that it is masking improvement if that is the only variable or a variable that is being used.

[Slide.]

So, more recently, other variables have been used,

and the first I am going to discuss is the frequency of drinking.

[Slide.]

In that same disulfiram study, this was about half the men who did drink, a subset of them, and you can see that on drinking frequency, drinking days, there was a significant reduction in drinking days in those that received a full dose disulfiram dose compared to the two control groups.

I have always been, if you will, tickled by this slide, if that is the appropriate word, because the cohabiting relatives and friends of those that received a full dose disulfiram also reported a significant reduction in that group compared to the two control groups, but you will notice that consistently these individuals reported more drinking days, consistently and significantly more drinking days than did the patients.

I would say in the last five or six years, the obverse of drinking days has become the measure of drinking frequency, that is, the frequency of abstinent days, and I think that is appropriate because I think it gives a more, if you will, optimistic and I think realistic picture.

[Slide.]

This is data from Project MATCH. These were outpatients. Prior to treatment, they were drinking more

than 70 percent of the days in the three months prior to treatment, as depicted here, and then following three months of treatment, for one year, they were followed and drinking frequency was assessed, and you can see that the percent days abstinence was 80 percent compared to the pretreatment percent days abstinence of 30 percent.

[Slide.]

Next, I am going to give some examples of quantity of drinking and intensity of drinking.

[Slide.]

This is another disulfiram study that was done in Edinburgh, Scotland. In this study, unlike the first study, the patients were observed to be ingesting the antabuse. In the first study that I showed, people were given the disulfiram to take at their discretion.

One of the variables they used was the quantity of alcohol consumed. A unit corresponds to about a drink. This was during a six-month treatment period. The reduction in the quantity of drinking was greater for the supervised disulfiram group than for a control group which received Vitamin C.

Dr. Winchell talked about that overall aggregate results can obscure finding, and that has been the major criticism of quantity or volume in that two people can drink 14 drinks during a two-week period. One person drinks two

drinks for that period, in other words, two drinks a day, probably unlikely to have problems on two drinks day. Another person drinks only for two days, but drinks seven days each week, and at least theoretically, one would think that person would be more likely to have problems from alcohol. There is some suggestive evidence that that is true with drinking in hypertension, and one can conceive that certainly driving while intoxicated might be more likely.

[Slide.]

Project MATCH has been alluded to in this discussion, and the investigators in Project MATCH were confronted with this problem of those variables that were available, what should they use, and they had access to three data sets. They looked at the correlation between frequency, quantity, and intensity.

This shows the correlations between those. There was quite a good correlation between quantity and frequency, and less of a correlation between intensity and frequency, and they elected then to use frequency and intensity. They used percent days abstinence for frequency, and they used drinks for drinking days as intensity, because they thought since they were less correlated, they were capturing more breadth of the drinking experience.

[Slide.]

Other people have combined measures of frequency and intensity. This is just one example. There are several variations on this scheme. This is one of the naltrexone studies, and I am showing this as an example.

They had one measure of frequency, and if one achieved these criterion, they were considered to have relapsed. Then, they had two measures of intensity, the five or more drinks on one occasion or a blood alcohol concentration over the legal definition.

They chose for intensity five drinks per occasion. Again, here there is no consistency. The usual range for a definition of heavy drinking is in the range of four to six drinks per day.

I can't prove my next assertion, but I have always had the impression that people chose this more or less based on what they consider the cultural norms for drinking, and that if one drinks five or six drinks a day, that is a lot of drinking.

That is higher, however, than say the Health and Human Services and Department of Agriculture guidelines for drinking. There, the definition, that people should not drink more than two drinks a day -- men should not drink more than two drinks a day, and women one. I believe those guidelines were taken from such literature as the hypertension literature where if you drink three or more

drinks a day, the risk of stroke increases.

But there has been these different perspectives in defining a heavy drinking day.

[Slide.]

Certainly, the reason that we are all concerned about drinking, if for some reason alcohol had no effect on us physically or didn't have adverse consequences, we would be less concerned about drinking, but I think more to the point, in people who are reimbursing both public and private are becoming very concerned in the services area that they want to see reductions in crime, they want to see increases in productivity, and there is a lesser use than of combinations of alcohol consumption and negative consequences.

I am going to skip ahead just for one slide and then come back to that.

[Slide.]

How many drinks are too many drinks? This is one example where maybe the guidelines from the Department of Agriculture and Health and Human Services are correct.

This was a large longitudinal study, not a randomized clinical trial, but just a longitudinal study supported by the American Cancer Society, and it was really looking at how diet influences the development of cancer. There were thousands of people enrolled in this study, and I

believe they were followed for as long as four years.

Because of the data they were collecting, they were able to correlate alcohol consumption with dying from liver cirrhosis, and you will notice that even at two drinks a day, the risk of dying from cirrhosis increases. Here, this difference is not significant, and then it really exponentially increases at six drinks a day, an 18-fold increase in dying from liver cirrhosis.

[Slide.]

Now, this is an example of combining frequency and consequences. This is the data for three months prior to treatment, and this is data for different three-month intervals, I believe three months, six months, and then this is nine to 12 months following treatment.

The blue represents people who had sustained abstinence for that period. The green represents those who were drinking, but reporting no consequences, no adverse consequences. Here, the definition was six days for men and five days for women. Here, people were either drinking more than that or having problems with whatever level of drinking they were having.

Here, the white represents heavy drinking as these investigators defined it and consequences. You can see that almost everyone was drinking heavily and had serious consequences when they entered the study, and these are the

results for the three months posttreatment.

One might say that the abstinent or the people drinking without consequences represents success, and these others represent failure.

[Slide.]

There was an article in last week's JAMA that was apropos of this. They evaluated studies for the pharmacotherapy of alcoholism, and they eventually winnowed the list down to 52 studies, and they looked at the outcome variables that were used, and they found this lack of standardization, and they also made the point that it makes it difficult to compare studied, but I was pleased to see that their numbers were not too different from my impression.

If you take abstinence and time to first drink as a type of abstinence, that is the most commonly used measure, but frequency of drinking is also commonly measured, quantity is in there, and then also criteria-based definition of relapse.

An example of that would be the slide I showed from one of the naltrexone studies.

I am going to end by saying that there is consistency of use in the alcoholism treatment research in terms of diagnostic criteria, and I think that is good because it does allow for standardization.

There is not yet consensus in the clinical trials community on the outcome measures.

I think I will stop at that point, and I am sure there will be a lively discussion, and there are a lot of experts here.

DR. MEYER: Can we ask some questions?

DR. FULLER: It's okay with me if it is all right with the organizers.

DR. STRAIN: Okay. Use the mike, please.

DR. MEYER: Number one, how does this compare with other fields, for example, where there are less than perfect pharmacotherapies as in oncology? Second, given the uncertainties about how these medications work, where would you lean in the direction of being very clear that there should only be one goal or because we are not really clear about how these medications work, should we be fairly open to looking at the variety of goals?

DR. FULLER: I can't answer your first question from a tremendous knowledge base. I am an internist by training. I do read that literature, but it appears to me it is the same.

DR. MEYER: It is the same problem as with rheumatoid arthritis.

DR. FULLER: Sure, asthma, cancer, right. So, I guess I can answer.

How would I lean based on this discussion? I think I would suggest that we use more than one variable. This may come up in a statistical question. I remember one study, and I haven't presented slides from it. They used actually 14 variables. That is too many, and you run into problems with statistical analysis because you are likely to have one positive finding just based on chance. But I would suggest using two or three variables.

DR. STRAIN: We will, of course, have some time for discussion after the break, but did anybody want to ask any other quick question to Dr. Fuller now?

[No response.]

DR. STRAIN: If not, thank you, Dr. Fuller.

We will next hear the statistics presentation by Sue-Jane Wang.

Statistics Presentation

DR. WANG: I am Sue-Jane Wang from the FDA.

We have heard from the open public hearing, Dr. Anton, Dr. McCormick, Drs. Winchell and Fuller, expert overview on the clinical development. It helps us lay down the problem issues we may face when designing clinical trials for drug to use for treatment for the alcohol use disorders.

[Slide.]

Here, I would like to share with you the

statistical considerations. Specifically, I will present utility of multivariate failure time analysis method and its appealing features in comparison to traditional survival analysis with possible applications to alcohol treatment trials.

[Slide.]

I will start by summarizing what we have learned from naltrexone NDA on the statistical experience, then, switch the gear to bring your attention to what should be the appropriate study population, what should be the outcome measures from among, say, number of heavy drinking days, counting the number of patients who become abstinent, measuring the length of time not excessively using the alcohol until time to first heavy drinking day, time to second heavy drinking day, time to third heavy drinking day, et cetera, and applicable statistical analysis method for the alcohol treatment trial, and hopefully that important consensus can be borne out from the discussion and questions for the committee later.

[Slide.]

Naltrexone is an orally administered opiate antagonist. Use of naltrexone in combination with psychotherapy has been approved for treatment of alcoholism. In this NDA experience, two trials, Volpicelli, et al., and O'Malley, et al., were conducted.

These trials were designed as a randomized, double-blind, placebo-controlled, 12-week treatment period. During this 12 weeks, it consisted of concurrent psychotherapy and pharmacotherapy of either naltrexone or placebo once daily.

[Slide.]

The primary objective of the study was to evaluate that the safety and the effectiveness of the pharmacotherapy of naltrexone or placebo when administered as an adjunct to psychotherapy for treatment of alcoholism over a 12-week period.

The efficacy outcome measures consisted of dose reported by patients, which includes time to first drink, time to first heavy drinking day.

In one study, it was defined as five or more drinks per day or five or more days per week. On the other study, it was defined as more than five per day for men, and more than four for women.

The relapse to heavy drinking, complete abstinence from drinking, number of days on which patients drank or were drunk, and craving for alcohol.

Those measures collected from the laboratory of blood alcohol, liver enzyme levels, et cetera.

[Slide.]

These efficacy outcomes can be divided into two

types: the clinical response of yes/no outcome, for example, percent not heavy drinking and time to first event outcome, for example, time to any drink.

First, let me describe the yes/no response outcome. In Volpicelli, et al., trial, there were 31 patients in naltrexone-treated patients and 41 patients in placebo-treated patients.

The right bar in the graph represents naltrexone-treated patients, and the bar on the left represents patients from the placebo group.

The number on the step bar represents the actual number of patients in each category, which adds up to 41 patients per group or 100 percent.

Blue represents the number of patients who have one or more heavy drinking days during 12-week period. This corresponds to 70 percent of naltrexone-treated patients versus 37 percent of placebo-treated patients. The statistical evidence is at most borderline significant p 0.05 from chi-square test.

The magenta color represents a number of patients who withdrew from the study before the trial was completed and without known heavy drinking as yet. That is about 34 percent in naltrexone-treated patients and 27 percent in the placebo-treated patients who withdrew from the study and had not had any known relapse at the time of withdrawal.

Although numerically, there were more patients who dropped out from the study than expected in naltrexone group, more importantly, reasons of various discontinuations needs to be checked for obvious imbalance between the two treatment groups, if any.

To better understand the treatment effect given that about a third of the patients, efficacy information missing, one may consider treatment successes just those patients who not only not relapsed by the end of the trial, but also completed he entire course of their treatment. That is shown in green color. So, green represents the number of patients who did not relapse at the end of the study and who completed the trial.

The 49 percent in the naltrexone group versus the 37 percent in the placebo group were not demonstrated to be statistically significant different, p-value of 0.37. There was numerical trend that naltrexone is better. These results are extracted from Dr. Permutt's statistical review and evaluation.

[Slide.]

In O'Malley trial, on the other hand, about 11 more patients were studied, that is, 52 patients per group. The incidence of heavy drinking appeared that there was about half as much of the patients in naltrexone-treated patients of 25 percent than those in the placebo group of 56

percent. This finding was highly statistically significant with a p value of 0.0025.

Again, given the efficacy information is missing on about a quarter to a third of the patients, using alternative approach of the treatment effectiveness that patients who not only completed the trial, but had no known relapse at the end, there were about twice as much of the naltrexone-treated patients, of 38 percent versus 19 percent in the placebo with a p-value of 0.05.

[Slide.]

Now, consider time to first event data or the time to first heavy drinking days. In Volpicelli's study, we see that the median time to first heavy drinking day was not reached even by the end of the 12-week treatment period in both the naltrexone-treated group and the placebo-treated group.

A survival curve comparison showed a p-value of 0.04 with log-rank test. A Cox regression analysis adjusting baseline drinking showed a p-value slightly above 0.05.

[Slide.]

In O'Malley trial, on the other hand, among the full treatment group, the first curve, naltrexone with coping skill therapy, the second curve from the top, naltrexone with supportive therapy, the third curve, placebo

with coping skill therapy, and the last curve, placebo with supportive therapy.

It turns out that irrespective of either a coping skill therapy or the supportive therapy, a survival curve comparison with the log-rank test or the Cox regression analysis adjusting for baseline drinking showed a p-value of 0.001, highly significant.

[Slide.]

To summarize, the statistical experience from the naltrexone NDA for treatment of alcoholism, analysis method of log-rank test and Cox regression analysis adjusting for important prognostic covariates were used to test the treatment effect on time to first drink and time to first heavy drinking day.

Analysis method of chi-square test or Fisher's Exact test was used to test the treatment effect on the binary outcome of percent of patients with at least one heavy drinking day, percent of patients becoming abstinent after the treatment.

The sponsor reported important efficacy outcome measures as described, however, in the FDA medical review clinical evaluation report, Dr. Curtis Wright believed that other efficacy outcomes, such as number of intoxication, number of blackouts using the Alcohol Consumption Inventory form are important, as well.

So far we don't really know what efficacy outcomes are really appropriate.

[Slide.]

Thus, for designing clinical trials for drugs to treat alcohol use disorder, the so-called alcohol treatment trials, we would like the committee's feedback, specifically, what kind of study population should alcohol treatment focus on, for example, alcoholics, nearly alcoholics, excessive alcohol users, or a combination of any two subsets, et cetera.

Dr. Longmire, the medical officer, will further elaborate this point later. When a study population can be more clearly defined, the study design can be tailored to target specific populations with schema planned to minimize the early withdrawal rates.

One frequently used approach in neuropharm drug area and others say to retrieve the dropouts, it is usually very helpful in capturing behavior patterns among those who drop out of the trial earlier than the planned trial period.

The idea of retrieved dropout is to recover efficacy information at best and/or patients status if possible. So, for example, the investigators, nurses try to contact the patients, make every effort to do so, or the patient's caregivers, by, say, telephone trace to know patient's status after they left the trial, but before the

trial ended.

[Slide.]

If alcohol treatment trial excluded patients who are alcohol dependent, it will lack combination or nearly alcoholic or excessive alcohol users. If nearly alcoholic users are included, then, the patient population will be very specific to just excessive alcohol users or the alcohols abusers in the medical term.

In order to show treatment effect or treatment successes with those excessive alcohol users or a combination of nearly alcoholic and excessive alcohol users, the FDA medical team seemed in favor of capturing the following efficacy information, namely, for the event of heavy drinking, treatment comparison would be more sensitive and relevant to the patient population studied if time first heavy drinking day, time to subsequent heavy drinking days, and the gap times in between these heavy drinkings are included, that is, time to all heavy drinking days.

For the quantitative measures, it is important to know the number of heavy drinking days, as well. Notice that time to all heavy drinking days collects information on both the length of time of interest and the frequency counts of heavy drinking episodes, whereas, the number of heavy drinking days counts the frequency, but not the time element.

On the other hand, the medical team believed that low-risk drinking can be beneficial when the recommendation to patients are moderation of drinking. Dr. Longmire will describe in detail this point later.

In this case, number of low-risk drinking days may be of interest. Other important yes/no clinical responses are percent of patients having one or more heavy drinking days, percent of patients with low-risk drinking days, or more stringent, percent of patients abstinent after treatment.

[Slide.]

From the previous slide we see that the treatment effect can be defined with the use of time to all heavy drinking days. Suppose a trial was to administer either the experimental treatment or the placebo treatment once daily over the entire 12-week period.

Since the FDA medical team leaned towards using the time to all heavy drinking days, for the moment just suppose that this time to all heavy drinking days is the primary efficacy outcome defined in the protocol.

Here, we introduce four patterns possibly seen in alcohol treatment trials. We would like to hear the committee's opinion of what constitutes improvement among the patterns shown and other patterns not included.

Given that inclusion/exclusion criteria had

defined the study population of interest, specifically, the baseline drinking criteria, pattern 1 points to patients who become completely abstinent after the treatment. The red star here represents the heavy drinking events or the heavy drinking episodes.

Pattern 2 depicts those patients who, after the regular administration of treatment, now only reduce the number of heavy drinking days, say, down to three, but also lengthens the time between the heavy drinking days and eventually becomes no more relapse at the end of the trial.

An important treatment success are both the time and the frequency of heavy drinking.

Pattern 3, on the other hand, describes patients who, after treatment, become so-called weekend heavy drinkers, that is, patients maintain one heavy drinking day weekly even by the end of the treatment period.

It is true that patients did not drink heavily for six out of seven days. The fact that they continue to heavy drinking weekly seemed to indicate that patients had good control of their drinking behavior.

Should this be considered a treatment effect? If a patient drank twice weekly at baseline, this pattern seemed an improvement, but if meaningful improvement, we don't know.

Pattern 4 may be unusual but possible. Patients,

after regular treatment administration, become not heavily drink for a while, say, seven weeks, but for whatever reason, treatment became ineffective after seven weeks, that the patients become heavy drinking many days a week again for the rest of the trial period.

With this pattern, treatment improvement appeared to be only temporary.

Among all these patterns here, are we considering them as some type of improvement with a ranking of pattern 1 being the best, pattern 2 being the second best, pattern 3 not so sure, et cetera? We may discuss this more later.

[Slide.]

When time to first event is the only interest, main objective will focus on just the time to first event, not any subsequent event. Several application areas make sure of such efficacy endpoints especially when treatment can be very effective with time to first event.

Of course, a mortality trial, time to death, or time to first event is the main focus. There is no time to subsequent event per se.

Nonetheless, when treatment effect cannot be distinguished based on time to first event, but can be teased out from time to all recurring event, then, it will be important to find a statistical method that can be sensitive to pick up differences from all the recurring

events.

[Slide.]

Here, we introduce an alternative statistical approach in reference to traditional approach of time to first event, namely, time to recurrent event analysis. It is also called multivariate failure time analysis, and sometimes referred to as accelerated failure time analysis method.

Using time to heavy drinking days as an example, the time to recurrent event analysis method incorporates a gap time between the heavy drinking days. It also takes into account time to each heavy drinking day, time to overall heavy drinking day, increased gap time between heavy drinking episodes and/or decreased frequency of the heavy drinking count.

[Slide.]

Here is a real life example extracted from Therneau 1996. It was from a randomized double-blinded trial of a new agent compared to placebo in 180 patients with primary biliary cirrhosis.

We used this chart to demonstrate that a patient may have just have one failure time, shown in the magenta line, or failure times with improvement, shown in the red line, or it could be several failure time without improvement, shown in the blue-green line.

Use of the multiple failure time analysis method may be useful to make a detection of alcohol failure or heavy drinking failure more sensitive.

[Slide.]

Time to recurrent event analysis method has been applied to many clinical trials. Application of this multivariate failure time analysis method included events of the same type like recurrences or events of different types, et cetera.

For instance, in cardiovascular trials, the recurrent event may refer to the number of infarctions occurring over time in a patient. In a chemotherapy trial, it may be of interest to study repeated infections reported by cancer patients.

As for asthma clinical trials, study of multiple asthma attacks in a patient could be helpful in identifying whether treatment is effective or not, or it may be more ethical to study recurrent seizures in a patient during a trial period rather than just time to first seizure in the anticonvulsant trials.

[Slide.]

So, with recurrent event approach, when time to first event can differentiate treatment, if all subsequent events show in the same general direction of a treatment improvement, then, time to recurrent event analysis method

would further strengthen the evaluation of treatment effect.

[Slide.]

If, however, when time to first event was not able to pick up the treatment differences, analysis of time to recurrent event analysis method may or may not show a treatment improvement depending on whether treatment is truly effective in subsequent events or not.

Here, we give you an example from published literature. In fact, in an NDA case study that I was assigned to, the sponsor originally planned the time to first event as the protocol-specified primary efficacy endpoint, however, after the trial was over, the trial showed a complete wash on that time to first event.

Further investigation showed that treatment was shown to be effective in subsequent event, so that the overall event was shown to be significant. From this example, it is important to learn from previous studies, pilot study or whatever, what kind of treatment improvement can experimental drug demonstrate.

Of course, such improvement needs the consensus from the clinical community before an appealing sophisticated statistical analysis tool of time to recurrent event analysis method be of valuable use to specific discussion area, such as alcohol treatment trial.

[Slide.]

There is abundant statistical literature available for analysis of time to recurrent event. Here, I listed a few. In particular, AG model has been applied to many clinical trials, let's say, recurrent infection in bladder cancer patients.

PWP model was proposed in 1981 to analyze data of recurrent event by taking into account the total event time or the gap time between events depending on which one is thought to be more relevant to the study of interest.

Marginal Model of WLW was advocated since 1989. It has also been applied to several clinical trials, for example, AIDS clinical trial. Other approaches, such as non-parametric model approaches are also available in the literature.

The research of the time to recurrent event is ongoing. This time to recurrent event analysis method initiated from around the '80s, and received quite a bit of attention since early '90s. With its popularity, the statistical analysis softwares are available. These are two examples.

[Slide.]

Finally, we would like to hear the committee advise on how can treatment success be measured. As Dr. Fuller pointed out, should it be only one primary or two or three co-primary endpoints?

What should be considered a more defined study population for alcohol treatment trial, specifically, if the time to heavy drinking days is of main interest, then, does our proposal of time to recurrent event analysis method effectively capture treatment effect outcome, or different approach should be more relevant?

Thank you.

DR. STRAIN: We have a couple of minutes. I think we are scheduled next for a break, but we are running a few minutes ahead. Are there any questions before we move to the discussion period for Dr. Wang? Let me ask just two if I may.

One, is possible to have a significant treatment difference using time to first event, but not show a difference in time to recurrent event analysis? In your Example 1, for example, you said that time to first event shows a treatment difference, and then you say time to recurrent event strengthens the evaluation of the treatment effect, implying that it will also show a significant effect. Can it be the case that you will not see a significant effect under a time to recurrent event analysis?

DR. WANG: The answer is depends.

DR. STRAIN: You are a statistician, aren't you.

[Laughter.]

DR. WANG: Because when the time to the first

event is very, very strong, the evidence is very strong, then, even if you don't have much of the information on the second and third, you are going to end up the overall time to all events significant.

If, however, the time to first event is not that overwhelmingly different, in theory, you would still end up with a not significant, and this was a useful discussion between myself and the FDA statistical consultant, Dr. D.Y. Lin, who is the leading expert in the area of the multivariate failure time analysis method.

DR. STRAIN: Just one other quick question. Has data from either Dr. O'Malley or Dr. Volpicelli's naltrexone studies been reanalyzed using time to recurrent event analyses or are you aware?

DR. WANG: I was not involved in original statistical evaluation. That was around 1994 of this NDA, but from the statistical review I was able to capture like what kind of information I could reconstruct to do a time to recurrent event analysis.

What I can say, because I don't have the data at hand, from that information, let's say in the Volpicelli trial, it was borderline only, but if you really look into the time to recurrent event in that particular study, you would then first come up with a 2 by K table -- K referred to the heavy drinking episodes that you are considering.

So, you will see a trend of the naltrexone become less percentages of patients who have two, three more heavy drinking, but you still see that in the placebo. So, this would be a tool to help the Volpicelli.

Although the numerical trends all show naltrexone being better, but statistically, it was really struggling of a borderline versus really significant, and it turns out the time to recurrent event was helpful.

DR. STRAIN: It was helpful?

DR. WANG: It was helpful, but I don't have the actual data.

DR. STRAIN: Dr. Meyer.

DR. MEYER: Putting your model, which I think is very interesting, in the context of the alcohol dependence, and Dr. Anton's notion about the three-month clinical trial, and also the elegant slide in which you had severity and motivation and looking at the Type II error problem, I am wondering about whether this method might be better in a longer trial given, you know, let's say a six-month window rather than a three-month window.

In some ways the sine qua non of alcohol dependence is the shorter time between heavy drinking episodes, the breaking down of control of drinking. So, I like your statistical model clinically. It is less useful in an heavy drinking or alcohol abusing population, but it

would be very interesting in an alcohol-dependent population.

But I am wondering in the context of Dr. Anton's three-month window, would we be better with a six-month window using your statistical model.

DR. WANG: I think that is one of the topics going to be discussed later on regarding the length of the trial, whether is should be just 12 weeks, or maybe 12 weeks is really too short.

For example, in the Volpicelli study, that median time to first heavy drinking day was not even reached by 12 weeks. So, that is an open question, I don't know. But in terms of using this time to recurrent event analysis method, they actually had some published work by Dr. Siegel from CBER FDA, who recommended when should one consider to use the time to recurrent event analysis approach.

Can you bring up the slide of question?

[Slide.]

Here is a slide to kind of help people to try to decide whether time to recurrent event analysis method is appropriate for a particular study. Dr. Siegel, in 1997, stated that when the irterest in the recurrent event, the same event over time, he suggests that one should be asking the following three questions: It is a central question how many events occurred rather than yes/no, having a list one

event, or should the patient be followed for a fixed time interval, and does the treatment effect change as a function of time or prior events.

The first question refers to what I call the frequency. The third question refers to the time that it delays the relapse or eventually diminished that relapse. The second question probably will address better about the question just asked - is the 12 weeks appropriate or six months more appropriate?

For whatever decision comes up, the thing is that it is more fair to compare between the two groups when each patient has a fixed time interval being measured.

DR. STRAIN: On that note, I think I am going to suggest that we take our break. I think that this whets our appetite for the sort of discussion that we will be having later this morning.

Let's go ahead. We are scheduled for a 15-minute break and we are stopping on time, so we will start at 10:45 sharp.

[Recess.]

DR. STRAIN: We will resume the meeting with a presentation by Jack Longmire from the FDA, Clinical Presentation.

Dr. Longmire.

Clinical Presentation

DR. LONGMIRE: Good morning.

[Slide.]

I am Jack Longmire, medical review officer with the division, and I would like to discuss alcohol treatment trials with a non-abstinence treatment goal from a clinical perspective.

[Slide.]

The essential questions will be: Who should participate? How should they be selected? What, short of abstinence, should be the treatment goals?

I have listed for you on this slide several outcome measures that have been submitted to the FDA in the past. In your binder that we have sent, there is a large clinical trial Project MATCH -- most of you are familiar with it -- in which endpoints included PDA or percent days absent, and DDD, as they call it, or drinks per drinking day.

There are also legal and social endpoints, as well as physical measurements of alcohol and other things, of course.

[Slide.]

I would suggest to you that one source of answers would be The Physician's Guide to Helping Patients with Alcohol Problems. This was published in 1995 by the National Institute of Alcohol Abuse and Alcoholism. This

was designed as a guidance document for a primary care provider who might be working in an environment where it would be appropriate to screen for, and advise for, those that were having problems with alcohol.

As such, it would seem very appropriate to what we are discussing this morning, because if we do, in fact, approve a product, this is the arena in which it is likely to be used.

[Slide.]

It suggests a screening and brief intervention procedure. Screening would be appropriate at such times as a routine physical examination or at such times perhaps as where one might be prescribing a medication that would interact with alcohol, and the approach would be an ask, assess, advise, and monitor approach.

Ask would be asking in terms of getting information to determine if an alcohol problem might exist, assessing for the degree of severity of the alcohol problem, and advising as to what would be appropriate action for this particular patient. In some cases it might be abstinence and in some cases it might be to cut down.

[Slide.]

For the first step of determining if an alcohol problem might exist, they suggest that you ask subjects about all forms of drinking - beer, wine, and mixed drinks,

and specifically, how much, how many days per week do you drink, how many drinks per drinking occasion, and what is the maximum number of drinks per occasion during the last month.

Then, they suggest that you ask the CAGE questions.

[Slide.]

Cage is an acronym standing for Cut Down, Annoyed, Guilty, and Eye Opener, a series of four questions.

The Cut Down question is: Have you felt that you should Cut Down in your drinking?

The Annoyed question is: Have people Annoyed you by criticizing your drinking?

The Guilty question is: Have you ever felt bad or Guilty about your drinking?

The Eye Opener question is: Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?

Now, if even one of these questions is positive, this should suggest that a drinking problem might exist.

The second way of assessing for a drinking problem is the amount of drinking that the person does.

[Slide.]

If a person has an immoderate amount of alcohol consumption -- and this is defined for us, for men, greater

than 14 drinks per week or 4 drinks per occasion, and in women, greater than 6 drinks per week or 3 drinks per occasion, or if they have even one question positive on the CAGE set of questions that has occurred in the past year, then, each of these should suggest that a drinking problem might exist.

[Slide.]

The second step, having decided that a drinking problem might exist, would be to assess for alcohol-related problems in terms of severity, and they suggest three tiers of severity, the first being just at increased risk for developing alcohol-related problems, the second being currently experiencing alcohol-related problems, and the third being may be alcohol dependent.

[Slide.]

For the first tier or the least severe tier, we have already mentioned that having an immoderate amount of drinking or having a positive CAGE question which suggests that a problem might exist, also, drinking in high-risk situations, such as pregnancy perhaps, or having a personal of family history of alcohol-related problems would also be suggestive that an alcohol problem might exist.

[Slide.]

The second tier of severity, currently experiencing alcohol-related problems, would be indicated b

one or two positive responses to the CAGE question that have occurred in the past year, and evidence of alcohol-related medical or behavior problems.

Alcohol-related medical problems in this sense would be things such as blackouts, cirrhosis, gastritis, sexual dysfunction, sleep dysfunction, or perhaps depression.

The alcohol-related behavioral problems are usually things that have to do with work or with family relations, such as has alcohol interfered with your ability to perform your work duty or has alcohol interfered with your family relation, or in terms of accidents, has alcohol led to an accident or an injury.

[Slide.]

The third stage, and most severe, is may be alcohol dependent. Here, you would expect more than two CAGE questions positive, and evidence of any one of the symptoms listed here suggesting loss of control or physical dependence, for instance, compulsion to drink or preoccupation with drinking; impaired control, unable to stop drinking once you have stopped; any alcohol withdrawal symptoms or drinking to prevent symptoms, or having a clear dose escalation of alcohol that is required to get the desired alcohol effect.

[Slide.]

Now, having assessed the degree of severity, the third step is advise. The advice should be to abstain if there is evidence of alcohol dependence, and it might also be advisable to abstain if the person has tried to cut down on their drinking and been unsuccessful, or if he has any medical condition that would make drinking alcohol inadvisable.

It may be appropriate to advise to cut down in some situations, such as drinking above the recommended low-risk drinking amount and no evidence of alcohol dependence.

[Slide.]

In advising to cut down drinking, one would advise a moderate amount of drinking, which has been defined for us in this document, as for men, no more than two drinks per day; for women and those over 65, no more than one drink per day, but being quick to add that for those subjects that alcohol dependent or have evidence of alcohol dependency, that have any type of medical condition that contraindicates alcohol, that these subjects should be advised to abstain.

[Slide.]

I, as the Commission, found this a very useful document as far as having a plan to approach subjects that might have an alcohol-related problem. I found it very direct, to the point, succinct, very useful, and I think it is also probably very useful to use in the discussions that

we are having today.

DR. STRAIN: Thank you, Dr. Longmire.

That then ends the FDA's presentations. I would like to thank the FDA staff for their excellent overview of the issues that we are going to be dealing with in the discussion and questions for the committee.

Before we move to the discussion and questions, there has been a request from the audience for further comment, and the way I would like to handle this is that I would like to open up the open public hearing once again for a few more minutes to allow Dr. Anton to comment once again. He has a further comment in response to some of our earlier discussion.

If there any other people who wish to speak, they should identify themselves to the committee. I don't want to have a long open public hearing. We will close the public hearing, and then the committee will go to its discussion, if that is agreeable to the committee. Then, we will go ahead and open the public hearing and Dr. Anton.

Open Public Hearing

DR. ANTON: Thank you, Dr. Strain.

I just wanted to respond to Dr. Meyer's very pertinent observation of the three months versus six months in regard to the repeated event analysis. I want to make two quick points about that.

One is that on Stephanie O'Malley's suggestion actually, we looked at our data set in relationship to the time between the first event and the second event.

I need to point out, first of all, that our data set may be a little bit unique, and may be the ideal to shoot for, in that we had 98 percent of all of the drinking data available to us for the whole 12 weeks. Our completion rate was 83 percent in a 12-week trial, but the people that dropped out were gotten back, so we have 98 percent of our drinking data, which I think is a crucial point.

Having said that, the time between the first the second event favored naltrexone at a p less than 0.05, such that the time between the first heavy drinking day and the second heavy drinking day for placebo for seven days, for naltrexone it was double that, at 14 days, and that was significant.

Now, that is sort of a poor man's way I think of looking at this repeated measure analysis. I think what was presented before is much more complicated, but it does suggest within the 12-week period, that you can go from the first event to a second event and get meaningful data, at least in our trial.

The second point I wanted to make is that I think one has to balance in this decisionmaking what one gains from a six-month trial as far as determining efficacy of the

pharmacology, that gain versus the loss that one might get from dropouts, decreased compliance, and not having that data available to do the more sophisticated analysis. I think that may be a tough decision to make.

I also would offer my data set to the FDA if they wanted to explore some of these alternative ways of looking at the data since it is a relatively complete data set, and if that is useful to you, you are welcome to discuss that with me, and for the committee to.

DR. STRAIN: Thank you, Dr. Anton.

If there are no other people who wish to speak in the second open public hearing, this will then be closed.

We will now move to the discussion and questions for the committee.

Discussion and Questions for the Committee

DR. STRAIN: I would ask the committee to turn to the second page of your handout, which poses seven questions the FDA has written for us. We already consider these seven questions, as well as a more general discussion, as well, and I believe that, in a way, these questions are obviously very interrelated, and I am not sure if it is useful for us to necessarily try to go through each one separately so much as to consider perhaps the first question and what we will find is that our discussion often is covering more than one question.

So that everybody is aware of what the questions are, let me go and read the seven of them, so that others in the audience know them, as well.

1. Are non-dependent heavy drinkers sufficiently different from alcoholics to warrant a different approach to treatment?

2. Are there subgroups of drinkers who meet criteria for dependence (alcoholics), but are sufficiently different from one another to warrant different approaches to treatment?

3. Can different groups be reliably separated from alcoholics through inclusion and exclusion criteria? Through clinically practical criteria?

4. What should be the treatment goal for alcoholics?

5. What should be the treatment goal for non-dependent drinkers?

6. What should be the treatment goal for groups identified in the second question, that is, the subgroups that we might be able to identify?

7. How can success be measured in these groups?

Let's begin with the first. Are non-dependent heavy drinkers sufficiently different from alcoholics to warrant a different approach to treatment?

I would ask people to use the microphones and to

raise your hands, please.

Dr. de Wit.

DR. de WIT: I have a question to start with. What do we know about treatment for alcohol abuse as distinct from alcohol dependence? Am I correct -- this is a question to the experts -- that Project MATCH, for example, was directed toward people who met criteria for alcohol dependence?

DR. KRANZLER: My understanding is that they included dependence or abuse. The vast majority of participants, though, were dependent.

DR. FULLER: The vast majority were dependent, easily 98 percent. In fact, I think they averaged approximately six of the nine symptoms in the DSM-III(r) at that time.

DR. de WIT: So, is it true that we have only a limited amount of information about the efficacy of treatment for people who meet only criteria for alcohol abuse?

DR. O'MALLEY: There are a series of studies in primary care settings with people that are drinking hazardously that aren't dependent, showing that brief advice to cut down is effective modestly, so there is that literature. I think pharmacotherapies haven't been employed very extensively in that group.

DR. KRANZLER: Except that most of those studies don't use DSM diagnoses. So, for example, the WHO collaborative study excluded people who had significant physical dependence, but didn't exclude people who were DSM-III or DSM-III(r), alcohol dependent.

I think the distinction based on abuse versus dependence is probably not going to get us far, because the vast majority of people who end up in treatment are people who are dependent, and in primary case I suspect that the largest proportion of people are people who are drinking more than is good for them, but who may not meet criteria for anything.

So, then the question becomes is that the group that we want to focus on, is that the group that is being considered as a target for pharmacotherapies, and then you get into applying quantity/frequency criteria.

For example, women who drink more than seven drinks a week, do you want to target them, or men who drink more than 14 drinks a week, do you want to target them for simple advice, and I think the consensus is probably yes, that it makes sense to advise people to reduce their drinking to less hazardous levels or to non-hazardous levels.

The question of where pharmacotherapy fits in that strategy is obviously a more complex one.

DR. STRAIN: Dr. Meyer.

DR. MEYER: It gets further convoluted in the constructs of severity and dependence in the different ways that that has been defined, because one of the repeated findings -- and I would ask my more expert colleagues who are closer to this literature now if this isn't true -- one of the more recurrent findings is that people with mild to moderate, at the milder end of the dependence spectrum, can in fact -- that that is the group that was targeted for moderate drinking interventions by psychologists. The more severely dependent, when they were targeted, they couldn't sustain a moderate drinking outcome.

Now, when we get to this construct that we heard about, about recurrences, this becomes a very critical differentiater then in terms of whether someone is mildly dependent or severely dependent.

I am not a great fan of DSM-IV and its ability to provide the gradations of severity that people talk about, and I think there is a need in doing a trial that is looking at this question using those statistical methods to give a much finer grain definition of severity, and that that actually would be more relevant than the issue of abuse.

DR. STRAIN: Dr. Andorn.

DR. ANDORN: Actually, I think it depends where you sit as to the issue of abuse. I sit right now, primary

care adolescent, college age, in a town that has a tremendous abuse problem, we are losing kids right and left to heroin overdose.

I think that is a population that we do need to address. The important thing is not to diagnostically contaminate studies, to be very clear about which group we are studying.

DR. JARVIK: I wonder if anybody has worked out a scale of harmfulness or hazardness of drinking. I guess motor vehicle bureaus have to some extent, and they are very arbitrary, and the harm is quite obvious there.

But when a particular treatment is being advocated, one would like to know what the goal is, especially when moderate drinking is going to be the goal. Is there no harm to moderate drinking either to the individual or to society?

DR. KRANZLER: It depends on what you mean by moderate.

The AUDIT, the Alcohol Use Disorders Identification Test, is an instrument that was developed by WHO as the precursor to the multisite brief intervention trial that I mentioned before. It is interesting, Dr. Longmire, that the NIAAA recommendations largely capture the AUDIT by asking quantity frequency and frequency of intoxication questions followed by the CAGE.

The AUDIT is actually a 10-item instrument that was developed in six countries, so it presumably has some cross-national relevance. It has been further validated since it was initially derived.

It starts with three questions on quantity frequency including the third being the frequency of heavy drinking, and then seven questions on consequences including some dependence symptoms.

It does appear to be more sensitive than more traditional instruments like the MAST, for example, and so it may be a useful basis for initial identification. Whether it is useful as a repeated measures instrument for assessing treatment outcome, I don't think anybody knows.

DR. STRAIN: I would like to ask Dr. Andorn, in follow-up to her comment, would she then suggest that non-dependent heavy drinkers should be the focus of pharmacotherapy clinical trials, or are you simply acknowledging that the critter exists?

DR. ANDORN: I would say they should be the focus of treatment intervention, whether that is pharmacologic or not, but they should not be the focus in the same trial as the dependent unless you have two arms in that trial and you are clearly delineating which, absolutely.

DR. STRAIN: If I could press you on that, though, since we are dealing mainly with pharmacotherapies here, so

is it the case that we should be suggesting to the FDA that they should look at the dependent heavy drinkers rather than the non-dependent heavy drinkers when they are considering pharmacotherapy?

DR. ANDORN: I would say either/or. How is that for a committed answer? I do think there is a population of non-dependent by DSM-IV criterion, abusers who are at high risk, both occupationally, socially, in terms of their function overall.

This tends to be a younger group, and this tends to be a very at-risk group for polysubstance use, and I do think we need to target that population, and not continue to neglect them.

DR. STRAIN: Thank you.

Dr. Mason.

DR. MASON: Just a follow-up to Dr. Andorn's comment. Another population that probably overlaps with hers are women of child-bearing age, between the ages of 19 and 29. Ten percent of women in that age group meet DSM-IV for abuse or dependence, and as little as 1.3 drinks a day have been associated with persistent neurocognitive and neurobehavioral deficits in the offspring.

So, that is an important group to target, again as Dr. Andorn said, for intervention, because most of the harm to the fetus takes place before the woman knows she is

pregnant, so it is really the pre-pregnancy drinking that has to be the focus of intervention, but as Dr. Andorn suggested, whether that is pharmacotherapy or not is, of course, up for grabs.

DR. KRANZLER: We are currently doing a trial in early problem drinkers whom we have defined using an alcohol consumption criterion, and as an exclusion, more than four DSM criteria, and no physical dependence, so it is a little bit of a hodgepodge in terms of inclusion/exclusion, but it is with naltrexone, it is naltrexone versus placebo, and it is a factorial design in which people are either getting the medication on a daily basis for eight weeks or are taking the medication on a descending frequency, basically starting daily and each week reducing by one with a focus on identifying high-risk situations and using the medication as a coping strategy for high-risk situations.

This is being done under an IND. We are about 100 patients into what was scheduled to be a 160-patient study, so we anticipate having some data on that. What might be interesting ultimately in terms of the repeated event approach to analysis is we have daily booklets that people are completing and mailing in to us, and we are getting about 80-plus percent people who are doing it with enough frequency and in timely enough fashion that we have confidence in those data.

I am not sure that that is going to give us all that much more on drinking than a time on follow back does. It gives you a little more definition in terms of pattern of drinking, but it gives us a lot of other events that occur during the day that we can use in a time series analysis for interrelations.

DR. STRAIN: Thank you.

Dr. de Wit.

DR. de WIT: Could you just clarify for us, they are using this drug basically on an as-needed basis, they are not taking it on a daily basis, but rather only when they see a difficult situation coming up?

DR. KRANZLER: The group that is not daily is getting the medication initially, for one week, daily, the second week they are getting it six times, they are urged to take it six times. They are given enough medication to take it six times, and they are urged to begin focusing increasingly, as the number of pills available declines, on those situations that are at highest risk for them.

This was a bit of a compromise in terms of the design between using it on an as-needed basis and the recognition that some people who end up not taking any medication at all, and we would have no real comparator.

DR. de WIT: It sounds like it will be difficult to analyze, especially if there is any kind of active drug

effect. I assume it is contrasted with a placebo.

DR. KRANZLER: Right, it's a 2 by 2 design.

DR. STRAIN: Dr. Lloyd.

DR. LLOYD: Dr. Andorn brought up an issue of polysubstance abuse, and I hadn't heard that mentioned before in our discussion, and wondered where that enters into this, because as I look at the studies and as I look at the background material that we have had, it all seemed to focus only on alcohol use or dependence.

My understanding is there are very few of those folks around that are just pure alcohol users.

DR. STRAIN: Dr. Franklin.

DR. FRANKLIN: Just to follow up on that, I guess globally, when I think about what a drug should do for different populations, I think of three or four different things.

One is for the severe alcoholic who other treatments haven't worked, that you are taking the approach this is primarily biological and psychosocial treatment hasn't worked, so that is one category where drugs might at some point be useful, and that is a population that needs to be studied, people that you are assuming psychosocial treatment doesn't work.

The second would be people that are in treatment, and you are trying to keep them in treatment long enough

that it sticks, the psychosocial treatment sticks. That is primarily the people in drug treatment programs.

The third is the primary care population. I guess I just don't have a lot of hope, even though we are saying we are targeting this towards primary care docs, of them ever really getting significantly involved in the abuse or dependent individuals. I think they are good at recognizing maybe, but we haven't done a good job with that either, at this point, that actually asks them to treat people, and the climate of managed care and everything, I don't know if that should be our target.

The fourth would be this dual diagnosis population, either psychiatric and drugs, or drugs and alcohol. If you are talking about drug treatment, you have to consider that as another population that you need to consider in terms of trials also.

In the real world, I think the pristine study -- that is a problem, we have problems transferring the technology to the real world.

DR. STRAIN: I think the answer to Dr. de Wit's question, which started our discussion, is that, or in part, what I hear from the committee is that there certainly are a variety of types.

There are, as Dr. Kranzler just implied in the study he was talking about, he, for example, is I believe

having no difficulty in recruiting people who are non-dependent heavy users or could be construed that way, and Dr. Andorn's comments and others, Dr. Lloyd's as well, would suggest that it would be very important to recognize at the start of a study distinct populations, that there may be populations that are non-dependent heavy drinkers, such as especially the youth, pregnant women that might be at risk, or women of child-bearing age, and so on, and so forth.

Is that the general sense of the committee and have we perhaps addressed that first question sufficiently? If so, then, the next question is are there sufficient gradations within the group of people we have considered as alcohol dependent, that it is worth distinguishing those subtypes.

Let me perhaps throw that question out, and, Dr. O'Malley, I didn't mean to chop off your comment.

DR. O'MALLEY: That is okay. My only comment I was going to make was one which I think you touched on, is that we have to be careful about generalizing from our treatment samples to the whole population of people with alcohol use problems.

Most people never seek treatment for their alcohol misuse. In addition, even though our advice to cut down is effective compared to no advice, again, it doesn't help everyone, so there may be people who have persistent

problems controlling their drinking, but aren't going to respond that well to simple advice to cut down.

So, I think the group of people who might benefit from pharmacotherapies may be much larger than we think, and they may not all be polysubstance abusers if you get into lower severity.

DR. STRAIN: Dr. Simpson.

DR. SIMPSON: Just from your comment, you are thinking of pharmacotherapy on its own independent of psychosocial counseling?

DR. O'MALLEY: Well, I think we need to probably accept the reality that if people go to primary care physicians for pharmacotherapy, they are going to get very minimal behavioral intervention.

So, if you were going to test something in that model, you would probably want to test it with something that is realistic in that setting.

To your question about within the alcohol dependent group are there differences, I would argue that there are. I mean there is a whole lot of work that has gone in typologies, but I would like to give you one example from my work with naltrexone, which is where we need to look at tolerability of naltrexone, the incidence of side effects, particularly nausea, and what we find is that different subgroups tolerate it better than others.

Interestingly, lighter drinkers don't seem to tolerate it as well as heavier drinkers. Similarly, women have more nausea than men. I think all of these patients met dependence criteria. Younger subjects don't tolerate it as well.

So, the process of heavy drinking leads to changes probably that make certain medications behave differently, and that needs to be considered. I think this also argues for dose ranging studies in whatever medications are being considered.

DR. STRAIN: Dr. Mason.

DR. MASON: In response to something that Dr. O'Malley said about an observation that patients vote with their feet in terms of treatment, and we run advertisements with the header, Drink Too Much, and to recruit patients for pharmacotherapy trials for alcoholism, and I don't think we have ever turned away a person for insufficient symptoms of dependence, and they usually tend to be in the moderate range.

I think that that is actually an important observation in terms of the question before the committee, is a pharmacotherapy for abuse indicated, because you have to think about whether it would be acceptable to the target population, as well.

Also, something that Dr. Franklin said about

dependence, actually, using a biological treatment for a biological disorder, I think we have a lot of data like the DSM-IV criteria involved more somatic type symptoms for dependence than for abuse, and animal data suggest a change in hedonic setpoint and alcohol deprivation effects in dependent animals, et cetera, suggesting some biologically based changes have occurred associated with dependence that may indicate more biologically based treatment is merited.

Whereas, in the population of women that I was referring, the reasons that drive their abuse are often related to peer group influences, the influence of a drinking spouse, more psychosocial type influences that really don't suggest a biological type of intervention would be particularly indicated or even appropriate before the issues that were driving the abuse have been addressed.

DR. STRAIN: Thank you.

DR. KRANZLER: If I could make one more comment, and then I am going to be quiet.

DR. STRAIN: No, no, don't be quiet.

DR. KRANZLER: I think the committee would be well advised to look at the nicotine dependence experience. Early reports out of England, for example, supported a brief intervention over no intervention, simply you shouldn't smoke, it's not good for your health, and although quit rates were modest, they were I think it was 7 or 8-fold

higher than people with spontaneous efforts to quit.

That, in itself, I don't think influenced people as much as the availability of pharmacological interventions and I think the availability of pharmacological interventions, nicotine gum, patch, et cetera, and ultimately, bupropion, are probably sensitizing the medical community, particularly primary care, to the issue.

I mean it is a bit of a clinical axiom that disorders are more prevalent as soon as there is a good cure for them, and so I think physicians will be motivated to identify and intervene with problem drinkers however we might define those if there is an efficacious, well-tolerated medication.

DR. STRAIN: I have this difficulty where I flip back and forth between what will happen clinically once a medication is available versus what we are recommending to the FDA, and the FDA, in turn, working with sponsors on in terms of how to optimally study and determine that a medication may be effective.

I think that is what we need to focus on right now is not what will happen once it's on the market, because once it's on the market, yes, PCPs could be trying it with everybody, maybe trying it with college kids who are drinking on the weekend, maybe trying it with pregnant women who drink a couple times a week, whatever, but what do we

recommend to the FDA at this stage, that they, in turn, might incorporate with going to a sponsor.

In part, I think we, as a committee, might want to say, well, we want to see a model for a situation which has the greatest likelihood of showing a beneficial effect. We don't want to miss an effect, not to steal Dr. Anton's thunder or his point.

Let me post it this way, and I am actually at this end of the table, but everybody, but you guys are the experts, and many experts, as well, but do you think if a sponsor comes to the FDA and says we have got a medication and we want to study it, but we don't want to study it in people who are alcohol dependent by DSM-IV criteria. We want to study it in heavy drinkers and see if we can moderate their heavy drinking, should the FDA say, yeah, that would be something worth doing?

Dr. Kranzler is nodding yes.

DR. KRANZLER: I think it would be. I think, though, that there needs to be the recognition that to the degree that there is less variability, depending on the variability in the measure of interest, and particularly the potential for floor effect, that very large sample sizes may be needed.

I mean if you are trying to reduce drinking from an average of 20 drinks a week to no more than 10 drinks a

week, it is very different in terms of the sample size you will need, in terms of the measures you will focus on compared with a relapse prevention trial where people are starting out drinking very large amounts, may be abstinent for a week or two, and then you look at how long it takes for them to relapse and how severe their relapse is.

But in terms of the philosophical issue or in terms of the relevance for pharmacotherapy, I think it is an important area that I think should not without good data be rejected as infeasible or unworthwhile.

DR. STRAIN: Dr. Meyer.

DR. MEYER: I have several questions. With regard to the self-report data, is the sensitivity and the validity of patient self-reports relative to going from 20 to 10 drinks sufficiently good with the problem drinker as distinct from the more severely alcohol dependent individual, there are not a great number of biological markers that might be used to help validate the information, the significant other may not really have as good information with regard to the problem drinking.

The question about the sensitivity and the validity measures really then begins to be important. I would ask you about your experiences with daily events recording and some of the new technologies related to the hand-held computers.

Secondly, there are several people in the group who have had a variety of different experiences around compliance, and Ray presented the slide with regard to riboflavin and pill counts. You have riboflavin, pill counts, and the MEMSCAP.

I think that it would be useful for us to get an understanding about where you think the state of the art is with regard to those compliance measures.

DR. STRAIN: Does anyone on the committee want to answer those questions?

[No response.]

DR. STRAIN: Dr. Fuller, I wonder if you might comment about the riboflavin, for example, since that was a marker used I believe in your antabuse clinical trial, and I think you also addressed it in the methodology paper for that study.

DR. FULLER: Yes. Let me put that in some context. That is, up to that point, interestingly enough, compliance to medications had not been, to my knowledge, measured in alcoholism treatment trials. That is not the case today.

We elected to use riboflavin because you can't poison people with riboflavin, and if you take a lot of it, the urine glows, but more importantly, it had been used in studies of compliance with isoniazid, so we used it, and I

think it was a contribution to the literature at that time.

Now, is the best measure? Well, one problem with it, it is only present for at most 48 hours after the last dose, so that is one disadvantage.

People have used other methods. One is the pill count. If you back into the history of measuring compliance, a pill count gives you more information than just asking a doctor or nurse whether the person has taken the medication.

So, there is pill counts, there is markers such as riboflavin, there is actually measuring the drug or a metabolite itself. That usually, though, suffers from the same problem that riboflavin suffers from.

Then, there is the MEMSCAP which indicates how often the lid is opened. There are certainly advocates of the MEMSCAP and feels that that is the best measure, but there can be problems with that. People can open it and not take the medication, discard it.

So, these are all methods for measuring compliance. I think it is very important to measure compliance in a trial. Which is the best method I think depends on whom you ask. Dr. O'Malley has worked with one of the leading advocates of the MEMSCAP.

DR. O'MALLEY: Or we should say electronic monitoring events, because there are different versions now.

I think the one thing I would say it probably depends on the trial, so if you were doing a study in which people were not seen frequently, for example, in a primary care setting, these methods where the pill bottle records the time and date of the opening might be better than something like the riboflavin marker or drug plasma levels, which just give you a picture of that moment.

So, I think it really depends on the trial and the frequency with which you see the individuals.

DR. STRAIN: Ms. Falkowski has been patiently waiting. Yes.

MS. FALKOWSKI: I would just like to address the committee's consideration on something that sort of begs the larger question that I don't think has yet been addressed, and that is, accepting alcoholism as a disease requires that you accept that it is progressive in nature, so that therefore there may be heavy drinkers, and the question is how many of those will advance to the disease.

If the best thinking on the topic suggests that most of them will or most of them won't, that would have bearing on the course of whether pharmacotherapy should be directed toward that group, if they are a transitory group and due to biology and all sorts of other things which we know contribute to the disease, if it is better directed there or not, and I would like people to comment on that.

I mean, for example, if we compare it to other chronic diseases, with diabetes, for example, we know that people who have family history, that have other high-risk factors, if they are, for example, eating -- and I am just doing this for the sake of discussion -- eating a lot of doughnuts, you know, are we advised to take those people who have not yet developed full-blown diabetes and give them a pharmacology for doughnut eating, so that they can eat them and not progress to the disease, or exactly, you know, what is the population that we are talking about?

DR. STRAIN: Dr. Mason, then Dr. Franklin, and then Dr. O'Malley.

DR. MASON: Well, in the absence of dependence, high blood alcohol levels are associated with many of the really important negative effects of alcohol use, and so I think that does make that group an important target.

Dr. Meyer had alluded to some of the new technology, and as Dr. O'Malley indicated, if these patients are not seen very frequently -- I know at the University of Vermont, John Helser and his group have gotten very high response rates in terms of daily drinking records by having a sample call in to a 800 number for increasing amount of very small compensation, but this worked very effectively for research purposes, and in terms of the statistical issues around very low level of consumption going to

slightly lower level of consumption, I think that the dysthymia trials might be looked at as a model, where you have like low depressive severity going to no depressive severity, so it is just a model I wanted to call to the committee's attention.

DR. STRAIN: Thank you.

Dr. Franklin.

DR. FRANKLIN: I guess I want to follow up a little bit on Dr. Falkowski's comments.

I was thinking about what you said, the patient or client who is drinking 20 drinks a week, and you want to come down to 10, philosophically, as the FDA, do we really want this person to quit entirely, or do we really philosophically just want them to cut down because of your concerns about progression and other things.

If you are looking at a three-month trial, what does that mean for somebody to cut down from 20 to 10 in the long run, what does that mean for that person's health, does that mean anything?

DR. STRAIN: Let me kind of back up a step, though. Well, no, Dr. O'Malley. I am sorry.

DR. O'MALLEY: I do think this kind of jumps to a different question, but if we are talking about reductions in drinking as the target, then, you may also want to think about some other target to help you decide whether that is

clinically meaningfully, whether it is some kind of quality of life measure that you feel good about or some kind of consequence measure, but I think it's hard for us to know, you know, what is the difference between 20 and 10.

A family member might be able to tell you something about whether that means something them, but again something that captures the quality of life index in addition to drinking might be useful.

DR. STRAIN: Could I ask in this vein - is it fair to say that simply self-reports alone are insufficient as an outcome measure regardless of the population that is being studied? In other words, do we want some other, or is self-report sufficient?

DR. O'MALLEY: Well, if you got differences on self-report, why would you ignore that?

DR. STRAIN: What about spousal reports are different? Look at Dr. Fuller's, the slide that has tickled him for years, it shows that you see those effects.

DR. O'MALLEY: You would assume that. I mean it's not really -- I don't think it is a totally fair assumption, but you assume that the propensity to misrepresent your drinking status may be similar across treatment conditions or, in fact, it might be greater in the group that is doing more poorly.

So, if you were, in fact, to find a difference

between two treatment groups on self-report, I think you could probably feel like that was a real difference. I think the additional measures are particularly useful if they actually end up adding something to ferret out the group of people that are misrepresenting, and you might actually get a more sensitive assessment.

I think the technology that Dr. Mason was talking about in terms of whether there are some ways of getting self-reports to be more valid is you probably saw the Science paper where adolescents are more likely to report negative behaviors and reported fewer pro-social behaviors when asked via computer versus interview.

So, again, if there were things that enhance the sensitivity of self-report or the validity of it, that might be good. However, I don't think that if you got a positive difference between two treatment groups on self-report, if you minimized demand characteristics that you would need to disregard that.

DR. STRAIN: Dr. Mason.

DR. MASON: There just also isn't anything better than self-report, more sensitive or specific, so you really don't have an alternative to it to consider.

DR. STRAIN: Dr. Simpson.

DR. SIMPSON: There has been some talk about compliance, but the extreme of noncompliance, of course, is

dropout. Would that be fair to say? And that seems to me a problem. It's a sort of varying problem from what Dr. O'Malley said in the sense that some of the dropout may occur because they don't see the treatment as being effective, but some of it may occur because of the side effects.

So, therefore, in the ones that have not reached a certain degree of tolerance, the side effects may be such that you get a huge dropout. On the other hand, if you have the severe alcoholics, the dropout may be huge because they don't receive the effect immediately.

So, you have got different design issues depending on who you are addressing, as well.

DR. STRAIN: Dr. Mason.

DR. MASON: I just wanted to add also data analysis issues to treat differential dropout rates between groups.

DR. KRANZLER: We did a literature review looking at completion rates is pharmacotherapy trials, and compared alcoholics, drug abusers, and groups of psychiatric patients, mood disorders, schizophrenics, and found that the alcoholics and the drug abusers had an overall completion rate of about 60 percent, and the other groups had an overall completion rate of about 80 percent.

There was no difference between alcoholics and

drugs abusers, but those two groups differed from all of the other groups. It didn't matter how long the trial was, although other predictors were limited because of we were dependent on what was already in the literature.

So, I think it is very clear that the patient groups that we are talking about here are unique in that regard in terms of treatment completion and probably also in terms of compliance, in terms of medication compliance.

In the study that I described before, we are getting daily reports. We are using MEMSCAPs, and we are also using the time on follow back, and what we see is that the concordance between the reported use of medication in the daily booklets and the MEMSCAP data is extremely high. It exceeds 90 percent just as a dichotomous yes/no. We are now looking at a little refinement of that in terms of when during the day. We have morning, afternoon, or evening, and haven't done those analyses.

We have also looked at daily reports relative to the time on follow back in relation to alcohol consumption, and we get also very high rates of concordance, and the daily events appear to provide daily events monitoring that the time line doesn't is a clearer definition of the frequency of the topography of drinking.

As you would expect with a retrospective recall, there is some averaging, well, yeah, I drank the same thing

every day last week, and basically, that is true, but when you look at the daily events, it is not quite. You get a little more definition.

I am not sure, frankly, at this point that in this population -- these are early problem drinkers, who have a higher rate of compliance, a higher rate of study completion, a higher proportion of women than our studies of more severely alcohol dependent patients do.

So, I am not sure that we could generalize beyond this group, but in this group it is not clear to me that daily events monitoring gives us a whole lot more in terms of drinking variable or medication compliance than the time line follow back in the MEMSCAP do.

We are still doing it because we are looking at variation in mood and a variety of other daily events that can only be acquired in using this approach.

So, I think it is going to be very important to tailor the methodology to the population and to the research question.

DR. STRAIN: Dr. O'Malley.

DR. O'MALLEY: I would like to add one thing, and if it is off the topic a little bit, it is in response to Dr. Simpson's comments about noncompliance due to medication side effects and dropout from a trial.

I am a big advocate of having a behavioral

platform for studying pharmacotherapies because they can enhance compliance with your medication, and enhance retention and treatment.

At the same time, I do want to mention what I feel needs to be a cautionary statement, which is if you remove people from your trial because of side effects, then, you are biasing you study results against the medication because our placebo group, which does not have side effects or has fewer side effects, is getting to enjoy the benefit of your behavioral treatment.

So, I would argue that in any pharmacotherapy trials where we have a behavioral platform, that we have some provisions for that behavioral platform to allow people to continue even if they can't continue the medication, and that is the way medications would be used in practice, as well.

DR. STRAIN: Dr. Meyer.

DR. MEYER: Are things like bogus pipelines more helpful with self-report data.

DR. STRAIN: Could you explain bogus pipeline?

DR. MEYER: Yes. Basically, you are collecting urine and throwing it away or collecting other tissue fluids. The patient has the assumption that their self-report is being monitored. I mean it is kind of sort of like having the MEMSCAP and collecting the self-report data

on medication use.

DR. STRAIN: Dr. Mason.

DR. MASON: We collect collateral informant reports, which is another form of pipeline, and I would say if we have 3 out of 100 discrepancies between self-report and collateral informant report, that would be quite high in our setting of alcohol dependent patients.

DR. MASON: But the question is do you have any sense that that increases the validity of the self-report having the other information there?

DR. MASON: No, I don't, sorry.

DR. O'MALLEY: I think Harriet knows the bogus pipeline literature.

DR. de WIT: No. I have a couple of leftover comments from earlier in the conversation. I have one comment on Dr. Falkowski's question. There is apparently evidence that alcohol abuse may be a separate disorder, and it may not be simply on the way to the progression to dependence.

On the other hand, people that get to dependence have to go through a period of heavy alcohol use, but certainly from an epidemiological point of view, it seems to be a separate disorder, which would argue for perhaps a separate specific treatment program for those people.

I had a separate comment from some of the other

discussion that came up, and it is interesting that at least from the point of view or the DSM-IV criteria, we define alcohol abuse and dependence in terms of problems of use and consequences of use, but then when we come to treatment goals, we talk about quantity of use.

So, there is sort of a mismatch there, and we are trying to match up the quantity of use, whether a reduction of use is appropriate, and maybe if it is possible -- and I can see how it would be very difficult -- to come up with a treatment goal that focuses on whatever it was that led to the criteria in the first place, the damaging consequences and the inability to control use.

DR. STRAIN: That is a very intriguing point.

DR. KRANZLER: It would be very difficult to do because the consequences tend to be relatively low frequency events that occur only with a long latency. So, unless you chose very carefully, I think you would be very hard-pressed to be able to --

DR. de WIT: But if those are the problem behaviors, then, that is probably what we want to reduce and target.

DR. KRANZLER: I don't disagree with the rationale. I am simply pointing out that the methodology becomes very tricky. There are studies that show a very clear relationship between either the average consumption or

frequency of intoxication and the adverse consequences, either medical or psychosocial, so there is a correlation there.

So, by showing an effect, it is an indirect one when you are showing an effect on drinking, but it is a proximal enough measure and one with enough variability that it is really reasonable, the best we can do.

DR. FULLER: Hank, I would agree with you that if the consequence is liver damage or automobile accident, that is a relatively infrequent criteria, but, for example, in Project MATCH, they developed a measure where they interviewed people about almost all potential problems. You have a drink, you know, getting in a fight, an argument, et cetera, and there they could document a rather dramatic decline even over a three-month period.

So, if you use some measure like that, I think it is possible.

DR. STRAIN: I would like to go back to something Dr. O'Malley said about having a platform of non-pharmacologic treatment involved in any studies, because it raises an interesting issue if we then go back even further to our endorsement of studying heavy non-dependent drinkers, because it suggests that it is all right to look at people with a lower severity pattern of use, but that we are advocating the inclusion of non-pharmacologic treatments

which may decrease an effect size that could be seen with the pharmacotherapy under those circumstances.

DR. O'MALLEY: I would argue that obviously, the intensity of that behavioral platform depends on the patient population, so again, with smoking cessation, you know, primary care providers don't see smokers weekly for the six-week trial, but they give advice, and then they have a follow-up phone call.

You can have a behavioral platform that is tied to the population, that would be acceptable to the population. My comment would be, though, whatever it is, everyone should get it even if they can't take the medication.

DR. STRAIN: I agree with that. It is an interesting contrast because in the smoking studies, you have got a relatively more homogenous population because you have got enrolled I think in those pharmacotherapy studies only people who are nicotine dependent.

What we are struggling with here is whether we are advocating an analogous population, say, people who meet some criteria for alcohol dependence or are we saying it is okay to propose a study that looks at heavy non-dependent users.

DR. O'MALLEY: I would agree that that would be an okay study to do.

DR. STRAIN: Let me follow it through then. We

want to create a situation where we think there is the greatest likelihood of seeing an effect, a significant effect, and so is it possible that if we take non-dependent heavy users, give them all a platform of non-pharmacologic treatment that has some moderate efficacy, that we are creating a situation where we may have an effective medication for more dependent populations, but we are not going to see that effect?

The field is going to say, ah, this doesn't work, this medication doesn't work, and it isn't that the medication doesn't work, it's that we have created, we are on Dr. Anton's slide, we are in one of those zones.

DR. de WIT: I would question your goal of seeing a medication work or seeing that the medication works. I think our goal is to decrease the drug use. So, if we can accomplish that by behavioral treatment alone, then, that is what we should go for. Our goal should not be to demonstrate that a particular drug is effective.

So, if psychosocial treatment is enough for heavy alcohol users, then, we need to find that out, and then looking for a pharmacological treatment on top of that is extra, it is redundant.

DR. STRAIN: You could take that a little bit further I think. I mean we know that psychosocial treatments can be effective, but you might say, well, you

know, can we create a more cost effective treatment, in other words, rather than spending $50 a week on psychosocial treatments, can we create a situation where we send $5 a week on psychosocial treatments on average and $10 a week on pharmacotherapy, and still get the same effect. But I certainly hear you.

Let me just say that I think this brings us in part to the questions of treatment outcome, so we also need to debate amongst ourselves what we think are the optimal primary outcomes measures, which are some of the questions in the lower half of our page.

Dr. Franklin.

DR. FRANKLIN: If I was looking at a grant, I would really want to be looking at the rationale of why this is the best population to study, the heavy drinkers, for a pharmacological intervention because the animal models and everything, you would want to be something biological.

Why would that be the population to study for a drug? Just going through the rationale of an animal model for something that you were treating in the brain, I mean it may be just by happenstance it works in heavy drinkers, but what is the rationale for using that population going up from an animal model?

DR. STRAIN: I might think that it would be better to look at a medication in a more dependent population

because, for example, you have got a greater likelihood of seeing an effect. So, to get back to Dr. Kranzler's example, if you are looking at people who drink alcohol 20 times a week, then, you are going to start to hit that floor, as he pointed out, in seeing decreases.

If you look at somebody who has got a heavy use pattern, then, you have got a greater chance of seeing a decrement in use, because there is a greater range.

MS. FALKOWSKI: I guess the point I was trying to make was how many people drink 20 or 40 drinks a week that don't move to dependence?

DR. KRANZLER: Many.

MS. FALKOWSKI: And then aren't we looking at a small population?

DR. KRANZLER: I don't think so. If you look epidemiologically, approximately 7 percent of the U.S. population obviously depends on which study, but, say, the National Comorbidity Survey, approximately 7 percent of the population meet alcohol DSM-III(r) alcohol dependence criteria in the preceding 12 months, and then you look at the National Alcohol Survey, and approximately two to three times that number don't really meet dependence criteria, but drink at heavy enough levels.

That would be I think the target population we are talking about. Those are probably people -- well, they are

certainly more numerous than those who are alcohol dependent, but I think a problem in studying them is that they are probably not as motivated, life has not gotten as difficult around their drinking problems.

We are also doing a study now, it's a purely psychosocial study looking at the mechanism of brief interventions, and finding that -- and we are excluding anybody that meets abuse or dependence criteria, they must only meet a consumption criterion -- they are very hard to recruit, and that is for a psychosocial study only.

I think it might be more difficult to recruit patients for a pharmacotherapy study or it certainly would be of comparable difficulty, I would think. So, I would say although I can see no philosophical reason or no clinical reason not to do this, or scientific reason not to do it, I would say --

DR. STRAIN: Not to do what?

DR. KRANZLER: Not to focus on this heavy drinker group that is not alcohol dependent. Caveat emptor, I think it will be a very difficult study to do particularly it is going to require large numbers, larger numbers because of the relatively small effect size that one might expect, and I think those larger numbers will be harder to recruit than the people that we have been recruiting in our trials, and I think Barbara was making that point.

MS. FALKOWSKI: And then getting to Eric's point, I mean is the goal of treatment then to get their drinking get to a moderate level, or would it also be an outcome measure to delay the onset of the disease, as well. Is that another outcome measure for this group?

DR. O'MALLEY: That just seems like a very hard outcome measure to get to. That takes years and years and years. So, I think one could look at a reduction in drinking as an outcome, but I think that kind of study, you probably would want to have a little bit longer window on to understand whether that is clinically significant, whether there is a tolerance that would develop to that effect.

DR. STRAIN: Dr. Simpson.

DR. SIMPSON: I was just thinking in light of what you were saying was that the nicotine analog has been brought up several times, and if we are going now into alcoholics, I guess, would the pharmacotherapy really be effective. I mean would it be reasonable just to look at a 12-week period, because there was some evidence produced in the Nicotine Workshop that, in fact, for several people it is not a matter of just chewing gum for three months, it is a matter of a lifetime habit to keep away from cigarettes, and so on.

So, it brings up then the issue of does a 12-week period really cover the right period.

DR. STRAIN: I am trying to get grants funded to look at people over their lifetime, but nobody wants that funding period.

Dr. Andorn.

DR. ANDORN: I couldn't agree more. I think we are looking at a chronic illness, and I don't think anybody would use a 12-week window for diabetes. It is pretty silly that we continue to use the 12-week window for everything, whether we are talking cocaine, nicotine, or alcohol, and we do need those long outcome studies.

We have no clue if a pharmacologic or even behavioral intervention that works for three months is effective at three years. What is the lifetime relapse rate? I do think we need to bear that in mind when we design pharmacologic studies.

DR. STRAIN: Well, then, back to Dr. Simpson and you both because you are saying you are agreeing, and not to make light of it, so what period would you say ?

DR. SIMPSON: Well, I don't know, but looking at the data that was presented today, if you looked at that graph that we were given with the three month and then the stuff after the three month, you can see the drug gradually getting up again to the placebo.

I don't know if that means anything, but when you look at it, that is what it seems to be saying.

DR. STRAIN: Dr. Fuller.

DR. FULLER: This question is for the FDA. You know, I can see where a longer period of time would be more informative, but it is my understanding for drug trials for arthritis, asthma, that often a three-month interval is rather standard for pharmaceutical firms to submit applications to the FDA. Am I mistaken on this?

DR. McCORMICK: No, you are not. It really varies with the disease that you are studying certainly for other neuropharmacologic drug products, for example, three weeks is a fairly typical window, but I think the question that we need to ask this group is, is that same window appropriate for this disorder or do you need a longer period of time to observe.

DR. KRANZLER: I once had the opportunity to present the results of a pharmacotherapy trial immediately before George Valiant gave a talk, and his question to me was at the end, very politely said, "So what do you think happens after 50 years," because he has got 50-year follow-up data, and that is a very humbling question, and I think it is an important question, but the cost of these trials is such that I don't think it makes sense to start out with a long trial.

I think we are to some degree -- and I am not wholly unsympathetic -- but we are to some degree self-

handicapping when we identify alcohol and drug dependence as so different from other neuropsychiatric disorders as to warrant a totally different approach.

In fact, there are trials now in family members of insulin dependent diabetics looking at pharmacologic interventions to prevent the onset of insulin dependent diabetes. There are trials in offspring of women at risk for breast cancer, looking at prevention of breast cancer.

So, I think it makes a lot of sense for us to be thinking about high-risk groups and particularly groups that have demonstrated problematic drinking behavior as a criterion for high risk, and both because some of them probably will go on to alcohol dependence, although I think it is probably a relatively small proportion, certainly not the majority, but certainly there are morbidities associated with that drinking behavior that warrant interventions including, I believe, pharmacologic interventions, because although psychosocial interventions have an impact, there are a substantial proportion of people who don't respond effectively.

We are not hitting a large proportion of the people in the general population because physicians don't have the confidence in a brief psychosocial intervention that they have in a pharmacological intervention, and there is also patient acceptability of medication that has been

demonstrated to be effective.

DR. McCORMICK: If I may continue my response to your question before we go on, and that is one observation that I would make that differentiates the approach that I have seen in the addiction area with the approach in the neuropharmacologic area, is that in the neuropharmacologic area we tend to have roughly three-month trials for many disorders, but with continued therapy well beyond that period of time, for many, many years.

In many disorders we see the diseases subside under treatment. In this case, what we frequently see is that the treatment stops, and then the follow-up is lost, and the disease continues.

Is this a reversal of that paradigm, and I wonder if you could comment on that.

DR. FULLER: I can't comment directly, but there was a recent article on depression where it did show -- I believe it was published in JAMA within the past year -- treatment for depression was stopped, the same phenomenon that has been shown here occurs in depression, and they went on then to design a trial trying to maintain the medications longer to prevent relapse to depression.

So, this may not be as different from, for example, depression as might appear on the surface.

DR. STRAIN: Dr. Falkowski.

MS. FALKOWSKI: If I could get back to Dr. Franklin's remark and also Dr. de Wit's, that it strikes me that really what we are talking about here is something that we really haven't captured the essence of yet in our discussion in the sense that we are talking about the idea of treating with medication that which is a behavior, and it is not a disease, it is just something people do, and it does have health down sides, but should we start pharmacotherapies on people who have too much fat in their diet or other things that are behavior --

[Laughter.]

DR. SIMPSON: There are studies for that.

MS. FALKOWSKI: I know there are studies, but I am saying is behavioral intervention the preferable course to go given the fact that now is as we are moving toward more pharmacotherapies, we don't know the long-term health consequences, for example, of being on the patch for all of your life, and we know that from other pharmacotherapy studies, for example, with Zyban, that once you get out at a six-month window, that the effect dwindles, so I think it is a huge issue.

DR. ANDORN: Eric, if you could go back to the point of open label, I agree it has really struck me that in all of the studies on my tenure on this committee, none have had an open label phase, whereas, all the neuropharm studies

have an open label phase, and we do out one, two, three years. We also have had these drugs on the market long enough to have 15-year famous outcome studies looking at recidivism rates, and so forth, and even though we have that experience in all the rest of psychiatry, that has not been applied to the way we approach the pharmacologic study of substance abuse.

DR. STRAIN: Dr. Mason.

DR. MASON: I just wanted to call to the committee's attention that there is some difference in terms of the European pharmacological trials of medications. I am thinking of [acamprosate] where the typical length of the trial is a year in duration, and they sustain drug placebo differences, you know, one year out.

Also, they have extended follow-up periods of a year where the differences are sustained. So, there are those data from Europe. In terms of your question about adding a pharmacotherapy, if it also ties in with the question about the type of behavioral intervention to have as your platform in the pharmacotherapy trial, I think it is important that the behavioral therapy have ecological validity, that it be typical of what would be routinely offered for the treatment of the target symptoms in the setting in which they present, and then if you do a placebo-controlled trial, you can look at whether the medication

adds anything above and beyond the effects of standard care.

That standard care would not be such that in all likelihood the effects of the pharmacotherapy would be washed out.

DR. STRAIN: Dr. Fuller.

DR. FULLER: Let me just again return to the issue of alcoholism treatment versus depression treatment, and you are absolutely correct that there is much more data for depression. The situation there, of course, is that effective antidepressants were developed 20 years ago, and there has been this opportunity to acquire this data.

I am a little concerned that if we don't allow pharmacological therapies for alcoholism, the same evolutionary course, we are going to miss out on some important things, and we perhaps have to begin with shorter duration trials and then add to that knowledge.

DR. ANDORN: I would just add shorter duration, but open label armed, so that we do get the longevity experience that we have with the other drugs.

DR. O'MALLEY: So, you mean after the trial is ended, that people are allowed to continue on --

DR. ANDORN: Absolutely. That is essentially what you are suggesting with the open label behavioral arm, that they continue on a treatment even if they drop out of the drug treatment.

DR. O'MALLEY: I will just add to this discussion we finished a trial of discontinuation of naltrexone in treatment responders, so I think that sort of science takes a while to catch up to what some of the questions are.

DR. STRAIN: Is it the case, then, that the committee feels that a three-month period of time is an adequate balance between gaining the data necessary to answer a scientific question while still not so long that it becomes cumbersome or you have attrition or whatever, or do members have a feeling that we should be looking at a six-month trial?

DR. KRANZLER: How about eight weeks?

DR. STRAIN: Or whatever.

DR. MEYER: I am not sure you go to six months, but I was really impressed with the statistical presentation that we got, and I am impressed that you may get that one second episode in the 12 weeks with a certain number, and that if you can carry the trial out for a longer period of time, I mean I agree that you would run into compliance problems if you run out six months, but maybe you do four months, maybe you do four and a half months.

I mean that three months has been the standard, but it is because we haven't been looking at this other statistical approach, and I think we should be following up on Dr. Anton's generous offer to the FDA to have the

statistical analysis done on his data to see what happens with the three months, but I don't think we should close the door to doing a trial longer, and I do think that the open label period ought to become an option and ought to be encouraged, because that is the way we are going to learn something in terms of, over time, issues of compliance and whether the drug continues to be efficacious.

DR. STRAIN: Dr. de Wit.

DR. de WIT: I think we are talking about a couple of different issues at once, but I certainly would not advocate using the three-month period to extend the standard for pharmacotherapies for the alcohol abuse, for the heavy drinkers, for the reasons that we came up with, that there is so much variability in the patterns of drinking that the three-month window might not be enough to actually -- but I might be mixing up issues here.

DR. MEYER: That is another issue, that is a third issue.

DR. de WIT: With regard to the dependence.

DR. STRAIN: So, your point being that for the heavy drinking population, a longer period is --

DR. de WIT: Definitely.

DR. STRAIN: Thank you. Dr. Winchell.

DR. WINCHELL: I think you probably foreshadowed what I was going to say, which is that before we decide how

long to measure something, we should probably have some agreement on what we are measuring and who we are measuring it in, and then we might be able to -- because otherwise we are going to have a lot of difficulty.

DR. STRAIN: Dr. Simpson.

DR. SIMPSON: I won't say anything more about the length of time, but traditionally, the length of time in a lot of drug trials has been determined by the rate of dropout. By the time you get to three months, you have got such a large dropout that you are in trouble anyway in interpreting the results.

When we were told that it was 60 percent remained in the trial, I thought that that sounded quite good. I mean an 80 percent sounded terrific, I mean I don't know, some of the stuff I have seen has been much, much less. I think that that is an issue anyway whoever you are looking at. If you are thinking about going out further, I don't know about interpreting the results.

DR. STRAIN: Thank you.

Dr. Franklin.

DR. FRANKLIN: In listening to the conversation, we are even using these terms interchangeably, heavy drinking versus abuse versus dependence, and in my mind, when I look at like Debra Hassan's work with abuse and dependence are closer together than heavy drinking, so again

I am not sure who we are talking about sometimes when we are talking about the 20-drink-a-week person who is a heavy drinker versus somebody who also has abuse, that meet the criteria for abuse.

If they meet the criteria for abuse, they are closer to dependence, and I think we need to separate these, so that when we have the discussion this afternoon which population are we talking about.

DR. STRAIN: Dr. McCormick.

DR. McCORMICK: I wonder if we can focus back on something we started to talk about a little bit earlier and go over the dichotomy that seems to have been drawn in the earlier part of the discussion.

It seems that in answer to the first two questions, we have heard delineation of four populations. One is the adolescent heavy non-dependent drinker, women of child-bearing potential, alcohol dependent, the severe recidivistic alcoholic, and the patient with the dual diagnosis.

What we have heard about the first two populations, which really I think are the populations that we are for the moment most concerned about whether or not we should even be studying them, was that we heard that there was a need for intervention, but a lot of sort of waffling as to what that intervention might be.

I would like to focus back on Dr. de Wit's comments and where she really brought us back to what is our goal here, what is the outcome that we are looking for in terms of the patient.

We can always design a study to help us show a difference between two treatments, and so on, but I think our goal really is the patient and how can we bring the patient to the point that we want them to be.

I think the reason that we want the field to comment on this is because you are really closest to the problem, and I think the real question that we have is, is there a need for pharmacotherapy at all in these two populations that you have said there is a need for intervention in. I wonder if we could bring the discussion back to that.

DR. STRAIN: So, those two populations, just to make sure everybody is clear, were?

DR. McCORMICK: The adolescent.

DR. STRAIN: The adolescent heavy user.

DR. McCORMICK: Right, and women with child-bearing potential.

DR. STRAIN: And women of child-bearing potential.

Yes, Dr. Fuller.

DR. FULLER: I have a concern limiting it to the groups that you have mentioned, because the epidemiology

data does suggest that there is a large proportion of people who meet alcohol abuse criteria, not just adolescents although that certainly is an important group, and I would be concerned about limiting it to the four groups that you mentioned.

DR. McCORMICK: Let me expand it then.

DR. FULLER: Please.

DR. McCORMICK: To any group for whom psychotherapy appears to be effective. Is there a threshold over which you feel that further intervention is necessary, and what might that threshold be?

DR. O'MALLEY: Wouldn't that really require us looking at what the -- I can't cite these numbers off the top of my head -- but how good are behavioral interventions for these subgroups, and if our success rate is 90 percent, and that is it, well, maybe we don't need to develop treatments for that population, but I am not sure that those are the success rates. So, that would be one condition.

Also, the distinction between alcohol dependence and hazardous drinking really lies in whether you have three versus one criterion. I mean you have the criterion of impaired controls, that you drink more than you intend to, and that are you not acknowledging the fact that your friends, you know, your mother is really concerned about your drinking, and your friends think you are doing this or

that you are taking advantage of women at the fraternity house.

So, I think it is an arbitrary distinction about where you cut off the criteria for making a diagnostic conclusion do they have dependence or not. In some ways I like the idea of thinking about a target group that is drinking at levels that have been deemed to be hazardous to health, maybe even apart from the psychosocial consequences, but it is based on some quantity frequency measures, as well.

DR. STRAIN: Dr. Andorn.

DR. ANDORN: I think the answer to your question depends on where you sit. When I hear from the family practitioners in my town a lot is have they come up with a pill yet because managed care is truly driving us -- and I am paraphrasing one of my colleagues -- is driving us that pharmacologic treatment is the only treatment we are going to be able to offer in a lot of settings because it is acceptable, because it's quick, because we don't have to spend a lot of time with the patient, and in the family practice setting they are looking for an intervention that they can do, which means that their answer would be all of these groups are target groups for that kind of study.

Those of us who sit in psychiatry, I think our answer would be very different, and we would go with the

clearly dependent criterion as the target group for study.

DR. de WIT: I guess I am a little concerned that at the same time we are talking about reducing the duration of the treatment and apparently the follow-up measure, as well, and then also there is a bias where it is looking for a pharmacological treatment, and yet we know that it is the behavioral treatments that have the most lasting effects, and now we are deciding to not look so much at the long-term effects and to focus more on the pharmacotherapy.

I am afraid that we might be losing what we have learned from the behavioral treatments, that whatever skills people acquire through psychosocial or behavioral interventions have a lasting effect.

DR. MASON: There are ways of making the behavioral treatment in more portable packageable forms that have been pioneered in the primary care setting, like the patient education materials that NIAAA has developed, the How To Cut Down On Your Drinking brochure, the materials to help with the diagnosis in primary care settings, because particularly in the population of females of child-bearing age, diagnosing is so often overlooked in the Ob-Gyn setting where they are most likely to present, that you do need these kinds of support materials, and that self-help kind of packages can be easily combined with pharmacotherapy, and that is the tradition.

DR. STRAIN: Dr. McCormick, have we addressed your --

DR. McCORMICK: I think we will hear more.

DR. WINCHELL: I would be interested to know whether you think that people who have not yet failed a non-pharmacologic intervention should be candidates for pharmacologic intervention, and then as a follow-on to that, if they have failed a non-pharmacologic intervention, are they still candidates for advice to moderate their drinking.

DR. STRAIN: The first question was a person who has not failed a non-pharmacologic intervention, is that correct, is that what you were saying?

DR. WINCHELL: This is your first intervention with the patient and you haven't yet given them advice or psychotherapy without medication, and maybe they can do it without medication, do we think that the field of medical practice is moving toward prescribing medication at the first intervention, in which case it would make sense to test it in that situation, or do we think that medication is reserved for people who have filed non-pharmacologic interventions, and if people fail non-pharmacologic interventions, does that by definition make them alcoholics and they should be advised to abstain.

DR. O'MALLEY: I would suggest that one strategy in a trial might be to give brief advice to cut down in

certain criteria, you know, drinking instructions, and then if someone is not able to do that, then, you provide the pharmacological intervention. I mean it is kind of a step care approach.

I think the problem with alcoholism treatment -- now, this is about alcoholism treatment, not about primary care management of heavy drinking, is that often people don't make very many attempts, so they come to your door, and if they don't succeed, they are out of there, and they may not be going for anything for many years after that.

You might want to consider the possibility of brief advice initially and then enrolling those people that are unable to do that into a trial.

Again, it probably depends on your medication about whether someone who fails the first step could be considered for a moderation goal. If your medication really only helps you with protracted withdrawal and abstinence initiation and maintenance, then, a moderation goal may be inappropriate for that medication, period.

If somehow the medication interacts with alcohol in a way that reduces the likelihood that you will continue drinking, then, maybe someone who has not been able to moderate their drinking with just advice might benefit from that pharmacotherapy.

So, those would be the kinds of considerations

that I would at least consider.

MS. FALKOWSKI: I think you have captured exactly the -- I mean that is the questions you pose, and it strikes me if a person is heavy drinking and is having no negative consequences at all from that heavy drinking, how motivated would they be to participate in anything, because nothing is happening, you know, what is the motivation.

When we look at the graphs that were on earlier where motivation is key, you know, how realistic is that. Can you comment on that?

DR. KRANZLER: I think it is important to recognize that 20 years ago, people who were smoking were not seen as having a problem behavior necessarily. I think that what has transpired, at least in the United States and in many of the industrialized countries is a totally different view of smoking behavior.

I think what this meeting, and others like it, probably reflect -- and I may be unduly optimistic here -- is an increased awareness that drinking at non-problem levels, despite the fact that there is good evidence that chronic drinking at that level causes certain medical problems, that there is the likelihood that there is going to be progression in a minority of people to heavier levels.

The point I am trying to make is that I think we are changing our views of drinking behavior, and as this

happens, physicians are more likely, and other health care practitioners, are more likely to begin to identify people. People themselves who are seeing a health care worker, for example, are going to be more open to hearing that their drinking is more than is good for them even though they are not currently having problems, so I grant you, at this point in time, there probably isn't a lot of motivation, just like there wasn't a lot of motivation for people to quit smoking when they didn't have a chronic cough, for example, 20 years ago, but I think we need to recognize that fact.

Getting back, however, to here and now and the FDA issue or the pharmacological issue, I think it is important to recognize that there are significant methodological problems despite the fact that it is desirable, I believe, to focus on this group pharmacologically.

The reason I think it is desirable is because whether we want to acknowledge it or not, managed care is having a progressively greater influence on the practice of health care. As a psychiatrist, I am reminded of a number of efforts that were made to treat schizophrenia without medication, so I think that there is -- you know, with only psychotherapy -- and they may be a leap, but my point is that I think we are very skeptical of medications, and I think at times it is an unhealthy skepticism, I think it goes beyond a healthy skepticism, I think it's a reluctance.

Now, I am not saying we should put naltrexone in the drinking water, although it might improve the taste sometimes, but I am saying that we are very free to use lipid-lowering drugs for people who don't have any symptoms because we know that elevated lipids are a risk factor for cardiac disease, and now subsequent to their approval, there is now evidence that, in fact, they may prevent myocardial infarction.

Why have a bias when we are talking about drinking behavior? Why are we using a double standard? I mean just as we need the kinds of studies of safety, the longer term studies in relation to drinking behavior, I think we ought to have an open mind to using pharmacologic treatments.

There is nothing magical about giving advice to people to reduce their drinking compared to reduce their doughnut intake. Some people respond by reducing their doughnut intake, some people respond by reduce their drinking behavior, but not everybody does.

DR. MEYER: I want to get back to Dr. Winchell's question because it is a tricky and slippery slope, and it sort of goes in all directions.

I really believe that psychosocial behavioral advice interventions substantially enhance nicotine replacement treatments, I think there is good evidence for it, and I also believe that many primary care physicians and

patients, who now can get the drug over the counter, may be just taking the replacement and not even reading the advice that is available through the manufacturer.

FDA is not in the business of psychotherapy assessment and review, and I think it is a tricky issue to get into, and I think if you begin to think about mandating the treatment is only for those who fail in the behavioral intervention, you run into all kinds of other consequences that you may not want to get into, so I think you have to be very careful about putting that as a requirement.

DR. WINCHELL: I think we are talking more about selected criteria.

DR. MEYER: I understand, but even doing it that way, it is a very tricky selection criterion, because in practice, we always end up moving toward the least intensive cognitive intervention in our system of health care. We are moving toward less and less cognitive intervention, more and more just straight take a pill and it is going to go away.

Whatever we may think about that, that is the way it evolves, and I think it is in the FDA's interest to make sure that what is out there is effective, efficacious, and doesn't produce adverse consequences.

The other side of that issue is that the medications may be adjunctive, adjuvant as they were described here, to the behavioral intervention, and if a

patient fails in the behavioral intervention and then is given the medication, you know, is there an order effect which reduces the effectiveness of the behavioral intervention because it wasn't given simultaneously.

I just don't know. You get into all kinds of other issues if you set that as the bar before you would use medication.

DR. STRAIN: Could I just respond to that actually, though, is it the case, though, could you conceptualize what Dr. Winchell was saying as a placebo washout period.

DR. MEYER: No, because a placebo washout period is a placebo washout period. It would be basically giving a placebo.

DR. STRAIN: With a basic level, basic platform of non-pharmacologic treatment.

DR. MEYER: But you are giving a treatment.

DR. STRAIN: But I mean I think many placebo washout periods do include some form of a non-pharmacologic treatment with that.

DR. MEYER: The placebo antidepressant trials, I don't believe offer cognitive behavioral treatment for the depression before they --

DR. ANDORN: If I may interrupt, most of the inpatient schizophrenia trials have a placebo washout

period, but certainly the patient is getting therapy, they are in groups, they are in a variety of other issues.

DR. MEYER: But that is a distinct group.

DR. ANDORN: I think most of the inpatient trials are that way.

DR. MEYER: Right, but in your outpatient depression trials, that does not happen.

DR. WINCHELL: There is no therapy at all in those trials, not even during the active medication treatment administration, there is no therapy at all.

DR. SIMPSON: I guess your comment about they are getting a treatment, and therefore it is not a placebo, I mean the placebo can be a treatment, and, in fact, the placebo in any psychopharm trial is really a treatment arm, it is not a non-treatment arm, so I don't think that is a fair criticism of building on the platform of psychosocial.

I think the real problem is how you interpret the results.

DR. FULLER: It still seems to me there is a difference between a placebo washout period, which may be one or two weeks, and a criteria where you are only going to give a pharmacological therapy when it has been demonstrated over a period of time that the non-pharmacological therapy has failed.

Again, I would go back to the depression model.

You know, if that requirement had been used for the pharmacotherapy of depression, it might have taken longer to realize that there are effective therapies, and I would just like to see the bar higher for these treatments than for depression treatments.

DR. WINCHELL: What I am harkening to is the advice that Dr. Longmire presented, which is that someone has made repeated attempts to cut down unsuccessfully, which means on their own or through suggestions by physician or family members or other concerned people. They have already tried, and they have failed, then, they are no longer considered a candidate for moderation.

I heard Dr. O'Malley say that if we thought we had a medication that could change that advice, that if there was a medication available that would make moderation possible for people who had made repeated unsuccessful attempts to cut down, we should find out about it, and that is one question I would like to get a general sense of, and then the second question is who should not be allowed to participate, who would have insufficient severity of illness, and who would have too great a severity of illness to be allowed to participate in a trial of that sort.

DR. KRANZLER: I am not sure that the DSM criterion of repeated unsuccessful efforts to cut down is really a good one for making this distinction, because it

also includes frequently thinking about cutting down, and I think that is very different than seeking treatment or being given advice by someone who is presumably a trusted adviser like physicians used to be, and I think that is a very different kettle of fish. I think people do respond to that, my cynicism notwithstanding, very differently than efforts -- that reflects something different than simply efforts on their own or thinking about it repeatedly or often or persistently.

So, I think it is going to be very difficult to operationalize that, and we have tried to do that by limiting people who have any evidence of physical dependence or who have more than a limited, that is four, which we considered mild dependence.

Now, I grant you that is arbitrary or it's somewhat arbitrary. I don't know of a good, hard criterion for that, no more than the drinking cutoffs. The 14 drinks a week for men, 7 drinks a week for women, that is not derived empirically.

Sanchez Craig has derived criteria that were published in the American Journal of Public Health from three treatment trials, and those are actually I think a little more -- they are not very different, I should add, but they are derived empirically, and so I think they have some greater force.

So, I think trying to limit people in terms of what we should recommend to them based on whether they have tried to cut down before doesn't make sense.

DR. WINCHELL: What is the minimum severity for inclusion in your trial, is it simply a level of drinking --

DR. KRANZLER: Yes.

DR. WINCHELL: -- or are there other indicators that you look at?

DR. KRANZLER: No, the minimal level is 21 drinks a week for men and, if I recall correctly, 16 drinks a week for women, which we calculated would provide, if we could then get them to reduce below the Sanchez Craig criteria, would provide enough of an effect size that it would be clinically meaningful, and we then powered the study based on that.

DR. WINCHELL: And the treatment goal for your patients in this trial is moderation?

DR. KRANZLER: It is to treat non-hazardously.

DR. WINCHELL: Do you have any preliminary data yet on how your placebo group is doing?

DR. KRANZLER: No. It is too early to break the blind. We have looked only at the validity of self-report versus the monitoring measures that I mentioned before.

I can tell you, though, we participated in the WHO study of early intervention, and what we found was that

literally five minutes of simple advice, six months later, showed an effect. That was literally five minutes of simple advice - you are drinking too much, these are the problems you have identified. It followed a 40-minute interview, but then groups either got five minutes of advice or not.

There was a demonstrable effect six months later, and it was solely attributable to the simple advice. We looked at a variety of other predictors. Now, that having been said, it was a modest effect on an aggregate basis.

We used Sanchez Craig criteria, everybody met it. Beforehand we looked at those who did versus those who didn't after six months, and simple advice differentiated those groups.

DR. MASON: I have a little data that might contribute to the discussion. In our pilot work with nalmefene, it was a double-blind, placebo-controlled trial, and it involved no concurrent behavioral therapy because it wasn't a funded study and we report, and what we found in the 90-day pretreatment time line was a decrease in drinking as people made the decision to make the phone call to make an appointment to come in, so you do see a decline in drinking level prior to even setting foot in the clinic, and then in terms of the placebo effect, there is a tremendous amount of activity in a clinical trial around monitoring and drinking and the patient's well being, et cetera, so there

is a lot of TLC that goes into the placebo group.

Nonetheless, we did get between-group differences on the outcome of heavy drinking that I think is probably the one that is most consistently affected by the opiate antagonist. However, when we then did the larger funded study and entered on the cognitive behavioral therapy, we got much better retention in treatment relative to the pilot study that didn't have behavioral therapy, but we also got an effect, I believe, of the cognitive behavioral therapy based on the finding from Project MATCH where the behavioral therapies influenced the percent of abstinence days, the number of drinks per drinking day.

We got across groups, all groups showed significant reductions from where they were pretreatment on those measures that also showed those effects for the behavioral therapy alone in Project MATCH, whereas, in the pilot study where we did not have behavioral therapy, we had also gotten statistically significant changes within treatment groups. I just wanted to let you guys know that.

DR. McCORMICK: Again, what were the inclusion criteria for those?

DR. MASON: These were alcohol dependent subjects.

DR. STRAIN: The time allotted for our discussion is coming to a close, and I wonder if the FDA feels we have addressed the questions, if there are particular questions

that we should take a couple minutes to focus upon or there are new questions that have come up that we should debate.

DR. McCORMICK: I guess I have the same old question, and I would like to hear just a little bit more on this. The reason is that when the FDA approves the pharmacologic agent, it may change the face of treatment, and I think that is important to keep in mind as we approach that and perhaps learn from some of the other pharmacotherapies that have been used for other psychiatric disorders or neuropsychiatric disorders.

I would like to ask again would approval of a drug in a setting of patients who are not dependent, but merely heavy drinkers, for whom psychotherapy has shown to be effective, would approval of a drug in that setting legitimize a treatment that may not be appropriate or that this group feels might not be an appropriate therapy. That is I think our biggest fear.

DR. STRAIN: Let me just make sure I understand that. You are saying that the labeling for the drug would not say that it is indicated for people with heavy drinkers?

DR. McCORMICK: No, I guess what I am really getting at is, is it appropriate to treat people with medications for whom there is another approach, because this may actually change the way people are treated.

DR. STRAIN: But isn't it the case, I mean

regardless of what we do, practitioners may then use off-label, you know, use the medication off label for other populations.

DR. McCORMICK: Let me try to paraphrase. I think the issue is a basic ethical issue - should the FDA even look at developing a drug for a disease that we know has efficacious treatment that is non-pharmacologic, i.e., behavioral.

DR. MEYER: I would submit that you have an absolute obligation to look at that. I mean there are different streams of thought within Alcoholics Anonymous. There are people in Alcoholics Anonymous who believe it is the only treatment, and you should therefore not be looking at treatments for alcohol dependence.

There are other streams within Alcoholics Anonymous that say, well, it is a disease, we are prepared to look at medications. I think it is very dangerous to come down and say, well, we have a treatment which is non-pharmacological and it works in 75 or 80 percent of the public, and therefore we shouldn't be looking for medications for this, and it may turn out that you have a treatment of medication that could turn out to be less or more efficacious than the behavioral intervention.

You have an obligation to look at that treatment. It may, in fact, change the way treatment is given. Like

Dr. Kranzler's point, when I was a resident, medications were considered copping out if you gave them to a schizophrenic. They were considered definitely copping out if you gave them to a depressed patient. You change the face of the way psychiatry is practiced.

Now, none of us thought it would go as far as it has gone, and it has gone too far in a particular direction, but had you done what NIMH was actually doing, preventing clinical trials in the early sixties, such that the Congress had to step in to say you will do clinical trials, you will set up a psychopharmacology service center, then, you would be really not serving the public interest.

MS. FALKOWSKI: But half of that discussion focused on people who don't have the disease, they are just heavy drinkers.

DR. MEYER: But the point is we do have people who eat too much fat who are now involved in taking medications that lower their low density lipoproteins and increase their HDLs. If you had a medication that caused people to exercise more and that caused people to eat less fat as an alternative to those, it would be perfectly fine, but the point is that the behavioral interventions for these people don't work all that well, and you have drugs that reduce their risk factors.

DR. STRAIN: Dr. Franklin.

DR. FRANKLIN: It seems like it is several questions. One, is this a promising area of research, can you do these studies. That is one thing. If it happens to work, then, I think you need to take a look at it.

DR. STRAIN: Dr. McCormick.

DR. McCORMICK: I think, Dr. Meyer, your response to my question presumes -- and you are the expert -- that what we are looking at really is a continuum from heavy drinking to addiction, and I would like to get opinions on that for the record, because I think that really goes to the heart of the matter.

DR. MEYER: No, I think the issue is not heavy drinking, but drinking which is potentially harmful or hazardous, and that we do have tools within primary care settings to identify that, and we do have tools in the context of the population of the college age drinkers, that we know that most of those people mature out of it, but if we save some lives in the process of people who are at serious risk of automobile accidents or creating other problems, the medications could be a helpful intervention, if nothing else, and there are limited other options.

DR. STRAIN: Dr. Fuller.

DR. FULLER: Dr. McCormick, you asked if you have an effective behavioral therapy, is it worth also looking to see if there is an effective pharmacotherapy, and I have

been interested in studies, and there has been actually several of them the past year looking at pharmacotherapies and behavioral therapies.

There was one study on urinary incontinence where there is an effective behavioral therapy, yet, they went ahead and studies pharmacotherapy. In that particular instance, the behavioral therapy actually did better than the pharmacotherapy.

In the other studies that I have reviewed -- and I am looking at non-alcoholism studies -- usually, the pharmacotherapy is superior or additive, but there can be effective behavioral therapies, and people still look at pharmacotherapies.

DR. WINCHELL: Some of these comments have been very revealing for us. When we first were asked to consider whether we think developing a medication to reduce drinking in people who weren't alcohol dependent, whether there was any logic to that, some of us thought, well, a study like that would be doomed to failure because these people would be responsive to simply advice, and I am hearing that the experts who are with us today don't think such a study would be doomed to failure, that a pharmacotherapy to help reduce their drinking could find a market, and there are people who could benefit from it and who need it.

Is there consensus on this?

DR. STRAIN: Dr. Kranzler.

DR. KRANZLER: I wouldn't say that they are doomed to failure. Obviously, I have said they are not. I do think, though, that it will be very difficult to demonstrate a between-group difference based on the kind of effect size that would be possible in a study of non-DSM diagnosable either abuse or dependence heavy drinkers.

So, I think you are going to need a very large sample size, and sources of error are going to have to be minimized to maximize the effect size and to minimize Type II error.

DR. STRAIN: Dr. Meyer.

DR. MEYER: I think there is another issue, and that is the whole issue of proof of concept and to try to see if there is something distinct biologically -- we believe there is -- in the alcohol dependent versus some of these other populations.

I think that it is always difficult to leap to conclusions from clinical trials, but I think the clinical trials could be informative to the basic science literature if we, in fact, found a significant difference even in the non-dependent group relative to what is actually going on in terms of are we reversing a biological process, are we affecting alcohol reinforcement, are we affecting mechanisms of carbohydrate metabolism or satiation or whatever.

I think that it would be informative if, in fact, you got an effect, and it could be of real interest in the context of the ways in which in this case the opiate system affecting alcohol consuming behaviors or satiation.

DR. WINCHELL: Do we have consensus that there are some people who should not be allowed to participate in a trial where the goal of treatment is reduction or moderation, or do we think that this ought to be open to everybody?

Dr. Kranzler proposed from his study of problem drinkers how he operationalized the group that probably ought to be told to abstain rather than to moderate. He excluded patients with physical symptoms of withdrawal and those who had more than four DSM-IV criteria for dependence.

Does that sound reasonable?

DR. KRANZLER: Let me just add one other thing. Under those circumstances, what we do is we then give the patient the option of either choosing a goal of abstinence or choosing to not exceed "safe" drinking limits.

In the context of evidence that efforts to drink moderately are unsuccessful, we then move into the abstinence in the context of this trial.

So, I think there needs to be some recognition that people -- we can't predict in advance who is going to succeed except within I think a range, and there is an awful

lot of motivation for people to participate in a study where they are not required to stop drinking.

Whether that is denial as it might classically be termed or just realistic effort to go where the patient is and meet the patient where he or she is, is a matter of debate, but I just wanted to add that.

DR. STRAIN: Dr. Franklin.

DR. FRANKLIN: This is not my treatment philosophy at all, but from a public health concern, even in the alcohol dependent population, if you decrease the actual quantity of drinking over a lifetime, you are probably going to save a certain percentage of livers and other kinds of -- there are going to be health benefits.

So, we really going to stretch the question from a scientific point of view without getting into the moral, ethical questions why exclude that population.

DR. MEYER: But also you are getting to the point that you actually raised in the beginning, which is are we talking about distinct studies, that if you are talking about the problem drinker, heavy drinker group that the audit that initially aimed at, that is a group where there are, in fact, drinking goals, whereas, in the alcohol dependent group, you are talking about abstinence being the goal, and moderate drinking may be an unexpected outcome.

I think that you really can't design a study in

which one size fits all. You really have to tailor it to the distinct populations, and I thought that was the direction that you were going in your presentation.

I think that is exactly the way it has to be done. These are really distinct groups, and they need to be studied that way, and they need to be treated that way.

DR. WINCHELL: One of the things we hope to come away with this afternoon before we all leave is pretty concrete operational criteria, how we can distinguish those groups, and we really appeal to the experts around the table to help us with that.

DR. STRAIN: On that note, I would like to end our discussion of these questions. I would like to thank the FDA and everyone else involved in the discussion for some fine presentations and for everybody's thoughts about this.

Before we adjourn for lunch, we have one little item of business that needs to be taken care of, so if people can just bear with me for a moment.

We have three members of the group who will be leaving as of this meeting: Drs. Andorn, de Wit, and Falkowski. Parting is always difficult to imagine, and we are exceedingly sorry to see that they need to rotate off the committee.

Dr. Falkowski has provided valuable insight and perspective especially with respect to epidemiologic issues,

Dr. de Wit and her perspectives on human behavioral pharmacology, and Dr. Andorn's wonderful clinical perspective and reminding us about vulnerable populations that we need to be constantly thinking of.

I think Dr. McCormick might want to say a word or two, as well, and we have some plaques here that are too small a token. Let me just say, as well, on a personal note, when I got on this committee, I thought, oh, great, this is going to be so much fun, and then the first committee came and about a week before I got the boxes of materials to read, and so doing this is a labor of love, you don't do it for the money, and you don't do it for the great breakfasts and the coffee.

So, personally, I just want to say thank you because I know what you have been doing since before I started on the committee, and it is truly appreciated by both the FDA and your peers on the committee.

Thank you.

DR. McCORMICK: I would like to add to that, that membership on an advisory committee represents a great deal of service and time and effort spent, and it is something that we really are truly grateful for. It is a real public service. Thank you.

DR. STRAIN: Just for the record, you can videotape this, we have these lovely plaques, so now you are

in the archives with a letter from the Commissioner, as well.

MS. FALKOWSKI: Too bad, you are losing all these Midwesterners, too.

DR. STRAIN: That is right.

DR. MEYER: The good sense, the common sense is leaving the committee.

DR. STRAIN: Dr. Somers, tell us what we are doing about lunch, please.

Let's resume at 2 o'clock for the closed session, please.

Thank you.

[Whereupon, at 1:00 p.m., the open session of the Advisory Committee was adjourned, to reconvene at 2:00 p.m. in closed session.]

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CERTIFICATE

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Lawyer's Notes