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AT

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
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Cynthia G. McCormick, M.D.
Atkinson W. Longmire, M.D.
Sue-Jane Wang, Ph.D.

C O N T E N T S

	<u>Page No.</u>
Call to Order Eric Strain, M.D.	4
Introduction of Committee	4
Conflict of Interest Statement Karen M. Templeton-Somers, Ph.D.	6
Open Public Hearing Raymond Anton, M.D. Patricia Owen, Ph.D., Hazelden Foundation (letter read by Dr. Templeton-Somers)	7 21
Welcome Cynthia G. McCormick, M.D.	25
Introductory Remarks Celia J. Winchell, M.D.	27
Expert Overview Richard K. Fuller, M.D.	37
Statistics Presentation Sue-Jane Wang, Ph.D.	51
Clinical Presentation Atkinson W. Longmire, M.D.	72
Open Public Hearing (Continued) Raymond Anton M.D.	78
Discussion and Questions for the Committee	80

P R O C E E D I N G S

Call to Order

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2
3 DR. STRAIN: I am Eric Strain. I am the Chairman
4 of the Drug Abuse Advisory Committee. I would like to call
5 this meeting to order and begin by asking members of the
6 committee and consultants and visitors to introduce
7 themselves. Maybe we could start with Dr. Somers.

Introduction of Committee

8
9 DR. TEMPLETON-SOMERS: I am Karen Somers. I am
10 the Executive Secretary to the committee, FDA.

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

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

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

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

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

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

25 DR. WINCHELL: Celia Winchell, Medical Team Leader

1 for Addiction Drug Products at FDA.

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

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

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

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

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

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

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

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

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

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

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

25 **Conflict of Interest Statement**

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

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

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

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

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

1 supported by NIAAA and Dupont's sharing of medication.

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

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

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

14 [Slide.]

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

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

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

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

9 [Slide.]

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

14 [Slide.]

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

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

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

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

6 [Slide.]

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

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

15 [Slide.]

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

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

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

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

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

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

1 II error on the other side of the equation.

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

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

10 [Slide.]

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

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

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

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

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

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

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

1 [Slide.]

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

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

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

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

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

1 error rate.

2 [Slide.]

3 Now, to exemplify this, this is some data from the
4 naltrexone and cognitive behavior trial, double-blind trial
5 that we recently completed. We used riboflavin as a marker,
6 and in an attempt to look at compliance of riboflavin as a
7 marker versus pill counts, we counted the number of people
8 that were 75 percent compliant with pill counts over the
9 course of the trial, and people that were 75 percent
10 compliant by urinary riboflavin measurements of at least
11 1,500 micrograms per milliliter.

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

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

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

1 intervention.

2 So, generally, one can expect possibly on the
3 order of 30 to 40 percent non-medication compliance over a
4 12-week trial.

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

12 [Slide.]

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

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

23 [Slide.]

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

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

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

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

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

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

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

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

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

23 [Slide.]

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

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

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

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

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

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

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

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

14 Thank you.

15 DR. STRAIN: Thank you, Dr. Anton.

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

18 [No response.]

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

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

24 DR. MEYER: Dr. Roger Meyer.

25 DR. STRAIN: Thank you.

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

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

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

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

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

25 Because alcohol dependence, as a disease, behaves

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

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

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

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

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

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

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

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

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

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

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

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

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

23 Thank you.

24 DR. STRAIN: Thank you, Dr. Somers.

25 That then ends the open public hearing portion of

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

3 **Welcome**

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

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

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

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

25 Psychotherapy seems to have been the mainstay for

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

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

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

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

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

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

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

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

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

21 Dr. Winchell.

22 DR. STRAIN: Thank you, Dr. McCormick.

23 **Introductory Remarks**

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

1 challenging problem which we cannot resolve without your
2 help.

3 [Slide.]

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

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

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

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

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

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

7 [Slide.]

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

17 [Slide.]

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

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

1 examples.

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

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

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

21 [Slide.]

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

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

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

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

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

21 [Slide.]

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

1 pharmacotherapy that helps reduce or moderate heavy
2 drinking.

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

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

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

23 [Slide.]

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

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

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

15 [Slide.]

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

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

1 interested in.

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

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

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

17 [Slide.]

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

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

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

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

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

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

25 [Slide.]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 [Slide.]

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

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

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

9 [Slide.]

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

16 [Slide.]

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

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

8 [Slide.]

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

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

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

24 [Slide.]

25 So, more recently, other variables have been used,

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

3 [Slide.]

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

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

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

23 [Slide.]

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

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

7 [Slide.]

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

10 [Slide.]

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

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

22 Dr. Winchell talked about that overall aggregate
23 results can obscure finding, and that has been the major
24 criticism of quantity or volume in that two people can drink
25 14 drinks during a two-week period. One person drinks two

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

10 [Slide.]

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

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

25 [Slide.]

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

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

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

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

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

1 drinks a day, the risk of stroke increases.

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

4 [Slide.]

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

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

17 [Slide.]

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

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

1 believe they were followed for as long as four years.

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

9 [Slide.]

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

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

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

1 results for the three months posttreatment.

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

5 [Slide.]

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

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

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

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

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

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

6 DR. MEYER: Can we ask some questions?

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

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

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

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

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

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

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

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

12 [No response.]

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

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

16 **Statistics Presentation**

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

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

24 [Slide.]

25 Here, I would like to share with you the

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

6 [Slide.]

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

20 [Slide.]

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

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

6 [Slide.]

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

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

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

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

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

24 [Slide.]

25 These efficacy outcomes can be divided into two

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

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

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

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

14 Blue represents the number of patients who have
15 one or more heavy drinking days during 12-week period. This
16 corresponds to 70 percent of naltrexone-treated patients
17 versus 37 percent of placebo-treated patients. The
18 statistical evidence is at most borderline significant p
19 0.05 from chi-square test.

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

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

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

14 The 49 percent in the naltrexone group versus the
15 37 percent in the placebo group were not demonstrated to be
16 statistically significant different, p-value of 0.37. There
17 was numerical trend that naltrexone is better. These
18 results are extracted from Dr. Permutt's statistical review
19 and evaluation.

20 [Slide.]

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

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

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

10 [Slide.]

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

17 A survival curve comparison showed a p-value of
18 0.04 with log-rank test. A Cox regression analysis
19 adjusting baseline drinking showed a p-value slightly above
20 0.05.

21 [Slide.]

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

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

3 It turns out that irrespective of either a coping
4 skill therapy or the supportive therapy, a survival curve
5 comparison with the log-rank test or the Cox regression
6 analysis adjusting for baseline drinking showed a p-value of
7 0.001, highly significant.

8 [Slide.]

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

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

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

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

3 [Slide.]

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

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

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

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

1 trial ended.

2 [Slide.]

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

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

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

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

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

11 [Slide.]

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

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

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

25 Given that inclusion/exclusion criteria had

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

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

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

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

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

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

25 Pattern 4 may be unusual but possible. Patients,

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

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

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

12 [Slide.]

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

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

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

1 events.

2 [Slide.]

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

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

16 [Slide.]

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

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

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

4 [Slide.]

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

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

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

21 [Slide.]

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

1 would further strengthen the evaluation of treatment effect.

2 [Slide.]

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

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

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

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

25 [Slide.]

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

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

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

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

21 [Slide.]

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

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

7 Thank you.

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

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

22 DR. WANG: The answer is depends.

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

24 [Laughter.]

25 DR. WANG: Because when the time to the first

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

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

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

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

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

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

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

9 DR. STRAIN: It was helpful?

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

12 DR. STRAIN: Dr. Meyer.

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

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

1 would be very interesting in an alcohol-dependent
2 population.

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

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

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

17 Can you bring up the slide of question?

18 [Slide.]

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

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

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

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

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

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

20 [Recess.]

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

24 Dr. Longmire.

25 **Clinical Presentation**

1 DR. LONGMIRE: Good morning.

2 [Slide.]

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

7 [Slide.]

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

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

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

21 [Slide.]

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

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

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

9 [Slide.]

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

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

22 [Slide.]

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

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

5 Then, they suggest that you ask the CAGE
6 questions.

7 [Slide.]

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

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

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

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

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

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

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

23 [Slide.]

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

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

7 [Slide.]

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

15 [Slide.]

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

23 [Slide.]

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

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

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

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

14 [Slide.]

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

25 [Slide.]

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

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

11 [Slide.]

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

20 [Slide.]

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

1 we are having today.

2 DR. STRAIN: Thank you, Dr. Longmire.

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

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

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

20 **Open Public Hearing**

21 DR. ANTON: Thank you, Dr. Strain.

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

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

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

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

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

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

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

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

10 DR. STRAIN: Thank you, Dr. Anton.

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

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

15 **Discussion and Questions for the Committee**

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

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

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

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

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

14 4. What should be the treatment goal for
15 alcoholics?

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

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

21 7. How can success be measured in these groups?

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

25 I would ask people to use the microphones and to

1 raise your hands, please.

2 Dr. de Wit.

3 DR. de WIT: I have a question to start with.

4 What do we know about treatment for alcohol abuse as
5 distinct from alcohol dependence? Am I correct -- this is a
6 question to the experts -- that Project MATCH, for example,
7 was directed toward people who met criteria for alcohol
8 dependence?

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

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

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

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

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

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

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

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

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

1 DR. STRAIN: Dr. Meyer.

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

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

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

23 DR. STRAIN: Dr. Andorn.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

14 DR. STRAIN: Thank you.

15 Dr. Mason.

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

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

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

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

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

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

7 DR. STRAIN: Thank you.

8 Dr. de Wit.

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

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

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

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

1 effect. I assume it is contrasted with a placebo.

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

3 DR. STRAIN: Dr. Lloyd.

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

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

12 DR. STRAIN: Dr. Franklin.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7 DR. STRAIN: Dr. Simpson.

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

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

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

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

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

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

11 DR. STRAIN: Dr. Mason.

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

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

25 Also, something that Dr. Franklin said about

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

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

16 DR. STRAIN: Thank you.

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

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

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

1 higher than people with spontaneous efforts to quit.

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

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

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

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

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

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

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

17 Dr. Kranzler is nodding yes.

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

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

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

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

11 DR. STRAIN: Dr. Meyer.

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

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

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

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

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

11 [No response.]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 DR. STRAIN: Thank you.

7 Dr. Franklin.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 DR. STRAIN: Dr. Mason.

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

23 DR. STRAIN: Dr. Simpson.

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

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

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

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

14 DR. STRAIN: Dr. Mason.

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

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

25 There was no difference between alcoholics and

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

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

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

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

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

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

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

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

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

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

20 DR. STRAIN: Dr. O'Malley.

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

25 I am a big advocate of having a behavioral

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

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

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

17 DR. STRAIN: Dr. Meyer.

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

20 DR. STRAIN: Could you explain bogus pipeline?

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

1 on medication use.

2 DR. STRAIN: Dr. Mason.

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

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

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

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

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

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

25 I had a separate comment from some of the other

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

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

13 DR. STRAIN: That is a very intriguing point.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

12 Dr. Franklin.

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

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

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

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

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

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

12 DR. KRANZLER: Many.

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

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

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

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

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

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

17 DR. STRAIN: Not to do what?

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

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

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

13 DR. STRAIN: Dr. Simpson.

14 DR. SIMPSON: I was just thinking in light of what
15 you were saying was that the nicotine analog has been
16 brought up several times, and if we are going now into
17 alcoholics, I guess, would the pharmacotherapy really be
18 effective. I mean would it be reasonable just to look at a
19 12-week period, because there was some evidence produced in
20 the Nicotine Workshop that, in fact, for several people it
21 is not a matter of just chewing gum for three months, it is
22 a matter of a lifetime habit to keep away from cigarettes,
23 and so on.

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

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

4 Dr. Andorn.

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

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

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

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

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

1 DR. STRAIN: Dr. Fuller.

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

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

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

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

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

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

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

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

1 demonstrated to be effective.

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

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

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

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

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

25 DR. STRAIN: Dr. Falkowski.

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

11 [Laughter.]

12 DR. SIMPSON: There are studies for that.

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

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

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

8 DR. STRAIN: Dr. Mason.

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

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

1 adds anything above and beyond the effects of standard care.

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

5 DR. STRAIN: Dr. Fuller.

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

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

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

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

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

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

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

12 DR. KRANZLER: How about eight weeks?

13 DR. STRAIN: Or whatever.

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

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

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

8 DR. STRAIN: Dr. de Wit.

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

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

19 DR. de WIT: With regard to the dependence.

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

22 DR. de WIT: Definitely.

23 DR. STRAIN: Thank you. Dr. Winchell.

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

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

5 DR. STRAIN: Dr. Simpson.

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

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

19 DR. STRAIN: Thank you.

20 Dr. Franklin.

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

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

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

9 DR. STRAIN: Dr. McCormick.

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

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

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

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

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

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

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

18 DR. McCORMICK: The adolescent.

19 DR. STRAIN: The adolescent heavy user.

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

22 DR. STRAIN: And women of child-bearing potential.
23 Yes, Dr. Fuller.

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

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

6 DR. McCORMICK: Let me expand it then.

7 DR. FULLER: Please.

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

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

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

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

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

11 DR. STRAIN: Dr. Andorn.

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

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

1 clearly dependent criterion as the target group for study.

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

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

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

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

2 --

3 DR. McCORMICK: I think we will hear more.

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

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

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

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

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

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

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

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

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

25 So, those would be the kinds of considerations

1 that I would at least consider.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 DR. MEYER: But you are giving a treatment.

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

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

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

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

3 DR. MEYER: But that is a distinct group.

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

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

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

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

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

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

25 Again, I would go back to the depression model.

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

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

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

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

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

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

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

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

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

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

6 DR. KRANZLER: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 DR. MASON: These were alcohol dependent subjects.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

25 DR. STRAIN: Dr. Franklin.

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

5 DR. STRAIN: Dr. McCormick.

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

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

22 DR. STRAIN: Dr. Fuller.

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

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

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

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

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

25 Is there consensus on this?

1 DR. STRAIN: Dr. Kranzler.

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

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

12 DR. STRAIN: Dr. Meyer.

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

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

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

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

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

15 Does that sound reasonable?

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

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

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

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

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

7 DR. STRAIN: Dr. Franklin.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18 Thank you.

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

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

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

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

5 DR. STRAIN: That is right.

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

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

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

12 Thank you.

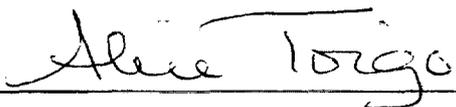
13 [Whereupon, at 1:00 p.m., the open session of the
14 Advisory Committee was adjourned, to reconvene at 2:00 p.m.
15 in closed session.]

16

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C E R T I F I C A T E

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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\$

\$10 115:4
\$5 115:3
\$50 115:2

0

0.001 57:7
0.0025 56:2
0.04 56:18
0.05 54:19; 56:9, 20;
79:12
0.37 55:16

1

1 61:2; 62:9; 67:16; 81:4
1,500 15:11
1.3 87:20
10 9:17; 38:23; 39:2;
97:25; 98:14; 103:12, 17;
104:4
10-item 86:1
100 54:13; 88:17; 110:5
10:45 71:18
10th 42:16
11 55:21
12 8:18; 20:7; 48:14; 53:3;
70:8, 8, 11; 71:8; 79:7;
116:20; 126:17
12-week 16:4; 53:2, 10;
54:15; 56:14; 60:16; 79:8,
20; 118:19, 24; 119:7, 8
14 44:25; 51:5; 75:1;
79:15; 83:19; 143:17
15 8:18; 9:17; 38:7
15-minute 71:17
15-year 124:3
16 144:10
160-patient 88:18
18-fold 48:7
180 63:19
19 56:8; 87:18
1981 66:6
1988 36:7
1989 66:10
1994 68:16
1995 72:24
1996 63:18
1997 22:17; 70:21

2

2 61:6; 62:10; 68:24; 81:7;
90:2, 2
20 41:12; 97:25; 98:14;
103:11, 17; 104:4; 116:3,
10; 125:10; 136:12; 137:9
20-drink-a-week 129:2

20th 25:7
21 144:9
25 41:12; 55:25
26-week 14:9
27 15:17; 54:23
29 87:19

3

3 61:13; 62:10; 75:2;
81:11; 110:5
30 16:3; 44:6
31 54:5
34 54:22
37 54:17; 55:15
38 56:8

4

4 61:25; 75:1; 81:14
40 14:11; 16:3; 116:10
40-minute 145:4
41 54:6, 12
48 100:3
49 55:14

5

5 81:16
50 120:19
50-year 120:19
52 49:9; 55:22
56 55:25

6

6 75:2; 81:18
60 106:23; 128:12
65 77:15

7

7 42:6; 81:21; 95:25;
116:16, 18; 143:18
70 44:1; 54:16
73 15:16
75 15:8, 9; 148:19

8

8-fold 95:25
80 44:5; 106:24; 128:14;
148:19
80-plus 88:23
800 102:22
80s 66:17
83 79:8
84 17:7

9

9 42:6
90 17:15, 16, 16, 18, 19;
23:9; 107:14; 131:15
90-day 145:19
90s 66:18
98 40:25; 79:6, 9; 82:13

A

ability 14:14; 38:14;
76:10; 84:17
able 13:4; 32:4; 35:23;
48:3; 65:3; 68:17; 81:20;
104:5; 111:18; 128:3;
132:18; 135:2, 22
above 56:19; 77:9; 125:1
Absence 33:11; 102:13
absent 72:16
absolute 148:10
absolutely 86:23; 125:8,
22
abstain 28:22, 24; 31:15;
32:19; 77:2, 4, 19; 134:23;
153:12
abstains 35:16
abstinence 21:23; 22:5;
24:10, 18; 26:5; 30:23;
31:2, 3, 18; 34:24; 35:8,
18; 41:1, 3, 6, 12; 42:2, 5,
10, 18; 44:5, 6; 45:21;
48:16; 49:15, 16; 53:19;
72:10; 73:20; 135:17;
146:11; 153:18, 22;
154:23
abstinent 22:6; 34:25;
35:17; 41:20; 43:20; 49:2;
52:12; 57:18; 60:9; 61:3;
98:4
abundant 66:1
Abuse 4:4; 5:13; 13:19;
14:18, 23; 21:16, 20; 25:7;
27:4; 36:6, 13; 37:1; 40:10;
72:25; 82:4, 10, 19; 83:6;
84:22, 25; 85:2; 87:20;
90:5; 91:6; 94:22; 95:4, 10,
15; 110:17; 111:3; 117:8;
124:7; 127:12; 128:23, 24;
129:3, 4, 5; 131:2; 152:7
abusers 21:18; 24:17;
59:8; 87:7; 93:5; 106:20,
22; 107:1
abusing 69:25
academic 28:4
acamprosate 10:24;
124:12
accelerated 63:7
accept 93:12; 101:16
acceptability 121:25
acceptable 21:20; 31:13;
33:7; 94:23; 113:10;
132:19
accepted 40:19; 41:7

accepting 101:15
access 45:14
accident 76:13; 112:9
accidents 76:12; 150:19
accomplish 29:25;
114:16
accomplishing 30:3
account 63:12; 66:7
accurately 21:14
achieve 31:3; 33:10
achieved 26:24; 46:6
acknowledge 31:2;
137:17
acknowledging 86:18;
131:23
acquire 125:11; 133:12
acquired 108:16
acronym 74:8
across 13:15; 104:22;
146:13
act 10:3
action 73:19
actions 25:10
active 23:7; 89:25; 141:9
activities 39:24, 25
activity 23:1; 145:24
actual 54:11; 69:11;
154:10
actually 14:2; 17:7; 18:1,
16; 19:19, 24; 33:25;
41:17; 51:5; 70:14; 79:2;
84:22, 24; 86:1; 91:9;
94:20; 95:1; 97:8; 100:11;
105:4, 6; 127:15; 140:9;
143:22; 147:24; 149:8;
151:1, 7; 152:22; 154:18
ad-hoc 26:22
adapts 17:18
add 10:10; 18:2; 77:16;
106:15; 108:21; 125:16,
17; 126:1; 143:23; 153:16;
154:6; 156:19
Addiction 4:24; 5:1;
25:14, 19; 27:15; 30:23;
122:5; 150:9
addictions 26:16
addictive 18:7
adding 105:4; 124:18
addition 7:1; 8:3; 9:1;
92:23; 104:8
additional 36:21; 105:3
additive 151:11
address 7:6; 20:11;
23:12; 29:11; 33:3; 71:7;
85:5; 101:12
addressed 92:10; 95:15;
99:15; 101:14; 134:1;
146:25
addresses 6:2
addressing 106:13
adds 54:12; 125:1
adequate 126:7
adjourn 155:16
adjunct 53:9

adjunctive 139:24
adjusting 56:19; 57:6, 11
adjuvant 139:24
administer 60:14
administered 22:21;
52:21; 53:9
administration 61:7;
62:1; 141:10
adolescence 38:22
adolescent 85:1; 129:16;
130:18, 19
adolescents 105:10;
131:2
advance 30:7, 11;
101:18; 153:24
advantage 132:1
advantages 24:8
adverse 47:7; 48:17;
112:1; 139:22
advertisements 94:14
advice 77:2; 82:22;
83:20; 92:23, 24; 93:2;
113:7; 134:9, 14, 25;
135:12, 23; 138:14, 23;
139:2; 142:7, 14; 143:3;
145:1, 3, 5, 7, 12; 151:20
advisable 77:4
advise 25:16; 28:20;
31:8; 66:23; 73:3, 15; 77:2,
8, 12; 83:21
advised 28:24; 32:18;
77:19; 95:21; 102:6;
134:23
adviser 143:3
advisers 25:5
advising 73:19; 77:12
Advisory 4:4; 25:7, 8;
156:20
advocate 108:25; 127:11
advocated 66:10; 85:13
advocates 100:15, 23
advocating 112:25;
113:19
affected 146:4
affecting 152:24, 24;
153:4
afraid 133:10
afternoon 9:13; 26:20;
27:9; 107:16; 129:7; 155:8
AG 66:3
again 14:13; 19:25; 20:5;
46:11; 56:3; 62:4; 78:10,
11; 87:23; 92:24; 104:6;
105:13; 113:5; 119:23;
125:6; 128:25; 135:14;
141:25; 146:20; 147:11
against 109:7
age 21:10; 85:1; 87:18,
19; 92:8; 133:21; 150:16
agency 6:6
agency's 26:15
agenda 6:5, 11; 27:20
agent 23:21; 63:19; 147:6
ages 87:18

aggregate 22:9; 44:22; 145:9
aggressive 13:21
 14:4; 16:6; 125:10;
 112; 137:10
agree 112:8; 113:13, 23;
119:5; 123:23; 126:19
agreeable 78:18
agreeing 119:17
agreement 15:12, 15;
33:16; 128:2
Agriculture 46:20; 47:20
ah 114:9
ahead 32:14; 47:15;
67:10; 71:17; 78:19; 151:6
AIDS 66:12
aim 29:10
aimed 154:21
al 52:24, 25; 54:5
Alcohol 4:15; 5:13; 8:12,
13, 22; 10:8; 11:3, 6;
12:13; 13:15; 16:5; 21:5,
15, 16, 16, 20, 21, 22, 25;
22:24; 24:14, 16; 25:20,
22; 26:10; 27:4; 28:6, 10,
11, 20, 23, 25; 29:2; 33:13,
21; 35:7; 36:6, 13, 24;
37:1; 38:24; 39:1, 6, 11;
40:2, 3, 5, 8, 9, 10; 41:22;
44:17; 45:6; 46:8; 47:6, 13;
48:3; 51:22; 52:4, 14, 17;
53:21, 23; 57:24; 58:5, 5,
59:3, 4, 5, 7, 10, 11;
62:64; 65:24; 67:2;
69:14, 21, 25; 72:4, 19, 24,
25; 73:4, 14, 17, 18, 23;
74:24; 75:14, 22; 76:10,
11, 12, 16, 21, 23, 24;
77:3, 6, 10, 17, 17, 19;
82:4, 5, 7, 18; 83:5; 85:19;
88:6; 90:9, 11; 91:14;
92:13, 21, 22; 93:18; 95:5;
97:13; 98:16; 102:14, 15;
107:19; 108:8; 110:7, 17,
21; 111:3; 113:20; 114:20;
116:3, 19, 19, 21; 117:1,
19; 119:9; 121:1, 13;
127:12; 129:17; 131:2, 19;
135:20; 146:22; 148:14;
151:17; 152:16, 24; 153:4;
154:10, 22
alcohol-dependent 70:1
alcohol-related 24:14;
36:11; 75:9, 12, 13, 21, 25;
76:2, 4, 8; 77:23
alcohol/drug 21:11
alcoholic 39:2; 40:4;
59:5, 5, 11; 90:17; 129:18
alcoholics 14:3; 15:23;
17:16; 26:6, 9; 29:3; 31:9,
10, 17; 38:15, 20, 25;
39:19; 58:8, 9; 81:5, 8, 12,
23; 106:10, 20, 22, 25;
117:134; 122; 148:11,
12, 15
Alcoholism 5:13; 8:5, 9,
17; 9:4, 25; 10:5, 13, 22;
11:3; 14:18, 22; 22:12, 18;

25:24; 26:15; 27:4; 34:20;
36:6, 10, 14, 16; 37:1, 20,
21, 24; 38:9, 13, 25; 40:9,
13, 14, 17, 20; 41:3; 42:12;
49:8, 23; 52:23; 53:10;
57:10; 72:25; 94:16;
99:20; 101:15; 125:7, 13;
135:5, 6
alcohols 59:8
allotted 146:23
allow 6:18; 13:1; 49:25;
78:11; 109:13; 125:12
allowed 125:21; 142:19,
22; 153:6
allows 24:4, 5; 38:10
alluded 45:11; 102:17
almost 14:6; 19:20;
37:25; 40:24; 48:24;
112:12
alone 24:10; 33:13;
104:10; 114:16; 146:16
along 12:8
already 6:11; 42:11;
75:17; 80:18; 107:4;
142:10
alternative 56:5; 63:3;
80:6; 105:22; 149:21
Although 11:4; 28:9;
55:1; 69:5; 95:24; 107:3;
117:14; 121:13, 18; 131:3;
138:2
always 17:14; 28:24;
31:3; 35:10; 43:10; 46:14;
130:5; 139:15; 152:18;
155:21
American 38:2, 3; 47:23;
143:21
among 35:23; 38:10;
39:8; 42:17; 52:11; 56:22;
58:18; 60:23; 62:8
amongst 115:9
amount 30:4; 74:22, 24;
75:17; 77:10, 13; 82:17;
102:22; 145:24
amounts 98:4
analog 30:4; 118:15
analogous 41:5; 113:19
analyses 23:16; 34:21,
22; 35:2, 3; 68:14; 107:17
analysis 19:14; 22:5;
23:12, 17; 27:8; 29:15;
30:14; 35:5; 42:12; 51:6;
52:2, 4, 16; 56:18; 57:6,
10, 11, 15; 63:5, 6, 7, 10,
64:1, 5, 7, 25; 65:4, 5, 22,
23; 66:2, 16, 19; 67:4, 15,
21; 68:10, 19; 70:13, 16,
20; 78:24; 79:18; 80:3;
88:21; 89:5; 106:16; 127:1
analytic 36:19
analyze 66:6; 89:25
ancillary 11:14, 25; 12:4,
23, 25; 16:15
and/or 58:21; 63:14
ANDORN 4:20, 20;
84:23, 24; 86:14, 19; 87:5;

24; 88:2; 90:4; 119:4, 5;
123:22; 125:17, 22;
132:11, 12; 140:24; 141:4;
155:20
Andorn's 87:16; 92:3;
156:2
Anucc'otally 38:15
Anesthetics 4:24; 25:18
animal 95:4; 115:16, 19,
23
animals 95:6
Anne 4:20
announcement 6:1
Annoyed 74:8, 12, 12
Anonymous 17:16;
148:11, 12, 16
antabuse 41:18; 44:13;
99:14
antagonist 52:22; 146:5
anticipate 88:19
anticonvulsant 64:20
antidepressant 140:21
antidepressants 34:12;
125:10
Anton 7:12, 15, 16;
20:15; 42:11; 51:19;
78:11, 19, 21; 80:10
Anton's 24:20; 69:15;
70:3; 97:6; 114:12; 126:25
anxiety 11:12
anxious 14:3
anybody 24:21; 51:10;
85:8; 86:13; 117:8; 119:6
anyone 99:9
anyway 128:10, 16
apart 132:8
apologize 10:9
apparently 110:16;
133:4
appeal 155:10
appealing 52:3; 65:21
appear 86:9; 107:21;
122:24
appearance 6:4
appeared 55:23; 62:6
appears 50:20; 131:9
appetite 71:15
applicable 52:16
application 62:15; 64:6
applications 52:4; 120:7
applied 64:6; 66:3, 11;
124:6
applying 83:16
appointment 145:21
appreciate 7:16; 8:7;
20:10
appreciated 156:16
approach 23:23; 24:4;
26:14, 15; 27:12; 28:7;
56:5; 58:16; 63:4, 4; 64:22;
67:6; 70:16; 73:14, 15;
77:22; 81:5, 24; 88:21;
90:18; 108:16; 121:3;
122:4, 5; 124:6; 126:24;

135:4; 147:7, 23
approaches 25:13; 34:4;
36:16; 66:12, 13; 81:9
appropriate 12:23; 18:4;
27:6; 28:20; 31:5, 12; 32:9;
43:11, 21; 52:10; 58:2;
70:21; 71:8, 9; 73:3, 5, 11,
19; 77:8; 95:14; 111:8;
120:12; 147:15, 16, 22
approval 138:6; 147:11,
14
approve 73:7
approved 25:24; 52:23
approves 147:5
approximately 8:18;
15:16; 42:6; 82:14;
116:16, 18, 21
April 25:7
apropos 49:7
arbitrary 85:11; 132:3;
143:15, 16
area 9:22; 12:17; 20:13;
26:17; 30:17; 47:10;
58:17; 65:24; 68:9; 98:9;
122:5, 6, 7; 150:2
areas 28:16; 62:15
arena 73:7
argue 93:19; 109:11;
110:23; 113:3
argued 42:21
argues 94:8
argument 112:13
Arizona 4:12
Arkansas 4:19
arm 125:23; 141:14, 15
armamentarium 25:21
armed 125:18
arms 86:22
around 11:9; 40:2; 66:17;
68:16; 90:11; 99:2;
102:25; 117:4; 145:24;
155:10
art 12:6; 99:7
arthritis 50:23; 120:5
article 49:6; 122:17
as-needed 89:10, 21
ASI 34:7
aspect 35:9
aspects 34:6
assertion 46:14
assess 73:15; 75:9
assessed 44:4; 77:1
assessing 23:21; 73:18;
74:21; 86:13
assessment 22:20, 23;
23:10; 105:6; 139:5
assigned 65:10
assist 25:9; 27:11
Associate 5:5, 16
associated 87:21; 95:7;
102:14; 121:15
Association 38:3, 4
assume 90:1; 104:19, 21

assuming 31:23; 90:22
assumption 104:20;
109:23
asthma 50:24; 64:15, 16;
120:5
at-risk 87:11
attacks 64:16
attempt 15:6; 28:21; 31:2
attempted 13:20
attempting 32:8, 19
attempts 135:8; 142:8,
17
attended 10:8
attention 36:12; 52:9;
66:18; 103:5; 124:10
attributable 145:7
attrition 23:3, 6; 126:9
audience 37:15; 78:8;
81:3
AUDIT 85:19, 24; 86:1;
154:21
automobile 112:9;
150:19
availability 96:3, 4
available 13:10; 28:9;
33:18; 45:14; 66:1, 13, 19;
79:7; 80:3; 89:18; 96:16;
139:3; 142:15
average 30:16; 97:25;
111:25; 115:4
averaged 82:13
averaging 107:25
avoid 32:21
aware 6:13; 28:19; 68:14;
81:1
awareness 136:19
away 94:17; 109:22;
118:22; 139:18; 155:8
awful 153:25
axiom 96:8

B

b 24:10; 75:25
back 34:5; 47:16; 79:9;
89:2; 96:15; 100:6;
103:20; 107:11, 19;
108:13; 112:18, 21; 116:2;
119:16; 123:1, 22; 129:10;
130:1, 2, 15; 137:11;
138:19; 141:25
background 90:8
bad 74:14
balance 79:24; 126:7
Baltimore 5:22
band 13:15
bar 42:1; 54:8, 9, 11;
140:6; 142:4
Barbara 5:8; 7:1; 117:25
base 50:19
Based 6:5; 15:14; 16:7;
21:10; 41:2; 46:15; 51:1, 7;
62:22; 83:6; 95:7, 8; 132:9;
144:2, 14; 146:10; 152:5

baseline 18:17; 33:5, 6, 7, 10; 56:19; 57:6; 61:2, 22
basic 140:15, 15; 148:5; 152:20
basically 14:4; 19:5, 18; 88:13; 89:10; 108:1; 109:21; 140:13
basis 86:11; 88:12; 89:10, 11, 21; 145:9
battery 22:23
bear 12:15; 119:14; 155:18
bearing 101:21; 130:21
became 62:3
become 39:2; 40:15; 42:12; 43:19; 52:12; 61:3, 14; 62:1, 4; 69:1; 127:4
becomes 61:10; 83:13; 84:14; 111:24; 126:9
becoming 47:10; 57:18
beer 73:25
Beforehand 145:11
began 38:17, 19
begin 4:5; 7:15; 39:20; 81:22; 89:17; 125:15; 137:2; 139:6
beginning 154:18
begins 40:1, 4; 98:22
begs 101:13
behave 94:7
behaves 21:25
behavior 9:6; 15:4; 17:5; 20:2; 23:25; 24:1, 2; 32:25; 33:9, 10; 34:3; 35:9; 58:18; 61:20; 76:3; 121:11, 16; 123:6, 10; 136:13, 16, 25; 138:10, 12, 18
behavioral 18:8, 10; 76:8; 93:14; 108:25; 109:10, 12, 13; 113:4, 9; 114:16; 119:12; 123:14; 124:19, 21; 125:23; 131:14; 133:7, 11, 12, 15; 138:22; 139:7, 25; 140:1, 3, 22; 145:17; 146:6, 8, 9, 10, 16, 17; 148:8, 23; 149:22; 150:24; 151:3, 5, 7, 12; 156:1
behaviors 105:11, 11; 111:20; 153:4
behooves 18:6
believe 6:17; 9:13; 39:7; 46:23; 48:1, 13; 80:20; 91:25; 99:14; 121:17; 122:18; 137:14; 138:22, 25; 140:22; 146:9; 148:12; 152:16
believed 57:22; 60:1
below 144:12
beneficial 60:2; 97:5
benefit 10:3; 93:3; 109:9; 135:23; 151:24
benefits 154:13
benign 32:21
bespeaks 14:13

best 22:19; 24:17; 58:21; 62:10, 10; 100:2, 16, 21; 101:19; 112:7; 115:15
better 12:8; 13:7; 24:6; 27:11; 55:6, 17; 69:6, 18; 70:4; 71:7; 93:25; 101:5, 24; 105:20; 115:24; 146:7; 151:7
between-group 146:2; 152:5
beyond 108:9; 122:8; 125:1; 137:25
bias 19:9; 133:5; 138:9
biasing 109:7
big 18:15; 37:13; 108:25
biggest 147:17
biliary 63:20
binary 57:17
binder 72:13
biological 33:21; 90:19; 95:1, 2, 13; 98:17; 115:17; 152:23
biologically 95:6, 8; 152:15
biology 101:23
Biostatistics 4:19
bit 12:6; 66:17; 79:5; 88:9; 89:20; 96:8; 103:9; 108:22; 114:23; 118:10; 129:11; 147:4
blackouts 57:24; 76:5
bladder 66:4
blind 144:22
blood 46:8; 53:23; 102:14
blue 48:15; 54:14
blue-green 63:25
Board 4:12
bogus 109:18, 20; 110:12
book 33:20
booklets 88:21; 107:13
borderline 54:18; 68:22; 69:7
borne 52:18
both 7:18; 17:12; 21:7; 22:16; 23:6, 12; 24:19; 28:4, 5; 32:18; 47:9; 56:15; 59:22; 61:11; 87:8; 119:17; 121:12; 156:17
bottle 101:4
bottom 11:1
boxes 15:16; 156:10
brain 17:18; 115:20
breadth 45:24
break 51:10; 67:9; 71:14, 18; 144:21
breakfasts 156:13
breaking 69:23
breast 121:8, 8
brief 73:10; 82:22; 85:21; 95:22; 117:6; 121:23; 134:25; 135:12
briefing 27:18
bring 52:9; 70:17; 130:7, 14

brings 115:7; 118:24
broad 13:15
brochure 133:18
brought 25:17; 26:7; 29:5; 90:4; 118:16; 130:2
building 141:16
bupropion 96:6
burden 30:13
bureau 8:2
bureaus 85:10
business 139:4; 155:17
businesses 11:8
bupirone 14:3

C

C 44:21
CAGE 74:5, 8; 75:4, 18; 76:1, 17; 85:25
calculate 30:17
calculated 144:11
Call 4:2, 4; 71:4; 72:16; 102:22; 103:4; 113:8; 124:9; 145:20
called 25:9; 30:12; 33:11; 63:6
came 14:2; 111:1; 127:13; 156:10
can 8:21; 10:24; 11:1, 21; 12:7, 20; 13:16; 14:9; 15:12, 15, 20; 16:2; 17:18, 20, 24, 25; 19:7, 10, 14, 18; 20:5; 26:24, 25; 28:15, 17; 29:3, 20; 30:12, 18; 31:23; 32:16, 25; 33:5, 16; 36:21; 42:18, 20; 43:5; 44:4, 23, 24; 45:7; 48:23; 50:6, 25; 52:18; 53:25; 58:12, 13; 60:2, 13; 62:17, 22, 24; 64:23; 65:19; 66:23; 67:20; 68:20; 70:17; 79:20; 81:11, 21; 84:8; 89:5; 97:14; 100:17, 17; 102:8; 108:16; 109:1; 111:9; 112:7; 113:9; 114:15, 25; 115:1, 3; 117:14; 119:22; 120:3; 124:25; 126:18; 129:10; 130:5, 7; 132:22; 133:24; 134:15; 136:10; 139:1; 141:13; 144:24; 150:2; 151:11; 155:9, 18; 156:24
cancer 29:25; 30:12; 47:23, 24; 50:24; 64:14; 66:5; 121:8, 8
candidate 142:12
candidates 31:25; 134:6, 9
capture 30:19; 36:21; 67:5; 68:17; 85:23
captured 123:4; 136:2
captures 104:7
capturing 45:23; 58:18; 59:12
carbohydrate 33:23;

152:25
cardiac 138:6
cardiovascular 64:10
Care 4:24; 11:8; 23:2; 25:18; 36:24, 25; 73:1; 82:21; 85:1; 91:3, 5, 10; 93:12; 96:7; 101:4; 113:6; 125:1, 2; 132:15; 133:16, 19; 135:4, 7; 137:1, 3, 17, 19; 138:25; 139:16; 150:14; 155:17
career 36:9
careers 38:17
careful 92:19; 139:10
carefully 111:17
caregivers 58:24
Carol 5:18
Carolina 7:13; 8:11
carry 126:18
Case 36:8; 60:5; 65:9; 67:20; 83:9; 87:1; 99:21; 122:11; 126:5; 134:18; 140:9; 147:25; 153:3
cases 22:2, 2; 73:20, 21
catch 126:4
categorical 42:3, 9
category 42:20, 21; 54:12; 90:20
caused 149:19, 20
causes 136:21
causing 40:7, 11
cautionary 109:5
Caveat 117:19
CBER 70:15
Cella 4:25; 27:14
Center 4:22; 5:11, 19; 6:7; 8:12, 13; 149:11
central 70:24
certain 26:25; 94:7; 106:8; 126:17; 135:1; 136:21; 154:12
certainly 41:12; 45:8; 47:5; 91:22; 100:15; 110:22; 115:6; 117:1, 12; 120:9; 121:14, 15; 127:10; 131:3; 141:1
cessation 26:13; 113:5
cetera 13:19; 16:16; 52:16; 53:23; 58:10; 62:11; 64:9; 95:6; 96:5; 112:14; 145:25
Chairman 4:3, 21; 25:4
challenging 28:1
chance 14:16; 51:7; 116:7
change 19:16, 19; 23:13, 14, 15, 24, 25; 24:4, 6, 8; 33:9; 71:2; 95:4; 142:14; 147:6, 24; 148:25; 149:4
changes 34:15; 94:6; 95:7; 146:18
changing 136:25
characteristics 12:5; 105:17
chart 63:21

checked 55:4
chemotherapy 64:12
chewing 118:21
chi-square 54:19; 57:15
Chicago 5:15
child 130:20
child-bearing 87:18; 92:8; 129:17; 130:22; 133:20
Children's 4:19
choose 29:15; 31:5
chooses 33:1
choosing 153:18, 19
chop 92:16
chose 46:10, 15; 111:17
chosen 30:19
chronic 11:2; 102:2; 119:6; 136:21; 137:9
chronically 11:16
churches 11:8
cigarettes 118:22
circumstances 26:25; 113:2; 153:17
cirrhosis 48:4, 5, 8; 63:20; 76:5
cite 131:13
City 5:19
clarify 89:9
classically 154:3
classify 21:15
clear 50:14, 15; 76:22; 85:6; 107:5; 108:10; 111:25; 130:17
clearer 107:22
clearly 58:13; 86:23; 133:1
Cleveland 36:8
client 23:25; 103:11
Clients 23:24; 24:5, 11
climate 91:10
clinic 145:22
clinical 21:4; 22:4; 23:19; 24:1; 25:19; 26:2; 27:6; 30:2; 32:7; 35:13; 36:5, 12, 17, 20; 40:19; 47:22; 50:1; 51:20, 21; 54:1; 57:22; 58:4; 60:6; 64:6, 15; 65:21; 66:4, 11, 12; 69:15; 71:22, 25; 72:5, 14; 86:17; 96:8; 99:14; 117:14; 145:24; 149:9, 10; 152:19, 19; 156:2
clinically 22:9; 23:13, 14, 24; 24:13; 29:13; 30:6, 20; 33:8; 34:15; 69:24; 81:13; 96:15; 104:1; 118:11; 144:14
clinician 32:16
clinicians 31:7
close 78:16; 127:2; 146:24
closed 9:13; 26:20; 80:12
closer 24:22; 84:6; 128:25; 129:6

closest 130:10
clue 119:11
co-primary 66:25
 scientific 8:12
 saine 25:15; 119:9
coffee 156:13
cognitive 9:6; 15:4; 17:5;
20:2; 139:16, 17; 140:22;
146:6, 9
cohabiting 41:21; 43:12
cojointly 10:4
collaborative 8:20; 83:3
collateral 110:3, 6
colleagues 7:19; 9:21;
10:9; 84:5; 132:16
collect 30:15; 33:6; 110:3
collected 34:19; 53:22
collecting 48:2; 109:21,
22, 25
collection 30:18
collects 59:21
college 85:1; 96:23;
150:16
color 54:20; 55:11
combination 52:22;
58:9; 59:4, 11
combinations 47:13
combined 46:1; 133:24
combining 48:10
coming 7:25; 36:7; 89:12;
24
Command 18:8
comment 7:8; 25:13;
78:9, 11, 12; 86:15; 87:17;
92:16, 17; 93:8; 95:17;
99:13; 101:25; 110:16, 25;
113:11; 122:15, 16;
130:10; 136:10; 141:11
comments 6:19; 37:11;
92:3; 103:9; 108:23;
110:15; 130:2; 151:14
commercial 28:5
commission 37:17;
77:21
committed 87:6
Committee 4:4, 6, 8, 10,
13; 7:18; 8:8; 9:12; 13:13;
16:17; 18:3; 20:22; 25:7,
12; 26:22; 52:19; 66:22;
78:6, 15, 17, 18; 80:9, 14,
15, 16; 91:22; 92:9; 94:21;
95:20; 97:3; 99:9; 123:24;
126:6; 155:23; 156:8, 10,
16, 17, 20
committee's 58:6; 60:23;
101:13; 103:5; 124:10
committees 25:8
common 42:3
commonly 41:13; 49:16,
24
communally 13:10
community 11:7; 18:6;
50:2; 65:21; 96:7
comorbid 21:11; 22:24

Comorbidity 116:18
company 8:4
comparable 22:14;
117:13
comparator 89:23
compare 49:12; 50:10;
71:11; 102:1
compared 43:8, 14; 44:5;
63:19; 92:24; 98:3;
106:19; 138:15
comparing 22:13; 40:21
comparison 38:10; 52:3;
56:17; 57:5; 59:14
comparisons 33:4
compensation 102:23
complaint 15:13
complete 22:1; 26:12;
53:19; 65:13; 80:7
completed 9:7; 15:5;
54:21; 55:10, 13; 56:6
completely 61:3
completing 88:22
completion 79:7; 106:19,
22, 24; 107:7; 108:7
complex 83:25
compliance 11:20; 13:1;
14:14, 17, 19, 23, 23, 23,
24; 15:6; 16:3, 9; 18:1;
80:2; 99:3, 8, 19, 25;
100:7, 20, 21; 105:25;
107:8, 8; 108:6, 12; 109:2;
126:19; 127:6
compilant 15:8, 10, 24
complicated 79:19
compounds 9:24; 10:3
Comprehensive 34:7
compromise 89:20
compulsion 76:19
computer 105:12
computers 98:25
conceive 45:7
concentration 46:9
concept 152:14
conceptualize 140:10
concern 130:24; 154:9
concerned 47:5, 8, 10;
125:12; 129:22; 131:4, 24;
133:2; 142:10
concerns 103:15
conclusion 132:5
conclusions 152:19
concomitant 11:12, 17,
24; 13:19; 17:4
concordance 107:12, 20
concordant 16:10
concrete 155:9
concretely 32:5
concurrent 53:3; 145:17
condition 77:6, 18;
131:18
conditions 16:11; 17:12,
12, 13; 104:22
conducted 36:10; 52:25

conference 24:21
confidence 23:11; 88:25;
121:23
conflict 5:23, 25; 6:2, 9;
7:21
confound 23:20
confronted 35:2; 45:13
Congress 149:9
Connecticut 5:11
consensus 50:1; 52:18;
65:20; 83:20; 151:25;
153:5
consequence 104:3;
112:9
consequences 32:25;
33:14; 47:7, 14; 48:11, 17,
18, 23, 25; 49:3; 86:7;
111:4, 11, 15; 112:1;
123:17; 132:8; 136:5;
139:8, 22
consider 18:3; 20:12;
24:12; 26:22; 37:13;
39:22; 46:16; 55:8; 56:11;
70:15; 80:18, 23; 91:15,
16; 105:22; 135:11; 136:1;
151:15
considerable 37:25
consideration 101:13
considerations 52:1;
135:25
considered 39:6; 46:6;
61:21; 67:1; 83:15; 92:12;
94:8, 10; 135:16; 142:12;
143:14; 149:2, 3
considering 29:8; 62:8;
68:25; 87:3
consisted 53:3, 12
consistency 37:25;
38:10; 46:11; 49:23
consistently 38:9; 43:15,
16; 146:4
consists 39:12, 14
constantly 156:4
constitutes 60:23
construct 84:13
constructs 84:3
construed 92:2
consultant 68:8
consultants 4:6; 7:19;
17:1; 27:19
consumed 44:17
consuming 153:4
consumption 21:21;
24:14; 33:13; 34:7; 47:13;
48:3; 57:24; 74:25; 88:7;
102:25; 103:1; 107:19;
111:25; 117:9
contact 58:23
contaminate 85:6
contend 17:24; 40:15
context 69:14; 70:3;
99:18; 150:16; 153:3, 20,
22
continue 27:8; 61:18;
87:12; 109:14, 14; 119:8;

122:2; 125:21, 24; 135:21
continued 18:10; 20:1;
40:6; 122:8
continues 122:13; 127:7
continuing 9:10
continuous 21:23; 24:18
continuum 12:8; 150:8
contraindicates 77:18
Contral 8:3
contrast 113:14
contrasted 90:1
contribute 101:24;
145:15
contribution 100:1
control 39:16, 21; 41:23;
43:9, 14; 44:20; 61:20;
69:23; 76:18, 20; 111:12
controlled 124:25
controlling 93:1
controls 131:22
controversy 28:19
conundrum 28:23
convergence 18:14
conversation 110:15;
128:21
convoluted 84:2
cooperative 9:2; 16:5;
41:17
coping 56:24; 57:1, 3;
88:16
copping 149:2, 3
copy 24:20
corollary 13:12
correctly 144:10
correlate 48:3
correlated 45:23
correlation 45:15, 18,
19; 112:2
correlations 45:17
corresponds 44:17;
54:16
cost 115:1; 120:21
cough 137:9
couldn't 84:11; 119:5
counseled 31:14
counseling 93:10
count 15:14; 63:15;
100:6, 7
counted 15:7
counter 139:1
counting 52:12
countries 86:2; 136:15
country 10:23; 11:9
counts 15:7, 8; 59:22, 24;
99:4, 5; 100:10
couple 67:8; 96:25;
110:14; 127:9; 147:1
course 15:9; 23:7; 51:9;
55:10; 62:18; 65:20;
72:20; 88:4; 101:21;
105:25; 123:14; 125:9, 14
covariates 57:12
cover 118:25

covering 80:24
Cox 56:18; 57:5, 11
Craig 143:20; 144:12;
145:10
craving 16:15, 21; 53:21
create 114:1; 115:1, 3
created 114:11
creating 114:6; 150:19
crime 47:11
criminal 23:1
criteria 28:11; 32:6, 10;
38:1; 39:3; 40:8, 13, 14,
16; 42:4, 18; 49:24; 60:25;
61:2; 81:8, 12, 13; 82:7,
18; 83:11, 16; 88:8; 94:4;
95:3; 97:13; 111:2, 11;
112:10; 113:20; 116:20,
22; 117:8; 129:4, 5; 131:2;
132:4; 135:1; 139:12;
141:21; 143:20; 144:12;
145:10; 146:21; 153:14;
155:9
criteria-based 49:18
criterion 46:6; 87:7; 88:7;
117:9; 121:12; 131:21, 21;
133:1; 139:14; 142:24;
143:16
Critical 4:24; 25:18;
84:14
criticism 44:24; 141:16
criticizing 74:13
critter 86:18
cross-national 86:3
crucial 10:12; 14:19;
79:10
cultural 46:16
cumbersome 126:9
cumulative 34:24; 35:18
cure 29:25; 96:9
current 7:6; 21:6; 38:6
currently 9:7; 75:13, 24;
88:5; 137:6
Curry 22:16
Curtis 57:22
curve 30:17; 42:11, 12;
56:17, 23, 24, 25; 57:1, 4
cut 73:21; 74:8, 10, 11;
77:4, 8, 12; 82:23; 92:23;
93:2; 103:14, 17; 132:4;
133:18; 134:25; 142:8, 17,
24; 144:3
cutoffs 143:17
cutting 143:1
cynicism 143:6
Cynthia 4:23

D

D.Y 68:8
daily 53:5; 60:15; 88:12,
14, 21; 89:11, 13, 14;
98:23; 102:21; 107:10, 13,
18, 21, 21; 108:2, 11, 15
damage 112:9

damaging 111:11
 dangerous 148:17
 data 7:24; 9:5; 10:9, 10;
 14:2; 15:3; 16:5, 18, 24,
 25; 17:10, 11; 18:16, 18,
 24; 19:2; 20:6; 30:15; 33:6;
 34:19; 40:18; 41:17; 42:3,
 13; 43:24; 45:15; 48:2, 11,
 12; 56:11; 66:6; 68:12, 20;
 69:11; 79:2, 4, 7, 10, 21;
 80:3, 5, 7, 7; 88:19, 25;
 95:2, 4; 98:9, 13; 106:15;
 107:13; 109:19, 25;
 119:20; 120:20; 124:17;
 125:8, 11; 126:7; 127:1;
 131:1; 144:19; 145:14
 date 101:5
 DATOS 22:16
 day 17:7; 21:21; 22:7;
 34:22, 25; 35:11, 16; 45:1,
 2; 46:13, 17, 22, 23; 47:1,
 3; 48:5, 7; 52:14, 15, 15;
 53:14, 16, 17; 56:13;
 57:14, 18; 59:16; 61:15;
 63:12, 13; 70:11; 72:17;
 77:15, 16; 79:13, 14;
 87:20; 89:5; 107:16;
 108:1; 146:12
 days 17:15, 17, 18, 19;
 19:3, 21; 22:7; 33:12;
 34:25; 35:17, 21; 43:6, 7,
 16, 17, 19, 20; 44:1, 5, 6;
 45:3, 4, 21, 22; 48:18, 19;
 52:11; 53:16, 20; 54:15;
 56:12; 59:16, 18, 20, 21,
 24; 60:5, 8, 8, 14, 18, 19;
 61:8, 9, 18; 62:4; 63:9, 11;
 67:3; 72:15; 74:1; 79:14,
 15; 146:11
 DDD 72:16
 de 5:14, 14; 82:2, 3, 16;
 89:8, 9, 24; 91:20; 110:14;
 111:19; 114:13; 123:2;
 127:8, 9, 19, 22; 130:1;
 133:2; 155:20; 156:1
 deal 156:20
 dealing 78:5; 86:25
 death 62:18
 debate 39:8; 115:9;
 147:2; 154:6
 Debra 128:24
 decide 31:22, 24; 33:2;
 70:20; 103:25; 127:25
 decided 30:7; 75:8
 deciding 133:8
 decision 71:10; 80:4;
 145:20
 decisionmaking 79:24
 decline 112:15; 145:21
 declines 89:18
 decrease 14:7; 113:1;
 114:15; 145:19; 154:10
 decreased 18:1; 63:14;
 80:2
 decreases 116:5
 decrement 116:8
 deemed 15:24; 132:7

deficient 33:23
 deficits 87:22
 define 29:14, 19; 41:11;
 96:12; 111:2
 defined 42:19; 48:23;
 53:15, 17; 58:13; 60:13,
 20; 61:1; 67:1; 74:25;
 77:13; 84:4; 88:6
 defining 29:11; 33:3;
 47:3
 Definitely 127:22; 149:3
 definition 30:6; 37:19;
 40:9, 19; 41:7; 46:9, 12,
 21; 48:18; 49:19; 84:21;
 89:3; 107:22; 108:3;
 134:22
 definitions 29:20; 31:1
 degree 73:18; 77:1;
 97:20; 106:8; 120:24, 25
 delay 35:10; 118:4
 delays 71:6
 deliberations 20:12
 delineating 34:14; 86:23
 delineation 129:15
 delirium 39:15
 Delores 4:14
 demand 105:17
 demarcates 19:12
 demonstrable 145:6
 demonstrate 23:24;
 34:15; 63:21; 65:19;
 114:18; 152:4
 demonstrated 55:15;
 121:11; 122:1; 141:22
 denial 154:3
 denigrate 16:20
 density 149:18
 Department 5:10, 19;
 46:20; 47:19
 departs 28:7
 dependence 11:4;
 12:13; 13:15; 21:16, 23,
 25; 25:15; 28:11; 38:13,
 24; 40:8; 69:14, 22; 76:19;
 77:3, 10; 81:8; 82:5, 8, 10;
 83:4, 7; 84:3, 8; 86:8;
 87:20; 88:8; 90:9; 94:4, 18;
 95:1, 4, 7, 21; 102:13;
 110:19, 20; 111:3; 113:20;
 116:11, 19, 22; 117:8;
 121:1, 13; 127:19; 128:23,
 25; 129:6; 131:19; 132:5;
 143:12, 14; 148:14; 152:7;
 153:14
 dependency 77:17
 dependent 11:7; 15:23;
 21:17; 24:16; 26:11;
 28:21, 24; 29:2; 39:6; 59:4;
 75:14; 76:16; 77:17;
 81:17; 82:11, 12, 22; 83:5,
 9; 84:11, 16, 16; 86:16, 22;
 87:2; 91:7; 92:2, 13; 93:19;
 95:6; 97:13; 98:16; 107:4;
 108:8; 110:7; 113:17;
 114:7; 115:25; 117:2, 19;
 121:5, 6; 129:17; 133:1;

146:22; 147:12; 151:17;
 152:16; 154:10, 23
 depending 14:8; 33:24;
 42:19; 65:6; 66:8; 97:20;
 106:12
 depends 67:22; 84:24;
 85:17; 100:22; 101:2, 8;
 113:4; 116:17; 132:13;
 135:14
 depicted 38:1; 44:2
 depicts 61:6
 depressed 149:4
 depression 11:12; 76:7;
 122:17, 19, 20, 22, 24;
 125:7, 9; 140:23; 141:7,
 25; 142:2, 5
 depressive 103:3, 3
 deprivation 95:5
 derived 86:4; 143:19, 20,
 24
 descending 88:13
 describe 36:20; 54:4;
 60:4
 described 57:21; 107:9;
 139:25
 describes 61:13
 describing 36:16
 design 25:19; 26:2;
 58:13; 88:11; 89:21; 90:2;
 106:12; 119:15; 122:21;
 130:5; 154:25
 designed 22:12; 53:1;
 73:1
 designing 10:17; 51:21;
 58:4
 desirable 137:14, 16
 desired 38:15; 76:24
 desk 24:20
 despite 40:6; 136:20;
 137:14
 detail 60:4
 detailed 34:4
 detection 64:2
 deteriorated 23:16
 determination 42:7
 determine 11:15; 73:17;
 96:18
 determined 6:6; 128:8
 determining 14:19;
 73:23; 79:25
 devastating 10:5
 develop 38:24; 118:12;
 131:16
 developed 13:15; 38:2;
 85:20; 86:2; 102:7;
 112:11; 125:10; 133:17
 developing 27:17; 75:12;
 148:6; 151:16
 development 8:9; 9:24;
 10:1; 13:13; 21:3; 34:12;
 47:24; 51:20
 devised 10:16
 devote 40:4
 devoted 36:11

diabetes 102:2, 7; 119:7;
 121:7
 diabetics 121:5
 diagnosable 152:6
 diagnoses 83:2
 diagnosing 133:21
 diagnosis 8:24; 37:20;
 91:12; 129:19; 133:19
 diagnostic 21:14; 38:1,
 4, 4; 49:24; 132:4
 diagnostically 85:5
 dichotomous 107:14
 dichotomy 129:12
 Diego 38:19
 diet 47:24; 123:10
 differed 107:1
 difference 12:19; 13:5;
 19:15; 20:9; 42:17; 48:6;
 67:14, 15, 17; 104:4, 25;
 105:2, 16; 106:25; 124:10;
 130:6; 141:20; 152:5, 21
 differences 62:25; 65:4;
 93:19; 104:14; 124:14, 16;
 146:2
 different 10:11, 25;
 14:19; 19:3; 21:19; 33:18;
 47:2; 48:12; 49:13; 55:16;
 64:8; 67:5; 68:6; 81:5, 5, 9,
 9, 11, 23, 24; 84:3; 90:15,
 15; 93:25; 98:1; 99:2;
 100:25; 103:23; 104:17;
 106:12; 121:2, 3; 122:23;
 127:10; 132:25; 136:16;
 143:2, 5, 7, 23; 148:11
 differential 106:16
 differentiate 21:17;
 64:23
 differentiated 145:12
 differentiator 84:15
 differentiates 122:4
 differently 94:7; 143:6
 difficult 35:4; 49:12;
 89:12, 24; 111:9, 14;
 117:4, 11, 20; 143:10;
 152:4, 18; 155:21
 difficulty 40:20; 92:1;
 96:14; 117:13; 128:4
 Dimensions 22:23
 diminished 71:6
 diminishes 16:9
 direct 77:24
 directed 82:7; 101:22, 24
 direction 12:16, 17;
 13:22; 15:18; 50:14;
 64:24; 149:7; 155:3
 directions 10:25; 138:21
 directly 122:16
 Director 4:11, 18, 23;
 8:11, 13; 36:5
 disadvantage 100:4
 disagree 111:22
 disagreement 15:17
 discard 100:18
 disclose 6:20

discontinuation 126:2
 discontinuations 55:3
 discrepancies 110:5
 discretion 44:15
 discuss 33:17; 34:18;
 43:1; 62:11; 72:4; 80:8
 discussed 70:7
 discussing 73:6
 discussion 27:5; 37:2,
 16, 18; 45:12; 50:4; 51:1,
 10; 52:18; 65:24; 67:11;
 68:7; 71:15; 78:6, 7, 13,
 18; 80:13, 15, 19, 24; 90:6;
 91:21; 102:5; 111:1;
 123:5; 126:1; 129:7, 13;
 130:14; 145:15; 146:23;
 149:13; 155:13, 14
 discussions 6:10; 27:11,
 19; 36:3; 77:25
 disease 21:25; 101:15,
 18, 24; 102:9; 118:4;
 120:9; 122:13; 123:7;
 138:6; 148:6, 16; 149:14
 diseases 22:1; 36:11;
 102:2; 122:10
 disorder 10:14; 58:5;
 95:2; 110:17, 23; 120:13
 disorders 11:13; 21:5,
 11; 22:25; 25:20, 22; 28:7;
 51:23; 85:19; 96:9;
 106:21; 121:2; 122:8, 10;
 147:10, 10
 disregard 105:18
 disrupts 22:18
 distinct 82:5; 92:5; 98:16;
 141:3; 152:15; 154:19;
 155:2, 5
 distinction 83:6; 131:19;
 132:3; 142:25
 distinguish 35:23; 40:23;
 155:9
 distinguished 25:5;
 36:9; 62:22
 distinguishes 17:7
 distinguishing 92:13
 disulfiram 41:18, 23, 25;
 43:4, 8, 13; 44:11, 15, 20
 divided 53:25
 division 25:12, 18; 36:5,
 19, 23; 72:4
 docs 91:5
 doctor 100:8
 document 73:1; 77:14,
 22; 112:14
 done 16:6; 19:1; 38:19;
 41:18; 44:11; 88:17; 91:8;
 107:17; 127:1; 149:8;
 155:4
 doomed 151:19, 22;
 152:2
 door 24:21; 127:3; 135:8
 dose 14:7; 41:24; 43:8, 8,
 13; 53:12; 76:23; 94:9;
 100:4
 double 79:15; 138:10

double-blind 15:4; 53:2; 145:16
double-blinded 63:18
doughnut 102:8; 138:16
doughnuts 102:6
down 49:9; 51:20; 61:8; 69:23; 73:21; 74:8, 10, 11; 77:4, 8, 12; 82:23; 92:23; 93:2; 103:12, 14, 17; 123:8; 133:18; 134:25; 142:8, 17, 24; 143:1; 144:3; 148:18
dozens 34:9
DR 4:3, 7, 9, 11, 16, 18, 20, 23, 25; 5:2, 4, 5, 8, 10, 12, 14, 16, 21, 23; 6:1, 20, 22, 24; 7:1, 11, 12, 15, 16, 16; 17:1; 20:15, 15, 19, 22, 24, 24, 25; 21:1; 24:19, 24, 24; 25:1, 4; 27:3, 14, 21, 22, 22, 24, 25; 36:4, 4, 9, 15, 18, 22; 37:6, 6, 7, 10, 10; 38:18; 42:10; 44:22; 50:6, 7, 9, 10, 18, 22, 24; 51:9, 11, 13, 13, 17, 18, 19; 55:18; 57:22; 58:11; 60:3; 66:23; 67:8, 11, 22, 23, 25; 68:8, 11, 12, 12, 15; 69:9, 10, 12, 12, 13, 15; 70:3, 6, 14, 21; 71:13, 21, 24; 72:1; 78:2, 2, 11, 19, 21, 21, 22; 80:10, 10, 82:2, 3, 9, 12, 16, 20; 84:1, 1, 2, 23, 23, 24; 85:8, 17, 22; 86:14, 14, 19, 24; 87:5, 14, 15, 16, 16, 24; 88:2, 5; 89:7, 8, 9, 13, 24; 90:2, 3, 3, 4, 4, 12, 12, 13; 91:20, 20, 24; 92:3, 3, 15, 17; 93:7, 7, 8, 11; 94:11, 11, 12, 12, 25; 95:16, 17, 19, 20; 96:14; 97:6, 17, 18; 98:11, 11, 12; 99:9, 12, 12, 17; 100:22, 24; 101:10; 102:11, 11, 11, 12, 13, 17, 18; 103:6, 7, 8, 9, 20, 21, 22; 104:9, 14, 16, 17, 19; 105:7, 19, 19, 20, 23, 23, 24; 106:2, 14, 14, 15, 18; 108:20, 20, 21, 23; 109:17, 17, 18, 20, 21; 110:2, 2, 3, 8, 11, 12, 14, 16; 111:13, 14, 19, 22; 112:8, 18, 19; 113:3, 13, 23, 25; 114:12, 13, 23; 115:12, 13, 24; 116:2, 12, 15; 117:17, 18; 118:6, 13, 13, 14; 119:1, 4, 5, 16, 16, 19; 120:1, 1, 2, 8, 15; 122:2, 16, 25, 25; 123:1, 2, 12, 22; 124:8, 8, 9; 125:5, 5, 6, 17, 20, 22; 126:1, 5, 12, 13, 14, 25; 127:8, 8, 9, 19, 20, 22, 23, 23, 24; 128:5, 5, 6, 19, 20, 21; 129:9, 9, 10; 130:1, 16, 18, 19, 20, 22, 23, 24; 131:6, 7, 8, 12; 132:11, 11, 12; 133:2, 14; 134:1, 1, 3, 4,

10, 13, 24; 136:11; 138:19, 19; 139:11, 13; 140:8, 10, 12, 15, 17, 18, 21, 24; 141:3, 4, 6, 8, 11, 19; 142:6, 7, 13, 23; 144:4, 6, 7, 9, 16, 18, 19, 21; 145:14; 146:20, 22, 23; 147:3, 18, 21, 25; 148:4, 9; 149:1, 16, 25, 25; 150:1, 5, 5, 6, 6, 12, 22, 22, 23, 23; 151:14; 152:1, 1, 2, 12, 12, 13; 153:5, 10, 16; 154:7, 7, 8, 17; 155:7, 12, 24; 156:1, 2, 5, 19, 24
dramatic 112:14
drank 53:20; 61:22; 107:25
draw 25:23; 26:17
drawn 129:12
drink 22:4; 31:8; 34:21, 23; 35:10; 38:14; 41:21; 42:10, 14, 16, 16, 20; 43:5; 44:17, 24; 46:22, 22, 25; 49:15; 53:13; 54:3; 57:13; 61:17; 62:2; 74:2, 17; 76:19; 77:15; 83:17, 18; 94:15; 96:25; 112:13; 116:3, 10, 23; 131:22; 153:20
Drinker 34:8; 98:15; 117:18; 129:3, 16; 154:20, 20
drinkers 6:22; 28:13, 15, 17; 29:9, 12; 31:12; 61:15; 81:4, 7, 17, 23; 86:16; 87:2, 3; 88:6; 92:6; 94:1, 2; 96:11; 97:14; 101:17; 108:5; 112:22; 115:15, 21; 127:13; 147:13, 20; 149:15; 150:16; 152:7; 153:11
drinking 16:18; 19:3, 7, 10, 21; 22:7; 28:15, 18, 21; 29:1, 4, 9; 31:6, 9, 17; 32:2, 20, 25; 33:4, 9, 12, 12, 14; 34:2, 6, 22, 25; 35:9, 11, 21; 36:24; 38:17, 17; 39:14, 17, 17, 20, 20, 21; 40:3, 6, 6; 43:2, 6, 6, 7, 16, 17, 19, 19, 25; 44:3, 9, 9, 19; 45:7, 22, 24; 46:12, 16, 18, 21; 47:3, 6, 8; 48:17, 19, 20, 22, 24; 49:3, 17; 52:11, 14, 15, 15; 53:14, 19, 20; 54:2, 15, 22; 55:23; 56:12, 13, 19; 57:6, 14, 18; 59:14, 16, 16, 18, 20, 21, 23, 24; 60:2, 3, 5, 7, 8, 14, 18, 19; 61:2, 4, 5, 8, 9, 12, 15, 19, 20; 62:4; 63:9, 11, 12, 13, 14, 15; 64:3; 67:3; 68:25; 69:3, 22, 23, 25; 70:11; 72:16; 73:25; 74:2, 11, 13, 15, 20, 21, 22; 75:5, 8, 18, 19; 76:20, 21, 22; 77:5, 6, 9, 10, 12, 13; 79:6, 10, 13, 14; 82:21; 83:10, 22; 84:10, 12; 85:9, 14, 15; 86:7; 88:1; 89:2, 4; 93:1;

94:6; 95:12; 96:24; 97:15, 24; 98:4, 20; 102:21; 103:11, 24; 104:8, 22; 107:23; 108:12; 112:5; 117:4; 118:2, 9; 121:11, 16; 127:14, 21; 128:23, 25; 131:20, 25; 132:7; 133:18; 134:9; 135:1, 7, 22, 23; 136:4, 5, 19, 21, 25; 137:5; 138:2, 9, 12, 15, 18; 143:17; 144:5; 145:3, 19, 22, 25; 146:3, 12; 150:9, 13, 13; 151:16, 23; 153:19; 154:2, 11, 22, 24
drinkings 59:17
drinks 21:21; 22:7; 34:25; 35:15, 16, 19; 44:25, 25; 45:1, 1, 2, 3, 3, 22; 46:8, 10, 13, 17, 17, 22, 23; 47:1, 18, 18; 48:4, 7; 53:16; 72:16; 73:25; 74:2, 3; 75:1, 1, 2, 2; 77:14; 83:18, 19; 87:20; 97:25, 25; 98:15; 103:11; 116:10; 143:17, 18; 144:9, 10; 146:12
drive 95:10
driving 45:8; 95:15; 132:15, 16
drop 16:8; 58:19; 125:24
dropout 11:20; 58:20; 106:1, 3, 9, 10, 16; 108:24; 128:9, 10
dropouts 58:17; 80:2
dropped 55:2; 79:9
Drs 51:19; 155:20
Drug 4:4, 15; 5:1; 6:8; 8:12; 20:8; 25:7, 19, 24; 26:2; 29:3; 30:12; 32:14, 16, 17, 21; 35:5, 7, 10; 37:1; 51:22; 58:16; 65:19; 89:10, 25; 90:14; 91:2, 14; 100:11; 101:6; 106:20, 22; 114:15, 18; 115:19; 119:22; 120:4, 10; 121:1; 124:13; 125:25; 127:7; 128:8; 139:1; 147:11, 14, 19; 148:6
drug's 34:15
drugs 21:5; 26:5; 58:4; 90:20; 91:13, 13; 107:1; 124:2; 125:19; 138:4; 149:23
drunk 35:22; 53:21
DSM 38:5; 39:16; 83:2, 4; 88:8; 142:23
DSM-III(r) 38:8; 82:14; 83:5; 116:19
DSM-IV 38:6, 8, 13; 40:9; 84:17; 87:7, 19; 95:3; 97:13; 111:2; 153:14
dual 8:24; 91:12; 129:18
due 101:23; 108:23
Dupont 6:21, 25; 7:3, 23; 8:2
Dupont's 8:1
duration 26:4; 27:7;

124:13; 125:16, 17; 133:3
during 13:20, 24; 17:8; 19:15; 20:3, 7, 12, 17; 23:7; 26:21; 34:23; 36:9; 39:2; 44:18, 25; 53:3; 54:15; 64:18; 74:3; 89:5; 107:16; 141:9
duty 76:11
dwindles 123:20
dying 48:3, 5, 8
dysfunction 76:6, 6
dysfunctional 24:1
dysthymia 103:2

E

each 23:9; 45:4; 54:12; 63:12; 71:11; 75:5; 80:22; 88:14
earlier 58:19; 78:12; 110:15; 129:11, 13; 136:8
early 6:22; 11:3; 38:17; 41:18; 58:15; 66:18; 88:6; 95:22; 108:5; 144:21, 25; 149:9
easier 10:19
easily 32:17; 82:13; 133:24
eat 102:8; 149:17, 20
eating 102:4, 5, 8
ecological 124:21
Edinburgh 44:12
edition 38:6, 8
education 21:10; 133:17
effect 12:20; 13:2; 18:15; 30:20; 35:7, 8; 38:15; 47:6; 55:6; 57:13, 16; 59:9; 60:13; 61:21; 62:21; 65:1; 67:5, 19, 20, 21; 71:2; 76:24; 90:1; 97:5, 6, 22; 106:11; 112:4, 5; 113:1; 114:2, 3, 8; 115:5; 116:2; 117:22; 118:12; 123:20; 133:13; 140:2; 144:13; 145:2, 6, 9, 23; 146:9; 152:5, 10; 153:2
effective 30:12; 62:17; 64:17; 65:7, 15; 82:23; 92:24; 96:19; 106:5; 114:6, 18, 25; 115:1; 118:18; 119:13; 122:1; 125:10; 131:9; 139:21; 142:3; 147:14; 150:24, 25; 151:5, 12
effectively 67:5; 102:23; 121:20
effectiveness 14:16; 18:19; 53:8; 56:5; 140:3
effects 40:3; 93:24; 95:5; 102:15; 104:18; 106:6, 8; 108:24; 109:6, 8, 9; 125:1, 3; 133:7, 9; 146:15
efficacious 10:3; 96:12; 127:7; 139:21; 148:7, 23
efficacy 13:23; 14:20; 18:5; 20:7; 25:11; 34:16;

53:12, 25; 55:7; 56:3; 57:20, 23; 58:1, 21; 59:13; 60:20; 62:15; 65:11; 79:25; 82:17; 114:5
effort 27:16; 58:23; 154:4; 156:21
efforts 96:1; 37:20; 142:24; 143:7, 8; 153:20
eight 88:12; 126:12
either 9:10; 10:3; 40:7; 48:19; 53:4; 57:3; 60:14; 68:12; 85:15; 88:11; 91:8, 13; 111:25; 112:2; 145:5; 152:7; 153:18
either/or 87:5
elaborate 58:12
elected 45:20; 99:22
electronic 100:24
elegant 69:16
element 59:25
elevated 138:5
else 150:21; 155:14
embarrassed 37:12
embrace 9:25
emphasis 26:10; 41:14
emphasize 20:5
empirically 143:19, 24
employed 82:24
employment 21:11
emptor 117:19
encourage 18:9
encouraged 127:5
end 18:22; 19:12; 49:22; 55:9, 12; 56:7, 14; 61:10, 16; 68:3, 6; 83:8; 84:8; 89:22; 97:9; 105:4; 120:18; 139:15; 155:12
ended 59:1; 125:21
endorsement 112:22
endpoint 26:5, 24; 65:12
endpoints 27:7; 62:16; 66:25; 72:15, 18
ends 24:25; 78:3
England 95:22
enhance 14:24; 105:13; 109:2, 2; 138:23
enjoy 109:9
enough 11:23; 20:2; 30:7; 88:23, 24; 89:16; 90:25; 99:18; 112:6, 6; 114:19; 116:23; 124:3; 127:15; 144:13
enrolled 47:25; 113:16
enrolling 135:12
ensures 20:6
entered 48:25; 146:6
enters 90:6
entire 55:10; 60:16
entirely 103:13
environment 73:2
enzyme 53:23
enzymes 33:22
epidemiologic 155:25

epidemiological 110:22
epidemiologically 116:16
epidemiology 130:25
episode 126:17
episodes 59:23; 61:5; 63:14; 68:25; 69:23
equation 12:1
Eric 4:3; 5:21; 123:22
Eric's 118:1
erroneously 32:18
error 10:20, 20, 25; 11:15, 22; 12:1, 3; 14:15; 15:1; 69:17; 152:9, 11
errors 37:16
escalation 76:23
especially 62:16; 85:14; 89:25; 92:7; 155:25
essence 123:4
essential 72:8
essentially 125:22
establish 8:16
estate 14:21
esteemed 7:17
et 13:19; 16:16; 52:16, 24, 25; 53:23; 54:5; 58:10; 62:11; 64:9; 95:6; 96:5; 112:13; 145:25
ethical 64:18; 148:5; 154:16
Europe 10:24; 124:17
European 124:11
evaluate 6:18; 25:21; 26:8; 53:7
evaluated 49:7
evaluating 27:12; 36:10
Evaluation 6:8; 55:19; 57:22; 65:1; 67:18; 68:16
even 6:4; 26:25; 27:7; 33:5, 16; 39:24; 48:4; 56:14; 61:16; 68:2; 70:11; 74:19; 75:3; 91:4; 92:23; 95:14; 109:14; 112:15, 21; 113:12; 119:11; 124:4; 125:24; 128:22; 129:23; 132:8; 137:5; 139:2, 13; 141:9; 145:22; 148:5; 152:21; 154:9
evening 107:16
event 6:10; 54:2; 56:11; 59:13; 62:13, 14, 15, 17, 19, 20, 22, 23; 63:5, 5, 10; 64:5, 11, 22, 23, 25; 65:3, 5, 11, 13, 15, 16, 23; 66:2, 7, 7, 15, 16; 67:4, 14, 15, 16, 18, 21; 68:1, 5, 13, 19, 23; 69:8; 70:13, 16, 20, 22, 23; 71:1; 78:24; 79:3, 3, 12, 21, 21; 88:20
events 61:4; 63:1; 64:7, 8, 24; 65:7; 66:8; 68:4; 70:25; 71:3; 89:4; 98:23; 100:25; 107:21, 21; 108:2, 11, 15; 111:16
eventually 49:8; 61:10; 71:6

every 10:13; 35:15, 16; 58:23; 108:1
everybody 11:4; 13:22; 81:1; 96:23; 97:9; 130:17; 138:18; 145:10; 153:9
everybody's 155:15
everyone 48:24; 92:25; 113:11; 155:14
everything 14:24; 91:10; 115:17; 119:8
evidence 45:6; 54:18; 68:1; 76:2, 17; 77:3, 10, 17; 110:17; 118:19; 136:20; 138:7, 24; 143:12; 153:20
evident 15:19
evolutionary 125:14
evolves 139:20
Exact 57:16
exactly 102:9; 136:2; 155:4
examination 24:4; 73:12
examine 20:4; 34:6
example 9:6; 25:10, 15; 35:15; 40:12; 46:2, 4; 47:19; 48:10; 49:20; 50:11; 54:2, 3; 58:8, 22; 63:9, 17; 65:8, 17; 66:12; 67:16, 16; 70:10; 82:6; 83:2, 17; 86:10; 91:25; 93:21; 95:22; 99:13; 101:3; 102:1, 2, 4; 112:10; 116:1, 3; 120:10; 122:24; 123:17, 19; 137:4, 9
examples 30:1; 41:15; 44:8; 66:20
exceed 153:19
exceedingly 155:22
exceeds 107:14
excellent 78:4
except 10:22; 83:1; 153:25
excessive 26:10; 40:2; 58:9; 59:5, 7, 10, 11
excessively 52:13
exclude 6:13; 32:10, 12; 83:4; 154:16
excluded 59:3; 83:3; 153:13
excluding 117:7
exclusion 6:14; 32:6; 81:12; 88:7
Executive 4:10, 11
exemplify 15:3
exercise 149:20
exhibit 39:3
exhibited 38:25
exist 73:17, 24; 74:20; 75:6, 9, 19, 22
existing 28:5
exists 86:18
expand 131:6
expect 13:14; 15:20; 16:2; 26:2; 35:10; 76:16; 107:24; 117:22

expectation 27:10
expectations 21:19
expected 26:4; 55:2
experience 10:18; 28:8; 41:2; 45:24; 52:8, 24; 57:9; 95:21; 124:5; 125:19
experienced 35:8
experiences 98:23; 99:2
experiencing 75:13, 25
experimental 28:6; 60:15; 65:19
expert 36:15; 37:8, 9, 12, 13; 51:19; 68:9; 84:5; 150:7
expertise 8:16
experts 7:18; 37:14; 50:5; 82:6; 97:10, 10; 151:21; 155:10
explain 109:20
explore 26:5; 80:6
exponentially 48:7
extend 127:11
extended 23:21; 124:15
extension 19:23
extensively 82:25
extent 22:6; 85:10
extra 114:22
extracted 55:18; 63:17
extreme 105:25
extremely 21:16; 107:13
Eye 74:9, 16

F

face 51:21; 147:6; 149:5
fact 10:21; 14:15; 61:18; 65:9; 73:6; 82:13; 84:9; 104:23, 25; 118:20; 121:4; 123:15; 131:23; 136:20; 137:10, 14; 138:7; 141:13; 148:25; 152:21; 153:1; 154:22
factor 138:5
factorial 88:11
factors 102:4; 149:24
faculty 36:7
fail 134:21; 139:7
failed 35:6; 134:5, 8, 11; 141:24; 142:11
fails 135:15; 140:1
failure 42:21; 49:4; 52:2; 63:6, 7, 22, 23, 24; 64:1, 2, 3, 7; 68:10; 151:19, 22; 152:3
fair 71:11; 104:9, 20; 106:1; 141:16
fairly 50:16; 120:11
fairness 7:6
FALKOWSKI 5:18, 18; 101:10, 12; 116:9, 13; 118:1; 122:25; 123:1, 13; 136:2; 149:13; 155:21, 24
Falkowski's 103:9;

110:16
familiar 72:14
family 39:24; 75:21; 76:9, 12; 102:3; 104:5; 121:4; 132:13, 20; 142:10
famous 124:3
fan 84:17
far 11:9; 58:1; 77:22; 79:25; 83:7; 149:6, 7
fashion 88:24
fat 123:9; 149:17, 20
favor 59:12
favored 79:12
FDA 4:10, 24; 5:1, 3, 4; 6:12; 9:20; 25:6, 8, 16; 27:3, 13; 30:25; 51:17; 57:21; 59:12; 60:17; 68:8; 70:15; 71:22; 72:12; 78:4; 80:5, 18; 87:1; 96:17, 17; 97:1, 11, 15; 103:12; 120:2, 7; 126:25; 137:11; 139:4; 146:24; 147:5; 148:5; 155:14; 156:17
FDA's 6:16; 78:3; 139:20
fear 147:17
features 52:3
feedback 58:6
feel 104:2; 105:2; 109:4; 131:10
feeling 126:10
feels 100:16; 126:6; 146:24; 147:16
feet 94:14
felt 74:10, 14
females 133:20
ferret 105:4
fetus 87:25
few 10:23; 66:3; 67:9; 78:11; 90:10
fewer 25:23; 105:11; 109:9
field 10:20; 26:23; 36:13; 114:9; 130:9; 134:16
fields 50:11
fifth 42:16
fight 112:13
figure 13:10
filed 134:20
fill 12:7
final 20:21
Finally 16:13; 18:24; 30:14; 34:18; 36:22; 66:22
financial 6:12; 7:7
find 12:20; 13:4; 25:22; 28:23; 42:16; 62:24; 80:24; 93:24; 104:25; 114:20; 142:17; 151:23
finding 10:3; 29:4; 32:15; 44:23; 51:7; 56:1; 117:7; 146:10
findings 84:5, 7
fine 149:21; 155:15
finer 84:21
finished 126:2

firm 7:7
firms 6:7, 11; 120:6
first 13:20; 15:15, 20; 17:9, 15; 18:4; 22:4; 30:22; 32:5; 34:21, 21; 35:10, 11, 19; 36:4; 42:10, 14; 43:1; 44:12, 14; 49:15; 50:18; 52:14; 53:13, 14; 54:2, 4; 56:11, 12, 13, 23; 57:13, 13; 59:15; 62:13, 14, 17, 19, 22; 63:5; 64:19, 23; 65:3, 11, 13; 67:14, 16, 25; 68:5, 24; 70:11; 71:4; 73:23; 74:17; 75:11, 16; 79:3, 4, 11, 13, 21; 80:23; 81:22; 92:10; 111:11; 129:14, 20; 134:10, 13, 18; 135:15; 151:15; 156:9
fish 143:5
Fisher's 57:15
fits 83:24; 155:1
five 35:16; 43:18; 46:8, 10, 17; 48:19; 53:15, 16, 17; 145:1, 2, 5
fixed 71:1, 12
flat 19:8
flip 96:14
floor 97:22; 116:5
fluids 109:23
focus 16:18; 27:9; 58:8; 62:14, 19; 83:14; 86:16, 19, 21; 88:2, 14; 90:9; 96:20; 98:2; 117:18; 129:10; 130:1; 133:9; 137:15; 147:1
focused 149:14
focuses 111:10
focusing 89:17
folks 90:11
follow 19:16; 29:20; 34:5; 89:2; 90:13; 103:8; 107:11, 19; 108:13; 113:25; 120:19
follow-on 134:7
follow-up 19:13, 24; 22:21; 23:8, 8, 9, 21; 86:15; 87:16; 113:8; 122:12; 124:15; 133:4
followed 38:23; 44:3; 48:1; 71:1; 85:25; 145:4
following 6:1; 23:19; 24:7; 44:2; 48:14; 59:13; 70:24; 126:24
foot 145:22
force 143:25
foreshadowed 127:24
form 39:12, 14; 57:25; 110:4; 140:19
forms 73:25; 133:15
forth 92:8; 96:15; 124:4
found 49:10; 77:21, 23; 106:21; 144:25; 145:18; 152:21
Foundation 5:19; 7:14; 20:20; 21:2
four 35:19; 46:12; 48:1;

53:18; 60:21; 74:9; 88:7;
90:15; 126:20, 21; 129:15;
131:4; 143:13; 153:14
— **th** 38:6; 91:12
ANKLIN 5:16, 16;
90:12, 13; 94:25; 102:11;
103:7, 8; 115:12, 13;
128:20, 21; 149:25; 150:1;
154:7, 8
Franklin's 123:2
frankly 108:4
fraternity 132:1
free 138:3
frequency 34:4; 43:1, 6,
20, 20; 44:4; 45:16, 18, 19,
20, 21; 46:1, 5; 48:10;
49:17; 59:22, 24; 61:12;
63:14; 71:5; 85:24, 24;
86:6, 6; 88:13, 24; 101:9;
107:23; 111:15; 112:1;
132:9
frequently 25:13; 58:16;
101:3; 102:19; 122:11;
143:1
friends 38:16; 43:12;
131:24, 25
fruitful 37:2
fulfill 42:4
full 43:8, 13; 56:23
full-blown 102:7
full-dose 41:23

— **LLER** 5:12, 12; 27:3;
4, 4, 9, 15; 37:7, 10;
50:7, 18, 24; 51:11, 13, 19;
66:24; 82:12; 99:12, 17;
112:8; 120:1, 2; 122:16;
125:5, 6; 130:23, 24;
131:7; 141:19; 150:22, 23
Fuller's 104:17
fun 156:9
function 71:2; 87:9
functional 24:2
functioning 22:19, 25;
24:16
funded 8:13; 119:1;
145:18; 146:5
funding 119:3
further 20:8; 58:11; 65:1,
14; 78:8, 12; 84:2; 86:3;
112:21; 114:24; 128:17;
131:10
future 19:25; 20:3, 4

G

gain 80:1
gaining 126:7
gains 79:24
gape 59:17; 63:11, 13; 66:8
gargle 76:5
gave 120:17; 149:2, 4
gear 52:9
gender 21:10
general 10:24; 12:19;

18:13; 64:24; 80:19; 92:9;
121:22; 142:18
generalizability 13:18;
23:4
generalize 108:9
generalizing 92:19
generally 12:2; 13:22;
16:2; 22:8
generous 126:25
Genesis 4:15
genetic 38:20
George 120:17
germane 16:17
gets 84:2
given 20:3; 44:14; 50:12;
55:6; 56:3; 60:25; 69:19;
89:16; 119:21; 123:15;
134:14; 140:2, 4; 143:3;
148:25
gives 43:21; 89:3, 4;
100:7; 108:11
giving 32:21; 39:25;
138:14; 140:13, 17
glad 27:24
globally 90:14
glows 99:24
goal 21:22; 23:5, 8; 26:12;
27:1; 29:10, 24; 30:3, 22;
24; 31:3, 6, 11, 13; 32:11;
40:23, 24; 41:1, 6; 50:15;
72:5; 81:14, 16, 18; 85:13,
14; 111:10; 114:13, 15, 17;
118:2; 130:3, 7; 135:16,
18; 144:16; 153:7, 18;
154:24
goals 26:1; 29:19; 50:17;
72:10; 111:5; 154:22
goes 137:25; 138:21;
146:1; 150:10
good 30:7; 38:10; 45:18;
49:24; 61:19; 72:1; 83:11;
91:7, 8; 95:24; 96:9; 98:9,
15, 19; 104:2; 105:15;
128:13; 131:14; 136:20;
137:5; 138:24; 142:25;
143:16
grabs 88:4
gradations 84:18; 92:12
gradually 119:22
grain 84:21
grant 115:13; 137:6;
143:15
grants 119:1
graph 54:8; 119:21
graphs 136:8
grapple 29:6
grappling 25:12
grateful 156:22
great 84:17; 98:17;
142:21; 156:8, 12, 20
greater 13:1; 44:19;
74:25; 75:2; 104:23;
116:1, 7, 8; 137:18; 143:25
greatest 97:5; 114:2
green 48:16; 55:11, 11

ground 12:3
group 7:17; 17:1; 18:14,
15; 19:7, 9, 14, 20, 20, 23;
22:16; 30:9, 10; 41:23;
43:14; 44:20, 20; 54:10,
13; 55:3, 14, 15, 22, 25;
56:15, 16, 23; 82:25;
83:13, 14; 84:9; 85:6;
87:10, 11, 19, 23; 89:13;
92:12; 93:3, 19; 95:11;
99:1; 101:22, 22; 102:16,
20; 104:23; 105:5; 108:10,
10; 109:8; 117:19; 118:5;
120:12; 131:3, 8; 132:6;
133:1; 137:15; 141:3;
144:20; 146:1; 147:16;
152:22; 153:11; 154:20,
21, 23; 155:19
groups 41:23; 42:17;
43:9, 14; 55:5; 71:11;
81:11, 18, 21; 105:1, 16;
106:17, 20, 23; 107:1, 2, 6;
121:10, 10; 130:25; 131:4;
132:23, 23; 141:2; 145:5,
13; 146:13, 13, 19; 155:5,
10
growing 9:23
guess 50:25; 85:9; 90:13;
91:3; 103:8; 116:9;
118:17; 133:2; 141:11;
147:3, 21
guests 6:16; 25:5; 26:22
guidance 34:13; 73:1
guide 27:19; 72:23
guidelines 46:20, 24;
47:19
Guilty 74:9, 14, 15
gum 96:5; 118:21
guys 97:9; 146:19

H

habit 118:22
hadn't 90:5
half 14:12; 43:4; 55:24;
115:11; 126:21; 149:13
HAM-D 34:11
hand 13:3; 29:2; 55:21;
56:22; 60:1; 61:13; 68:21;
106:9; 110:20
hand-held 98:25
handful 25:23
handicapping 121:1
handle 78:9
handled 36:24
handout 9:15; 37:3;
80:17
hands 82:1
hangover 74:18
Hank 112:8
happen 96:15, 21; 141:7
happening 136:7
happens 120:19; 127:1;
137:1; 150:3
happenstance 115:21

hard 32:13; 104:3; 117:9;
118:6; 143:16
hard-pressed 111:17
harder 117:23
harkening 142:6
harm 85:11, 15; 87:24
harmful 32:11
harmfulness 150:13
Harriet 5:14; 110:12
hasn't 90:20
Hassan's 128:24
haven't 51:4; 82:24;
90:18; 91:8; 107:17;
123:4; 126:23; 134:14
hazardness 85:9
hazardous 83:22;
131:20; 132:7; 150:14
hazardously 82:22
Hazelden 5:19; 7:13;
20:20; 21:2
HDLs 149:19
head 131:14
header 94:15
Health 4:21; 5:11; 11:8;
23:2; 46:19; 47:20; 95:24;
103:18; 123:8, 16; 132:8;
137:1, 3, 19; 139:16;
143:21; 154:9, 13
healthy 137:25
hear 9:12; 36:4; 37:7;
51:14; 60:22; 66:22;
91:22; 115:6; 132:13;
134:3; 147:4
heard 51:18; 84:13; 90:5;
129:15, 20, 23; 142:13
Hearing 7:10, 11; 20:17;
24:25; 51:18; 78:10, 16,
17, 19, 20; 80:12; 137:4;
151:20
heart 150:11
heavier 94:2; 136:23
heavily 48:24; 61:17;
62:1
heavy 19:3, 10, 21; 26:11;
28:14; 31:12; 32:1; 33:12;
34:22; 35:11; 46:12; 47:3;
48:22; 52:11, 14, 15, 15;
53:14, 19; 54:2, 15, 22;
55:23; 56:12, 13; 57:14,
18; 59:14, 16, 16, 17, 18,
20, 21, 23, 23; 60:7, 13,
18, 19; 61:4, 4, 8, 9, 12, 14,
15, 18; 62:4; 63:9, 11, 12,
13, 13, 14; 64:3; 67:3;
68:25; 69:2, 22, 25; 70:11;
79:13, 14; 81:4, 23; 86:6,
16; 87:2, 3; 92:2, 6; 94:6;
97:14, 15; 101:17; 110:21;
112:22; 113:21; 114:4, 19;
115:15, 21; 116:6, 23;
117:18; 127:12, 21;
128:22, 25; 129:2, 16;
130:19; 135:7; 136:4, 5;
146:3; 147:13, 20; 149:15;
150:8, 12; 152:7; 154:20

hedonic 95:5
held 36:7
help 10:17; 28:2; 29:3, 9,
14; 31:16; 37:3; 69:4;
70:19; 92:24; 98:18;
103:25; 130:5; 133:19;
151:22; 155:11
helpful 22:14; 34:13, 14;
35:1; 58:18; 64:16; 69:8, 9,
10; 109:19; 150:20
Helping 72:23
helps 29:15; 32:1; 51:20;
135:17
Helser 102:20
Henry 5:10; 6:20
hepatic 33:22
heroin 85:3
high 23:3, 10; 87:7;
102:14, 20; 107:13, 20;
110:6; 121:12
high-risk 75:19; 88:15,
16; 102:3; 121:10
higher 46:19; 96:1;
108:6, 6, 7; 142:4
highest 30:17; 89:19
highly 15:22; 56:1; 57:7
historical 33:7
history 75:21; 100:6;
102:3
hit 116:4
hitting 121:21
hodgepodge 88:9
hold 18:21; 20:3
home 31:23
homogenous 113:15
hope 9:17; 27:10; 29:24;
36:1; 37:2; 91:4; 155:7
hopefully 52:17
Hopkins 5:21
Hospital 4:19
hours 39:13; 100:3
house 132:2
huge 106:9, 10; 123:21
Human 46:20; 47:20;
156:1
humbling 120:20
hypertension 45:7;
46:25

I

I 148:7
idea 12:4, 8; 13:9; 30:11;
58:20; 123:5; 132:6
ideal 22:8; 79:5
Ideally 30:19
ideas 20:11; 35:1
identification 85:20;
86:11
identified 81:19; 145:4
identify 24:5; 29:12; 32:4,
8; 78:15; 81:20; 96:11;
121:1; 137:2; 150:15

identifying 64:16; 88:15
ignore 104:15
II 10:19, 25; 11:15, 21;
12:1, 3; 13:6; 14:15, 25;
69:17; 152:11
III 83:5
illness 10:5; 119:6;
142:21, 21
illustrates 40:18
imagine 155:21
imbalance 55:4
immediately 106:11;
120:16
immoderate 74:24;
75:17
impact 121:18
impaired 39:16; 76:20;
131:22
implicit 17:17
implied 91:24
implying 18:19; 19:25;
67:19
important 10:11; 14:22;
16:20; 17:22; 20:13;
21:13, 17; 22:15; 25:17;
31:18; 32:3; 33:2; 35:2;
39:10, 22, 25; 52:17;
57:12, 20, 25; 59:19; 60:6;
61:11; 62:24; 65:17; 85:5;
87:23; 92:4; 94:20; 98:9,
22; 100:20; 102:15, 16;
108:17; 120:21; 124:21;
125:15; 131:3; 136:11;
137:12; 147:7
importantly 55:3; 99:24
impossible 29:5
impressed 126:15, 16
impression 46:15; 49:14
improve 10:2; 138:2
improved 21:22, 23;
23:15
improvement 16:16;
18:11; 22:3; 24:15; 30:7;
42:22; 60:23; 61:23, 23;
62:6, 9; 63:23, 25; 64:25;
65:6, 18, 20
improves 23:10
inability 111:12
inadvisable 77:7
inappropriate 135:19
incidence 55:23; 93:23
include 34:20; 140:19
included 29:20; 59:6, 18;
60:24; 64:7; 72:15; 82:10
includes 53:13; 143:1
including 8:20; 34:3; -
86:6, 7; 121:17
inclusion 32:6; 81:12;
112:25; 144:5; 146:20
inclusion/exclusion
60:25; 88:9
inconsistent 26:14
incontinence 151:4
incorporate 97:2
incorporates 63:10

increase 48:8; 149:18
increased 63:13; 75:11;
136:19
increases 47:1, 11; 48:5,
7; 110:9
increasing 102:22
increasingly 89:18
incredibly 10:5
IND 88:17
independent 93:9
index 104:7
indicate 61:19; 95:8
indicated 75:25; 94:22;
95:14; 102:18; 147:20
indicates 100:14
indicators 33:21; 144:7
indirect 112:4
individual 12:13, 24;
13:11; 19:6; 24:5, 11; 33:5;
85:16; 98:17
individuals 8:25; 11:7;
13:17; 14:25; 15:25; 18:7;
20:1; 28:24; 43:15; 91:7;
101:9
industrialized 136:15
industry 9:24; 25:6
ineffective 41:24; 62:3
infarction 138:8
infarctions 64:11
infeasible 98:10
infection 66:4
infections 64:13
influence 38:21; 95:11;
137:18
influenced 26:2; 96:2;
146:11
influences 47:24; 95:11,
12
informant 110:3, 6
information 6:5; 9:16;
17:19, 24; 36:21; 55:7;
56:3; 58:21; 59:13, 21;
68:2, 18, 21; 73:17; 82:17;
98:18, 20; 100:7; 110:10
informative 120:4;
152:20; 153:1
infrequent 112:10
ingesting 44:13
ingestion 39:1, 14
initial 13:25; 86:11
initially 86:4; 89:14;
135:12; 154:21
initiated 66:17
initiation 135:18
injury 76:13
inpatient 140:25; 141:4
insight 155:24
instance 64:10; 76:19;
151:7
Institute 5:13; 27:4; 36:6;
72:25
instructed 31:8
instructions 135:1

instrument 33:1; 85:20;
86:1, 12
instruments 22:12, 14;
33:18; 34:5, 9, 14; 86:10
insufficient 94:17;
104:10; 142:20
insulin 121:5, 6
intake 138:16, 17
intend 131:22
intended 23:5; 39:17, 18
intensity 44:9; 45:16, 19,
20, 22; 46:2, 7, 10; 113:4
intensive 11:25; 139:15
interact 12:14; 18:10;
73:14
interaction 14:13
interactions 18:10
interacts 135:20
interchangeably 128:22
interest 5:24, 25; 6:2, 9,
12; 7:6, 21; 9:23; 28:4;
59:22; 60:6; 61:1; 62:13;
64:13; 66:9; 67:3; 70:22;
97:21; 139:20; 149:12;
153:2
interested 8:4; 28:12, 14;
34:1; 39:9; 134:4; 151:1
interesting 17:16; 38:19;
69:14; 70:1; 85:22; 88:20;
111:1; 112:21; 113:14
interestingly 94:1; 99:18
interests 6:7, 17
interfered 76:10, 11
interfering 40:10
internist 50:19
interpret 35:4; 141:17
interpreting 128:11, 18
interrelated 34:20; 80:21
interrelations 89:6
interrupt 140:24
intersect 19:25
interval 71:2, 12; 120:5
intervals 22:22; 23:22;
48:13
intervene 96:11
intervention 16:1, 22;
18:21; 32:20; 73:10;
85:21; 86:20; 87:24; 88:2;
93:14; 95:13, 23, 23;
115:16; 119:12; 121:23,
24; 123:14; 124:19;
129:24, 25; 130:14;
131:10; 132:21; 134:6, 7,
8, 11, 13, 18; 135:3; 139:8,
16, 17, 25; 140:1, 4;
144:25; 148:23; 150:20
interventions 9:4; 10:4;
84:10; 96:3, 5; 117:7;
121:6, 16, 17, 18; 131:14;
133:13; 134:21, 22;
138:23; 149:22
interview 21:14; 34:3;
105:12; 145:4
interviewed 112:12
intimidated 37:14

into 8:15; 20:3; 27:8;
51:5; 53:25; 63:12; 66:7;
68:22; 83:16; 88:18; 90:7;
93:5; 100:6; 118:16;
126:19; 135:13; 139:6, 8,
9; 140:5; 146:1; 153:21;
154:15
intoxicated 39:21; 45:8
intoxication 57:23;
85:25; 112:1
intriguing 111:13
introduce 4:6; 20:23;
60:21; 63:3
Introduction 4:8
Introductory 27:23
Inventory 57:24
Investigation 65:14
investigations 31:20
investigator 6:23; 7:2
investigators 45:12;
48:23; 58:22
invited 6:16; 26:22
involve 6:10; 9:2
involved 8:17, 20, 23, 23;
9:3, 11, 21; 68:15; 91:6;
95:3; 112:20; 145:17;
149:17; 155:14
involvement 6:14
involvements 7:7
irrespective 57:3
isoniazid 99:25
issue 6:2; 32:3; 39:9;
84:22, 25; 90:4; 96:7; 98:7;
112:21; 118:24; 123:21;
125:6; 127:17, 18; 128:16;
137:12, 12; 139:5, 23;
148:5, 5; 150:12; 152:13,
14
issues 10:7; 12:12;
25:12, 17; 36:1, 12; 51:21;
78:5; 95:15; 102:25;
106:12, 16; 127:6, 10, 16;
140:6; 141:2; 155:25
item 155:17
itself 96:2; 100:12
IV 39:17

J
Jack 5:2; 36:22; 71:22;
72:3
Jacobson 23:23
JAMA 49:6; 122:18
JARVIK 4:16, 16; 85:8
Jim 19:1
job 39:24; 91:8
John 5:16; 102:20
Johns 5:21
joined 20:22
Journal 143:21
judged 41:20
jumps 103:22

K
K 68:24, 24
Karen 4:9
keep 10:17; 90:25;
118:22; 147:7
kettle 143:5
key 10:7; 136:9
kids 85:2; 96:23
kind 37:11; 58:7; 65:18;
68:18; 70:19; 89:25;
103:20, 22; 104:1, 2;
109:24; 118:9; 132:23;
133:23; 135:3; 152:5
kinds 133:23; 135:25;
138:11; 139:8; 140:5;
154:12
knock 42:20
knowing 40:6
knowledge 50:19; 99:19;
125:16
known 26:6; 54:22, 25;
56:6
knows 86:13; 87:25;
110:12
KRANZLER 5:10, 10;
6:20; 82:9; 83:1; 85:17;
88:5; 89:13; 90:2; 91:24;
95:17, 20; 97:17, 18;
106:18; 111:14, 22;
116:12, 15; 117:18;
120:15; 126:12; 136:11;
142:23; 144:6, 9, 18, 21;
152:1, 2; 153:10, 16
Kranzler's 116:2; 149:1

L
label 123:23, 25; 124:1;
125:18, 23; 127:4; 148:2, 2
labeling 147:19
labor 156:11
laboratory 27:6; 53:22
lack 11:20; 49:10; 59:4
large 47:21; 72:13; 97:22;
98:4; 117:21; 121:21;
128:10; 131:1; 152:8
largely 85:23
larger 21:10; 93:4;
101:14; 117:21, 23; 146:5
largest 83:10
last 9:7, 8, 11; 13:7;
35:21; 38:7; 43:18; 49:6;
57:1; 74:3; 100:3; 108:1
lasted 26:6
lasting 133:7, 13
lastly 40:5
late 38:22
latency 111:16
later 52:19; 58:12; 60:4;
62:11; 70:7; 71:16; 145:1,
6
Laughter 67:24; 123:11

lay 51:20
Leader 4:25; 27:15
leading 68:9; 100:23
lays 40:20; 94:6
layman 50:14; 51:1
learned 60:17
leap 137:22; 152:18
learn 65:17; 127:5; 147:8
learned 10:1; 52:7; 133:11
least 15:10; 17:10; 19:18; 40:14; 45:4; 57:17; 75:16; 79:22; 111:1; 136:1, 14; 139:15
leave 155:8
leaving 155:20
led 76:13; 111:10
left 54:9; 58:25; 85:2
leftover 110:14
legal 40:12; 46:9; 72:18
legitimize 147:15
leisure 39:25
length 22:4, 5, 5; 52:13; 59:22; 70:7; 124:12; 128:7, 7
lengthens 61:9
less 21:21; 22:8; 30:10, 11; 45:19, 23; 46:15; 47:8; 50:11; 69:2, 24; 79:12; 83:22; 97:20; 128:15; 139:17, 17; 148:22; 150:20
lessor 22:6; 47:12
letter 7:13; 20:19; 21:1; 24:20
level 8:16; 12:12, 18, 18, 21, 22; 19:19, 21; 21:14; 34:6; 48:20; 102:25; 103:1; 118:3; 136:21; 140:15; 144:5, 9; 145:22
levels 13:18; 16:7, 8; 31:9; 33:12, 13; 53:23; 83:22, 23; 101:6; 102:14; 116:23; 132:7; 136:20, 23
lid 100:15
lies 131:20
life 21:22, 24; 40:1, 10; 63:17; 104:2, 7; 117:3; 123:18
lifetime 22:1; 118:22; 119:2, 13; 154:11
light 118:14; 119:18
lighter 94:1
likelihood 97:5; 114:2; 116:1; 125:3; 135:21; 136:22
likely 11:18; 16:19; 39:1; 45:5, 9; 51:6; 73:7; 105:10; 133:22; 137:1, 2
limit 144:1
limited 82:17; 107:3; 143:13; 150:21
limiting 130:24; 131:4; 143:12
limits 23:4; 153:19

Lin 68:9
line 17:7, 11; 19:12; 34:4; 63:23, 24, 25; 107:22; 108:13; 145:19
linear 19:5
lines 19:24
lipid-lowering 138:4
lipids 138:5
lipoproteins 149:18
list 8:19; 9:10, 12; 11:1; 27:18; 41:10; 49:9; 70:25
listed 33:18; 39:7, 8, 16; 66:2; 72:11; 76:18
listening 128:21
literally 145:1, 2
literature 46:24, 25; 50:20; 65:9; 66:1, 14; 82:24; 84:6; 100:1; 106:18; 107:4; 110:13; 152:20
lithium 8:21; 16:5, 7, 8
little 12:6; 25:22; 26:16; 42:19; 79:5; 87:20; 88:8; 89:3; 103:9; 107:15; 108:3, 22; 114:23; 118:10; 125:12; 129:11; 133:2; 143:23; 145:14; 147:4; 155:16
lively 50:4
liver 48:4, 8; 53:23; 112:9
livers 154:12
lives 150:18
LLOYD 4:11, 11; 90:3, 4
Lloyd's 92:3
Llyn 4:11
location 14:21, 22, 22
log-rank 56:18; 57:5, 11
logic 151:18
long 17:23; 28:19; 29:22; 48:1; 78:16; 90:25; 98:5; 103:18; 107:2; 111:16; 119:10; 120:23; 124:2; 126:8; 128:1
Long-term 4:15; 41:3; 123:16; 133:8
longer 17:20, 21; 18:9, 20; 39:17; 69:19; 118:10; 120:3, 13; 122:22; 126:18; 127:3, 21; 138:11; 142:2, 11
longest 22:5
longevity 125:18
longitudinal 47:21, 22
LONGMIRE 5:2, 2; 36:22; 58:11; 60:3; 71:22, 24; 72:1, 3; 78:2; 85:23; 142:7
look 15:6; 17:10; 19:14, 15, 21; 24:22; 30:14; 32:14; 34:24; 68:22; 87:2; 90:7, 7; 93:22; 95:21; 98:5; 104:17; 108:2; 112:23; 115:25; 116:6, 15, 20; 118:8, 18; 119:2, 25; 124:25; 128:24; 133:8; 136:8; 144:8; 148:6, 10; 17, 24; 150:4; 151:12

looked 19:2; 45:15; 49:9; 79:2; 103:2; 107:18; 119:20; 144:22; 145:8, 11
looking 18:24; 19:6; 28:17; 33:8, 13, 14; 47:24; 50:17; 69:17; 79:18; 80:6; 84:19; 103:16; 106:18; 107:15; 108:14; 114:21; 115:13, 14; 116:3, 13; 117:6; 119:6, 19; 121:5, 8; 124:3; 126:10, 23; 128:16; 130:3; 131:13; 132:21; 133:5; 148:13, 20; 150:8, 24; 151:2, 10
looks 16:25; 17:14; 23:23; 33:25; 113:21
lose 18:18
losing 85:2; 133:10
loss 76:18; 80:1
lost 42:5; 122:12
lot 46:17; 50:4; 89:4; 91:4; 93:20; 95:2; 99:23; 102:5; 108:11; 121:9; 128:4, 8; 129:24; 132:14, 18, 20; 137:7, 8; 146:1; 154:1
love 156:11
lovely 156:25
low 12:3; 31:9; 33:12; 77:9; 102:25; 103:3; 111:15; 149:18
low-risk 60:2, 5, 8
lower 93:6; 103:1; 112:24; 115:11; 149:18
lunch 155:16

M

magenta 54:20; 63:22
magical 138:14
mailing 88:22
main 62:14, 19; 67:3
mainly 86:25
mainstay 25:25
maintain 61:15; 122:21
maintenance 135:18
major 36:25; 44:23
majority 82:10, 12; 83:8; 121:15
makes 11:15; 29:4; 49:11; 83:21; 120:22; 121:9
making 25:9; 117:25; 132:4; 133:14; 142:25
man's 79:17
managed 91:10; 132:15; 137:17
management 135:7
mandating 139:6
manual 38:4, 5, 5
manufacturer 139:3
many 9:22; 11:4; 14:8; 16:25; 17:11; 23:14, 15; 15; 25:8; 30:18; 31:1, 2; 32:24, 24; 33:17, 19, 19; 34:23; 38:15, 24; 39:19;

41:2; 47:18, 18; 51:5; 62:4; 64:6; 66:3; 70:25; 74:1, 2; 97:10; 101:18; 102:14; 116:10, 12; 122:7, 9, 9, 10; 135:8, 10; 136:15; 138:25; 140:18
Marginal 66:10
marital/family 23:1
markedly 16:8
marker 15:5, 7; 99:14; 101:6
markers 98:18; 100:10
market 96:21, 22; 124:2; 151:23
marketed 32:15
masking 42:22
MASON 5:8, 8; 7:1; 87:15, 16; 94:11, 12; 102:11, 13; 105:7, 19, 20; 106:14, 15; 110:2, 3, 8, 11; 124:8, 9; 133:14; 145:14; 146:22
MAST 86:10
MATCH 9:1; 12:21; 17:13; 22:15, 16; 43:24; 45:11, 12; 72:14; 82:6; 111:7; 112:11; 146:10, 16
matched 7:4
matches 12:18
matching 12:4, 22
material 8:15; 90:8
materials 27:18; 133:17, 18, 23; 156:11
matter 107:2; 118:21, 22; 150:11; 154:5
mature 150:17
maximize 152:10
maximized 12:20
maximum 74:3
may 7:8; 9:19; 13:16; 20:1, 2; 22:1; 23:18, 20; 33:22; 35:9; 51:3, 21; 55:8; 60:5; 61:25; 62:11; 63:22; 64:2, 11, 13, 17; 65:5, 5; 67:12; 75:14; 76:15; 77:8; 79:5, 5; 80:4; 83:11; 86:11; 92:5, 25; 93:4, 5; 95:8; 96:19; 97:22; 98:4, 19; 101:17; 103:24; 104:22; 106:3, 5, 8, 10; 110:17, 18; 113:1; 114:6; 115:21; 122:2, 23; 126:16; 135:10, 18; 136:18; 137:22; 138:7; 139:1, 9, 19, 24; 140:24; 141:20; 147:6, 15, 24; 148:1, 21, 25; 154:24
Maybe 4:7; 9:17; 17:17; 19:9; 47:19; 70:8; 91:8; 96:23, 24; 111:8; 126:20, 21; 131:16; 132:8; 134:15; 135:22
McCORMICK 4:23, 23; 25:2, 4; 27:22, 25; 51:19; 120:8; 122:2; 129:9, 10; 130:18, 20; 131:6, 8; 134:1, 3; 146:20; 147:3, 21; 148:4; 150:5, 6, 23;

156:5, 19
mean 19:3; 29:24; 85:17; 92:16; 93:20; 96:8; 97:24; 102:1; 103:17, 18, 19; 104:19; 109:24; 114:24; 115:20; 118:2, 18; 125:20; 126:19, 22; 128:14, 14; 131:21; 135:3; 136:3; 138:10; 140:18; 141:13; 147:25; 148:10
meaningful 29:14; 30:6; 33:8; 61:23; 79:21; 144:14
meaningfully 104:1
means 104:6; 119:24; 132:22; 142:9
measure 16:18, 20; 21:14; 33:2, 16, 17; 42:3, 9; 43:19; 46:5; 49:17; 79:18; 97:21; 100:2, 16, 20; 104:2, 3, 11; 112:6, 11, 16; 118:4, 5, 7; 128:1; 133:4
measured 22:11, 20; 24:2; 42:15; 49:18; 66:23; 71:12; 81:21; 99:20
measurement 16:14; 30:5
measurements 15:10; 16:15; 30:19; 72:19
measures 16:21; 22:3, 7, 8; 24:8; 27:7; 29:15, 19; 30:2; 32:24; 33:24; 34:2; 46:1, 7; 50:2; 52:11; 53:12, 22; 57:21; 59:19; 72:12; 86:12; 98:2, 22; 99:8; 105:3; 115:10; 132:9; 144:23; 146:15
measuring 33:1; 40:16; 52:13; 100:6, 11, 19; 128:2, 2
mechanism 117:6
mechanisms 152:24
median 56:13; 70:10
Medical 4:25; 5:2; 7:12; 8:10; 10:13; 11:5, 10; 16:11; 36:22; 57:21; 58:11; 59:8, 12; 60:1, 17; 72:3; 76:3, 4; 77:6, 18; 96:6; 112:2; 134:16; 136:21
medication 6:21; 7:3, 22, 23; 8:1; 9:2; 11:19, 21; 13:2; 14:15, 17, 20; 15:13; 16:11; 18:5, 9, 14, 19, 20; 19:12, 22, 22; 20:1; 26:24; 27:1, 2; 28:25; 29:1, 8; 30:4; 31:16; 73:13; 88:12, 13, 15; 89:14, 16, 23; 96:13, 16, 19; 97:11; 100:9, 18; 107:8, 12; 108:12, 23; 109:2, 7, 14; 110:1; 113:12; 114:7, 10, 11, 14, 14; 115:25; 121:25; 123:6; 124:25; 134:15, 16, 17, 19; 135:14, 16, 19, 20; 137:21; 140:2, 7; 141:9; 142:14, 15; 148:2, 22; 149:19; 151:16

medication-placebo 12:19
medications 8:9; 13:14, 16, 18; 25:14; 28:6, 9, 12; 32:22; 34:19; 50:13, 16; 94:7, 9; 99:19; 109:15; 122:21; 124:1; 137:23; 139:24; 147:23; 148:17, 21; 149:1, 17; 150:20
Medicine 5:7, 9
meet 28:11; 39:3; 81:7; 82:18; 83:11; 87:19; 113:19; 116:19, 22; 117:9; 129:3, 5; 131:2; 154:5
meeting 4:5; 6:3, 4, 9; 25:1, 7; 26:8, 18; 27:11, 14, 17; 40:12; 71:21; 136:17; 155:20
meetings 17:16
meets 117:8
member 4:12; 20:21; 104:5
members 4:5; 25:6; 26:22; 121:4; 126:10; 142:10; 155:19
membership 156:20
MEMSCAP 99:5; 100:14, 16, 23; 107:13; 108:13; 109:25
MEMSCAPs 107:10
men 38:21; 43:5; 46:22; 48:18; 53:17; 74:25; 77:14; 83:18; 94:3; 143:18; 144:10
mention 16:13; 39:5; 109:4
mentioned 27:25; 75:17; 85:22; 90:5; 130:25; 131:5; 144:23
merely 147:12
merited 95:8
message 17:17; 31:18
met 82:7; 94:4; 145:10
metabolism 152:25
metabolite 100:12
method 30:19; 34:5; 52:2, 16; 57:10, 15; 62:24; 63:8, 10; 64:1, 5, 7, 25; 65:5, 23; 66:16; 67:4; 68:10; 69:18; 70:13, 20; 100:21
methodologic 36:12
methodological 137:13
methodology 24:7; 99:15; 108:18; 111:23
methods 23:6; 29:16; 30:14; 36:19; 84:20; 100:5, 19; 101:4
metric 10:16; 12:11
Meyer 20:22, 24, 24; 50:6, 10, 22; 69:12, 13; 84:1, 2; 98:11, 12; 102:17; 109:17, 18, 21; 126:14; 127:17; 138:19; 139:13; 140:12, 17, 21; 141:3, 6; 148:9; 149:16; 150:6, 12;

152:12, 13; 154:17
Meyer's 78:22
Miami 5:8
micrograms 15:11
microphones 81:25
mid-1980s 41:19
middle 12:3
might 11:25; 12:11; 13:4, 6, 24; 17:21; 19:24; 20:12; 26:1; 29:4; 31:13, 14; 32:11; 35:12, 14; 38:20; 45:8; 49:2; 69:18; 73:2, 13, 17, 20, 21, 24; 74:20; 75:6, 9, 19, 22; 77:3, 23; 80:1; 81:20; 88:19; 90:20; 92:7; 93:3; 96:12; 97:2, 3; 98:18; 99:12; 101:5; 103:2; 104:5, 8, 23; 105:5, 14; 114:25; 115:24; 117:11, 22; 122:24; 127:15, 16; 128:3; 129:25; 131:11; 133:10; 134:25; 135:11, 23; 138:2; 142:2; 145:14; 147:16; 154:3; 156:5
mike 50:9
mild 11:3, 6; 15:22; 84:7; 143:14
milder 84:8
mildest 39:12
mildly 84:15
milliliter 15:11
mind 10:17; 12:12; 119:14; 128:23; 138:13; 147:7
mine 7:19
minimal 93:14; 144:9
minimize 14:25; 58:14; 152:10
minimized 105:17; 152:10
minimum 24:13; 144:4
Minnesota 5:20
minority 136:23
minus 20:8
minute 12:15; 14:18
minutes 9:17; 67:8, 10; 78:11; 145:1, 2, 5; 147:1
mismatch 111:6
misrepresent 104:21
misrepresenting 105:5
miss 29:4; 97:6; 125:14
missing 55:8; 56:3
mistaken 120:7
misuse 92:23
mixed 35:3; 73:25
mixing 127:16
model 18:25; 66:3, 6, 10, 13; 69:13, 24; 70:5; 93:16; 97:4; 103:2, 4; 115:19, 23; 141:25
modeling 19:5
models 115:16
moderate 11:6; 28:18, 21; 29:3, 9; 31:17; 32:1; 77:13; 84:8, 10, 12; 85:14;

15, 18; 94:18; 97:15; 114:5; 118:3; 134:9; 135:23; 153:12; 154:24
moderately 15:22; 153:21
moderation 31:14; 32:8; 33:4; 36:23; 60:3; 135:16, 18; 142:12, 15; 144:17; 153:8
modest 95:25; 145:9
modestly 82:23
modifying 35:8
moment 60:18; 101:7; 129:22; 155:18
money 156:12
monitor 73:15
monitored 109:24
monitoring 100:25; 107:21; 108:11; 144:23; 145:24
month 16:7; 35:19, 20; 74:4; 119:21, 22; 126:11
months 16:8, 9; 17:24, 25; 18:1, 4; 26:6; 44:1, 2; 48:11, 13, 13, 14; 49:1; 71:9; 78:23, 23; 116:20; 118:21; 119:12; 126:14, 20, 21, 21, 22; 127:2; 128:9; 145:1, 6, 12
mood 106:21; 108:15
moral 154:15
morbidity 121:15
more 11:6; 12:6, 7, 24, 24; 14:11; 15:24; 33:19; 34:4; 38:14, 16, 18, 23; 39:1, 9, 17; 42:12, 25; 43:16, 16, 21, 25; 45:5, 8, 23; 46:8, 15, 22, 23, 25; 47:8; 48:19; 51:2; 53:15, 16, 17, 18; 54:15; 55:1, 3, 22; 58:13; 59:14; 60:7, 9; 61:10; 62:11; 64:3, 17; 66:9; 67:1, 6; 69:2; 71:9, 11; 76:16; 77:14, 15; 78:11; 79:19; 80:3, 19, 24; 83:11, 17, 19, 25; 84:5, 7, 10, 22; 86:9, 9; 88:7; 89:2, 3; 94:3; 95:3, 8, 12, 17; 96:9; 97:25; 98:16; 99:24; 100:7; 104:24; 105:6, 9, 10, 21; 108:3, 8, 11; 109:18; 113:15; 114:7; 115:1, 25; 117:1, 11; 119:5; 120:3; 123:15; 125:8; 128:6; 131:22; 133:9, 15; 134:3; 137:1, 2, 4, 5; 139:11, 17, 18; 143:13, 17, 23; 147:4; 148:23; 149:20; 153:14
Moreover 32:14
morning 26:21; 71:16; 72:1; 73:6; 74:17; 107:16
morning's 27:14
mortality 62:18
most 10:21; 13:17; 34:14; 35:2; 39:14, 22; 41:13, 15; 49:16; 54:18; 72:14;

76:15; 83:1; 87:24; 92:22; 100:3; 101:20, 20; 129:22; 133:7, 22; 140:24; 141:4; 146:4; 150:17
mother 131:24
motivated 13:4, 5; 15:22; 96:10; 117:3; 136:5
motivation 12:13, 16, 18, 21; 69:17; 136:7, 9; 137:7, 8; 154:1
motor 85:10
move 67:10; 78:7; 80:13; 116:11; 153:21
moves 24:1
moving 123:15; 134:17; 139:15, 17
much 10:19; 14:12, 15; 17:18, 24; 22:1; 30:11; 31:8; 33:7; 39:1; 42:12; 55:24; 56:7; 68:2; 74:1; 79:19; 80:22; 84:21; 89:2; 93:4; 94:15; 96:3; 123:9; 125:8; 127:14; 128:15, 15; 133:8; 145:3; 146:7; 149:17; 156:9
multidimensional 22:20
multiple 64:1, 15
multisite 85:21
multivariate 52:2; 63:6; 64:7; 68:10
Murray 4:16
must 23:24; 33:10; 117:8
myocardial 138:7
myself 37:11, 13; 68:8

N

nalmefene 145:16
naltrexone 6:24; 7:24; 9:6; 10:23; 15:4; 16:24; 17:6; 18:12; 19:2, 7, 20; 46:3; 49:21; 52:8, 21, 22; 53:4, 9; 54:8; 55:2, 14, 17; 56:23, 25; 57:10; 68:12; 69:1, 5; 79:12, 15; 88:10, 10; 93:22, 23; 126:2; 138:1
naltrexone-treated 17:2; 54:6, 16, 23; 55:24; 56:8, 15
namely 59:13; 63:5
National 5:12; 22:15; 27:3; 36:6; 72:25; 116:18, 21
nature 101:16
nausea 39:13; 93:24; 94:3
NDA 25:11; 52:8, 24; 57:10; 65:9; 68:16
nearly 58:8; 59:4, 5, 11
neat 19:13
necessarily 80:22; 136:13
necessary 126:7; 131:10
need 6:13; 9:25; 10:7; 14:24; 18:20; 20:1; 29:9;

11, 13; 31:11, 24; 32:4, 5, 12, 14, 22; 33:3, 17; 34:18; 35:11, 13, 23; 79:4; 84:19; 85:4; 87:12; 91:15; 93:11, 22; 96:20; 98:2; 105:17; 114:20; 115:8; 119:10, 14; 120:12, 13; 129:6, 24; 130:12, 13; 131:16; 133:22; 137:10; 138:11; 150:4; 151:24; 152:8; 155:5, 6, 22; 156:4
needed 12:25; 97:23
needs 23:20; 24:13; 29:1; 32:16; 55:4; 65:20; 90:21; 94:8; 97:19; 109:5; 153:23; 155:17
negative 10:22; 41:22; 47:13; 102:15; 105:11; 136:4
neglect 39:24; 87:13
nerves 74:17
neurobehavioral 87:22
neurocognitive 87:21
neuropharm 58:16; 123:25
neuropharmacologic 120:10; 122:6, 6
neuropsychiatric 121:2; 147:10
new 18:24; 63:19; 98:24; 102:17; 147:2
Next 5:23; 25:1; 37:7; 44:8; 46:14; 51:14; 67:9; 92:11
NIAAA 8:1, 13; 9:2; 33:20; 36:7; 85:23; 133:17
nicotine 25:14; 95:21; 96:5; 113:17; 118:15, 20; 119:9; 138:23
NIH-funded 7:2
NIMH 149:8
nine 48:14; 82:14
nobody 119:2
nodding 97:17
noise 18:2
non 69:21; 81:16; 86:15; 92:1; 112:19; 134:5; 148:18
non-abstinence 32:11; 72:5
non-alcoholic 31:12
non-alcoholism 151:10
non-compliant 15:13
non-dependent 28:12, 17; 81:4, 22; 87:3, 7; 92:6; 112:22; 113:21; 114:3; 129:16; 152:22
non-DSM 152:6
non-hazardous 83:22
non-hazardously 144:18
non-medication 16:3
non-parametric 66:13
non-pharmacologic 28:16; 112:25; 114:4;

134:8, 11, 20, 21; 140:16, 19; 148:7
non-pharmacological 23
 a-problem 136:19
non-treatment 141:15
noncompliance 15:21; 105:25; 108:23
none 123:24; 149:6
Nonetheless 62:21; 146:2
normative 24:2
norms 46:16
North 4:21
Northwestern 5:17
note 71:13; 155:12; 156:8
noted 6:14; 23:20
nothing 136:6; 138:14; 150:21
notice 43:15; 48:4; 59:20
notion 69:15
notwithstanding 143:6
number 7:19; 8:22; 10:11, 19, 23; 11:6, 10; 14:5; 15:7; 16:6; 19:3; 35:21; 50:10; 52:11, 12; 53:20; 54:11, 12, 14, 20; 55:12; 57:23, 24; 59:20, 23; 60:5; 61:8; 64:11; 74:3; 89:18; 98:17; 102:22; 116:22; 126:17; 137:19; 142:12
numbers 49:13; 117:21, 21, 23; 131:13
numerical 55:17; 69:5
numerically 55:1
numerous 117:1
nurse 4:15; 100:8
nurses 58:22

O

O'MALLEY 5:5, 5; 6:23, 24; 17:1; 52:25; 55:21; 56:22; 68:12; 82:20; 92:16, 17; 93:11; 94:13; 100:22, 24; 102:12, 18; 103:21, 22; 104:14, 19; 106:3; 108:20, 21; 110:12; 112:19; 113:3, 23; 118:6; 125:20; 126:1; 131:12; 134:24; 142:13
O'Malley's 79:1
Ob-Gyn 133:21
objective 53:7; 62:14
objectively 6:18
obligation 148:10, 24
obscure 44:23
obscuring 22:9
 observation 78:23; 94:13, 21; 122:3
observe 120:14
observed 44:13
obtain 23:9

obtainable 22:2
obtaining 40:2
obverse 41:8, 11; 43:19
obvious 55:4; 85:11
Obviously 12:24; 39:11; 80:20; 83:25; 113:3; 116:17; 152:3
occasion 46:8, 10; 74:2, 3; 75:1, 3
occupationally 87:8
occur 31:24; 89:4; 106:4, 5; 111:16
occurred 17:11; 70:25; 75:4; 76:2; 95:7
occurring 64:12
occurs 122:20
off 92:16; 108:22; 131:13; 132:4; 148:1, 2; 155:22
offer 80:5; 126:25; 132:18; 140:22
offered 124:23
Officer 5:3; 36:23; 58:11; 72:3
offspring 87:22; 121:7
often 34:20; 80:24; 95:10; 100:15; 120:5; 133:21; 135:7; 143:9
old 147:3
omission 37:16
once 18:12, 19; 19:22; 32:15; 34:19; 35:20; 39:19; 53:5; 60:15; 76:21; 78:10, 11; 96:15, 21, 22; 120:15; 123:19; 127:10
oncology 50:12
one 7:12; 10:24; 11:15; 12:20; 13:24; 14:8, 17; 16:2; 17:1, 21; 19:13, 14; 20:5, 7; 23:5; 26:1, 14; 30:17; 32:3; 33:1; 39:22, 25; 41:19, 23, 24; 42:2, 19; 44:3, 16, 25; 45:4, 7; 46:2, 3, 5, 8, 17, 23; 47:15, 18; 49:2, 21; 50:10, 15; 51:2, 3, 7; 53:15; 54:15; 55:8; 57:17; 58:16; 60:7; 61:15; 63:22; 66:8, 24; 67:13; 68:11; 70:6, 15, 23, 25; 72:22; 73:13; 74:19; 75:3; 76:1, 17; 77:12, 15; 79:1, 24, 24; 80:1, 22, 24; 81:9; 83:25; 84:4, 6; 85:13; 88:14; 89:14; 90:17, 20; 92:18; 93:21; 95:17; 100:2, 4, 5, 22; 101:1; 108:21; 110:15; 112:4, 6; 114:12; 117:22; 118:8; 122:3; 124:1, 14; 126:16; 129:16; 131:18, 21; 132:16; 134:24; 141:21; 142:18, 25; 146:4; 150:2, 3; 151:4; 153:16; 155:1, 7, 16
one's 40:1, 10
ones 30:24; 106:7
ongoing 9:11; 66:16
only 10:13; 31:12; 42:22;

45:3; 50:15; 55:9; 56:6; 61:7; 62:7, 13; 66:24; 68:22; 82:16, 18; 89:11; 90:9; 92:17; 100:3; 108:16; 111:16; 113:17; 117:9, 10; 132:17; 135:17; 137:21; 139:7; 141:21; 144:22; 148:13
onset 118:4; 121:6
open 7:11; 20:17; 24:25; 50:16; 51:18; 70:12; 78:10, 10, 16, 19, 20; 80:12; 100:17; 123:23, 25; 124:1; 125:18, 23; 127:3; 137:4; 138:13; 153:8
opened 100:15
Opener 74:9, 16
opening 101:5
operational 155:9
operationalize 143:11
operationalized 153:11
opiate 52:21; 146:4; 153:3
opinion 60:23
opinions 150:9
opportunity 7:17; 8:6, 7; 20:11; 120:15; 125:11
opposed 24:17
old 147:3
optimal 115:9
optimally 96:18
optimistic 43:22; 136:18
option 127:4; 153:18
options 150:21
orally 52:21
Order 4:2, 5; 13:23; 14:2, 25; 16:3; 33:11; 39:7, 8; 59:9; 140:2
organizers 50:8
organizing 27:17
original 68:15
originally 65:10
others 34:9; 37:4; 49:4; 58:17; 81:2; 92:3; 93:25; 136:17
otherwise 16:19; 31:14; 128:3
ought 127:4, 4; 138:12; 153:8, 12
ourselves 28:23; 115:9
out 12:5; 13:10; 16:7; 17:19, 20; 19:21; 20:8; 33:25; 52:18; 55:2; 57:3; 58:19; 61:18; 62:23; 66:24; 69:7; 79:4, 9; 85:8; 92:15; 95:22; 98:4; 105:4; 110:5; 111:23; 114:20; 116:5; 120:22; 123:19; 124:1, 14; 125:4, 14, 24; 126:18, 20; 128:17; 135:9; 139:21; 142:17; 148:21, 22; 149:2, 3; 150:17
outcome 16:13, 15, 18, 20; 21:18, 20; 22:11, 12, 19; 24:7, 10, 12, 17; 27:7; 29:15, 19; 30:2; 32:24; 33:1, 25; 36:13; 37:21;

49:9; 50:2; 52:10; 53:12; 54:1, 3, 5; 57:17, 20; 60:20; 67:5; 72:12; 84:12; 86:13; 104:11; 115:8; 118:3, 5, 7, 9; 119:10; 124:3; 130:3; 146:3; 154:24
outcomes 16:21; 22:10; 26:3; 53:25; 57:23; 58:1; 115:10
outnumber 11:9
outpatient 15:23; 141:6
outpatients 43:25
outside 24:21
outwards 19:24
over 10:18; 15:8; 16:3, 9; 17:18, 23; 23:7, 21; 27:14; 28:19; 33:25; 41:11; 46:9; 53:10; 60:16; 64:12; 65:12; 70:23; 77:15; 95:23; 112:15; 119:2; 127:6; 129:12; 131:10; 139:1; 141:23; 154:11
overall 11:7; 22:6; 25:13; 44:22; 63:13; 65:16; 68:3; 87:9; 106:22, 24
overdose 85:3
overlaps 87:17
overlooked 133:21
overview 36:15; 37:8, 9, 13; 51:20; 78:4
overwhelming 13:14
overwhelmingly 68:6
Owen 21:2
own 10:10; 29:21; 93:9; 142:9; 143:8

P

p 54:18; 56:2; 79:12
p-value 18:16, 17; 55:16; 56:9, 17, 19; 57:6
packageable 133:15
packages 133:24
packet 17:6
page 80:17; 115:11
pain 29:25; 30:10, 16
pain-free 30:9
panoply 34:20
paper 99:15; 105:10
paradigm 122:14
paraphrase 148:4
paraphrasing 132:16
part 6:3; 7:21; 9:1; 91:21; 97:3; 115:8; 129:13
partial 8:19
participant 6:12
participants 6:6, 13, 18; 7:5; 82:11
participate 23:18; 72:9; 136:6; 142:20, 22; 153:6; 154:1
participated 144:24
participating 10:18

particular 9:20; 12:22; 33:9; 42:15; 66:3; 68:23; 70:21; 73:20; 85:12; 114:18; 146:25; 149:7; 151:6
particularly 93:24; 95:14; 96:7; 97:21; 105:3; 117:20; 121:10; 133:20
Parting 155:21
past 18:22; 26:16; 41:12; 72:13; 75:4; 76:2; 122:18; 151:2
patch 96:5; 123:17
patient 12:5; 21:5, 6; 32:15; 35:19, 21; 59:6, 15; 61:22; 63:21; 64:12, 16, 18; 71:1, 12; 73:20; 98:14; 103:10; 107:5; 109:23; 113:4; 121:25; 129:18; 130:4, 7, 8; 132:20; 133:17; 134:14; 140:1; 141:1; 149:4; 153:18; 154:4, 5
patient's 22:18; 58:24, 25; 145:25
patiently 101:10
patients 21:15; 28:10; 30:9; 34:23; 43:17; 44:13; 52:12; 53:13, 20; 54:6, 6, 6, 7, 9, 10, 12, 13, 14, 16, 17, 20, 23, 24; 55:1, 7, 9, 12, 22, 22, 24, 25; 56:4, 6, 8; 57:17, 18, 28, 21, 23; 59:3; 60:3, 7, 8, 9; 61:2, 6, 13, 15, 17, 19, 25; 62:4; 63:19; 64:14; 66:5; 69:2; 72:23; 88:18; 94:3, 13, 15; 102:18; 106:21; 108:8; 110:7; 117:12; 139:1; 144:17; 147:12; 153:13
Patricia 21:2
pattern 14:7; 33:9; 61:2, 6, 13, 22, 25; 62:6, 9, 10, 10; 89:3; 112:24; 116:7
patterns 58:18; 60:21, 24, 24; 62:8; 127:14
PCPs 96:22
PDA 72:15
peer 23:1; 95:11
peers 38:16; 156:17
pending 25:10, 11
Penn 17:1
people 10:17; 11:5, 9, 10; 13:7; 14:10, 11; 15:7, 9, 13, 21, 23; 17:2, 3, 4, 22; 18:6, 7, 9, 20; 20:3; 21:17; 28:11; 31:2, 8, 14; 32:5, 8, 10, 12, 18, 19, 22; 41:2, 19; 42:1, 4, 5, 21; 44:14, 24; 46:1, 15, 21; 47:9, 25; 48:15, 19; 49:2; 70:19; 74:12; 78:14; 79:8; 80:11; 81:25; 82:7, 18, 21; 83:3, 4, 8, 8, 10, 10, 21; 84:7, 18; 88:11, 21, 23; 89:22; 90:22, 24; 91:2, 9; 92:1, 12, 20, 22, 25; 93:3, 12; 96:1, 2, 97:13; 98:3; 99:1,

23; 100:5, 17; 101:3, 25;
102:3, 6; 105:5; 109:6, 13;
110:20, 24; 112:12, 23;
113:17, 19; 116:3, 10, 25;
117:24; 118:20; 119:2;
121:19, 22; 123:7, 9;
125:21; 131:1; 133:12;
134:5, 20, 21; 135:7, 12;
136:12, 23; 137:2, 3, 8;
138:4, 15, 16, 17; 142:10,
16; 143:5, 12; 144:1;
145:20; 147:20, 22, 24;
148:12; 149:14, 16, 19, 20,
22; 150:17, 18; 151:12, 17,
19, 23; 153:6, 24; 154:1;
155:18
per 15:11; 19:4, 10, 21;
22:7; 34:25; 46:10, 13;
53:16, 16, 17; 54:13;
55:22; 62:20; 72:16; 74:1,
2, 3; 75:1, 1, 2, 2; 77:14,
15; 146:12
perceive 9:19
percent 15:8, 9, 17, 17;
16:3; 22:6; 23:9; 34:25;
35:17; 40:25; 42:6; 44:1, 4,
5, 6, 6; 45:21; 54:2, 13, 16,
17, 23, 23; 55:14, 15, 25;
56:1, 8, 8; 57:17, 18; 60:7,
8, 9; 72:15; 79:6, 8, 9;
82:13; 87:19; 88:23;
106:23, 24; 107:14;
116:16, 18; 128:12, 14;
131:15; 146:11; 148:19
percentage 33:8; 154:12
percentages 69:2
perfect 50:11
perfectly 149:21
perform 76:11
perhaps 11:20; 19:23;
29:2; 73:12; 75:20; 76:6;
80:23; 92:10, 15; 110:23;
125:15; 147:8
period 17:8, 8; 18:20;
19:13, 16, 17; 20:3; 23:7;
44:18, 25; 45:1; 48:16;
53:2, 11; 54:15; 56:14;
58:19; 60:16; 61:16; 62:5;
64:19; 67:11; 79:20;
110:21; 112:15; 118:19,
25, 25; 119:3, 18; 120:3,
13; 122:9; 126:6, 18;
127:4, 11, 21; 135:19;
140:11, 12, 13; 141:1, 20,
23
periods 124:15; 140:19
Permutt's 55:18
persistent 87:21; 92:25
persistently 143:9
person 11:2, 13; 40:1;
44:25; 45:3, 5; 74:22, 24;
77:4; 94:17; 100:8;
103:13; 129:2; 134:10;
136:4
person's 103:18
personal 75:20; 156:7
personally 9:25; 156:14
perspective 72:6;

155:25; 156:3
perspectives 10:11;
47:2; 156:1
pertinent 78:23
Pharma 8:4
pharmaceutical 9:23;
120:6
Pharmaceuticals 6:21,
25; 7:3, 23
pharmacologic 14:7, 16;
20:6; 86:20; 112:20;
119:11, 15; 121:5, 17;
124:6; 132:17; 134:6, 7;
138:13; 147:6
pharmacological 23:21;
96:3, 4; 114:21; 115:16;
121:24; 124:11; 125:13;
133:6; 135:3; 137:12;
141:22; 148:19
pharmacologically
137:15
pharmacology 13:24;
17:23; 18:2; 80:1; 102:8;
156:2
pharmacotherapeutic
32:20
pharmacotherapies
25:20; 50:12; 82:24;
83:15; 86:25; 93:4; 109:1;
123:9, 16; 127:12; 147:9;
151:2, 13
pharmacotherapy 8:5,
17; 10:8, 22; 17:13; 26:8;
32:1; 49:8; 53:4, 8; 83:24;
86:17; 87:4; 88:3; 93:9, 13;
94:16, 22; 98:8; 101:21;
106:19; 109:11; 113:2, 16;
115:5; 117:12; 118:17;
120:16; 123:18; 124:18,
20; 125:3; 130:12; 133:9,
24; 135:24; 142:2; 150:25;
151:6, 8, 11, 22
Pharmacy 4:12
phase 123:25; 124:1
phenomenon 122:19
philosophical 98:7;
117:14
philosophically 103:12,
14
philosophy 154:8
phone 113:8; 145:20
phrase 37:12
physical 40:7; 72:19;
73:12; 76:18; 83:4; 88:8;
143:12; 153:13
physically 47:7
physician 142:9
Physician's 72:23
physicians 36:25; 93:13;
96:10; 121:22; 137:1;
138:25; 143:4
pick 30:16; 62:25; 65:4
picture 22:4; 43:22;
101:7
piecewise 18:25
pill 15:7, 8, 14; 99:4, 4;

100:5, 7, 10; 101:4;
132:15; 139:18
pills 89:18
pilot 65:18; 145:15;
146:7, 17
pioneered 133:16
pipeline 109:20; 110:4,
13
pipelines 109:18
Pippa 4:18
pivotal 9:19
place 87:25; 111:11
placebo 7:4; 13:8; 17:6,
11; 18:14; 19:9, 20, 20;
20:8; 30:10; 32:13; 53:5, 9;
54:10; 55:15, 25; 56:9, 25;
57:1; 60:15; 63:19; 69:3;
79:14; 88:10; 90:1; 109:8;
119:23; 124:13, 24;
140:10, 12, 13, 14, 18, 21,
25; 141:12, 13, 14, 20;
144:20; 145:23; 146:1
placebo-controlled
53:2; 145:16
placebo-treated 17:3;
54:7, 17, 24; 56:15
placed 13:11
plan 21:4; 77:22
planned 58:14, 19; 65:10
planning 27:16, 18; 40:4
plaques 156:6, 25
plasma 101:6
platform 109:1, 12, 13;
112:19; 113:4, 9; 114:4;
124:20; 140:15; 141:16
please 50:9; 82:1; 131:7
pleased 49:12
point 17:19, 23; 18:2;
37:25; 47:9; 49:11; 50:3;
58:12; 60:4; 77:24; 79:4,
10, 23; 90:21; 91:9; 97:7;
99:18; 108:4; 110:22;
111:2, 13; 116:9; 117:25;
118:1; 123:23; 127:20;
130:8; 136:24; 137:6, 22;
149:1, 16, 22; 154:15, 17
pointed 66:24; 116:5
pointing 111:23
points 12:8; 17:9; 61:2;
78:25
poison 99:23
politely 120:18
polysubstance 87:11;
90:5; 93:5
poor 79:17
poorly 104:24
popular 42:12
popularity 66:18
Population 10:12; 21:10;
29:11; 31:25; 52:10; 58:7,
12; 59:6, 15; 61:1; 67:2;
69:25; 70:2; 85:4; 87:6, 12,
17; 90:21; 91:3, 13, 15;
92:20; 94:24; 95:9;
102:10; 104:11; 108:5, 18;

113:5, 10, 10, 15, 19;
115:15, 18, 22, 25; 116:14,
17, 19, 24; 121:22; 127:21;
129:8; 131:17; 133:20;
150:16; 154:10, 16
populations 21:6; 23:5;
26:3; 27:6; 58:14; 90:15;
92:5, 6; 114:7; 129:15, 21,
21; 130:13, 16; 148:3;
152:17; 155:2; 156:3
portable 133:15
portion 24:25; 27:13
pose 136:3
poses 80:17
positions 36:7
positive 51:7; 74:19;
75:3, 18; 76:1, 17; 105:15
possibility 135:11
possible 13:23; 14:16;
29:5; 42:7; 52:4; 58:22;
61:25; 67:13; 111:8;
112:17; 114:3; 142:16;
152:6
possibly 16:2; 60:21
post 97:8
posttreatment 17:8;
22:21; 24:9, 9; 49:1
potential 6:8; 16:21;
97:22; 112:12; 129:17;
130:21, 22
potentially 13:2; 20:6;
150:13
powered 144:14
powerfulness 11:21
practical 81:13
practically 32:17
practice 109:15; 132:21;
134:17; 137:18; 139:15
practiced 149:5
practitioners 132:14;
137:2; 148:1
pre-IND 26:8
pre-pregnancy 88:1
precedent 25:23; 26:4,
17
precedents 26:23
preceding 116:20
preclude 6:3
precursor 85:21
predict 153:24
predictors 107:3; 145:8
preferable 35:23; 123:14
pregnancy 75:20
pregnant 88:1; 92:7;
96:24
preliminary 144:19
preoccupation 76:20
prepared 148:16
prescribers 36:25
prescribing 73:13;
134:17
present 6:8; 40:18; 52:1;
100:3; 120:16; 124:24;
133:22

presentation 24:20;
51:14, 16; 71:22, 23, 25;
126:15; 155:3
presentations 78:3;
155:15
presented 51:4; 79:19;
99:3; 119:20; 142:7
presenting 7:25; 9:16;
26:19; 42:3
President 21:3
press 86:24
presumably 86:2; 143:3
presumes 150:7
pretreatment 22:21;
24:8; 44:5; 145:19; 146:14
pretty 119:7; 155:8
prevalent 96:9
prevent 76:22; 121:6;
122:22; 138:7
preventing 149:8
prevention 8:24; 36:5;
98:3; 121:8
previous 7:7; 15:22;
30:23; 36:17; 38:7; 60:12;
65:17
primarily 25:9; 90:19;
91:2
primary 16:18, 19; 36:22,
24, 25; 53:7; 60:20; 63:20;
65:11; 66:24; 73:1; 82:21;
83:9; 84:25; 91:3, 5; 93:12;
96:7; 101:3; 113:6;
115:10; 133:16, 19; 135:6;
138:25; 150:14
principal 6:23; 7:2
prior 14:5, 8, 10; 36:7;
43:25; 44:1; 48:11; 71:3;
145:22
priority 39:8
pristine 91:17
private 21:7; 25:5; 47:9
pro-social 105:11
probably 26:2; 45:2;
71:7; 77:25; 83:7, 20;
87:17; 93:11, 16; 94:7;
96:6; 101:1; 105:2, 9;
107:7; 111:20; 116:25;
117:3; 118:10; 121:13, 14;
127:24; 128:1; 135:14;
136:18; 137:7; 146:3;
153:11; 154:11
problem 6:22; 21:15;
22:24; 24:14; 28:1; 34:6;
45:13; 50:22; 51:21;
69:17; 73:17, 18, 24;
74:20, 21; 75:5, 9, 19, 22;
77:23; 85:2; 88:6; 91:18;
96:11; 98:15, 20; 100:2,
13; 106:2, 2; 108:5;
111:19; 117:2; 130:11;
135:5; 136:13; 141:17;
153:10; 154:20
problematic 121:11
problems 28:10; 40:7, 7,
11, 11, 12, 12; 45:2, 5;
48:20; 51:6; 72:24; 73:4;
75:10, 12, 13, 21, 25; 76:3,

4, 8; 91:18; 92:21; 93:1;
100:17; 111:3; 112:12;
117:4; 126:20; 136:22;
147:6, 14; 145:3; 150:20
cedure 73:11
PROCEEDINGS 4:1
process 37:18; 94:6;
150:18; 152:23
produce 139:22
produced 118:19
producing 35:3
product 73:7
productivity 47:12
Products 4:24; 5:1; 6:11;
7:7; 8:4; 25:19; 24; 27:15;
120:10
professions 11:8
Professor 4:16, 20; 5:6,
17; 8:10
Profile 34:8
prognostic 57:12
program 110:24
Programs 8:12; 21:7;
40:25; 41:1, 2, 14; 91:2
progress 102:9
progression 19:6, 10,
23; 103:15; 110:18;
136:23
progressive 101:16
progressively 137:18
ject 9:1; 17:12; 22:15;
24; 45:11; 12; 72:14;
72:6; 112:11; 146:10, 16
promising 150:2
promoting 31:19
proof 152:14
propensity 104:21
proportion 42:1; 83:10;
108:7; 121:14, 19, 21;
131:1
proposal 26:8; 27:9; 67:4
propose 113:21
proposed 23:23; 26:12,
17; 66:6; 153:10
prospective 26:7
protocol 26:19; 60:20
protocol-specified
65:11
protracted 135:17
prove 13:16, 23; 20:6;
46:14
proven 16:19; 23:17
provide 37:8; 84:18;
107:21; 135:2; 144:11, 13
provided 6:6; 155:24
provider 73:2
providers 113:6
provides 24:10
viding 6:21; 7:3
provisions 109:13
proximal 112:6
psychiatric 21:11; 22:24;
38:3, 3; 91:13; 106:20;

147:9
psychiatrist 137:19
Psychiatry 4:17, 21; 5:6,
11; 8:10; 124:5; 132:24;
149:5
psychological 40:7, 11
psychologists 84:10
psychopathology
11:12, 13, 17, 24; 13:19
psychopharm 141:14
psychopharmacology
149:11
psychosocial 9:3; 10:4;
11:14, 18; 12:25; 15:25;
16:16, 22; 17:12; 18:6, 8,
21; 90:19, 22; 91:1; 93:10;
95:12; 112:2; 114:19, 24;
115:2, 4; 117:6, 10;
121:18, 23; 132:8; 133:12;
138:22; 141:16
Psychotherapy 25:25;
26:1; 52:23; 53:4, 10;
131:9; 134:15; 137:22;
139:4; 147:13
public 6:17; 7:10, 11;
20:17; 21:7; 24:22, 25;
25:6; 47:9; 51:18; 78:10,
16, 17, 19, 20; 80:12;
143:21; 148:20; 149:12;
154:9; 156:22
publication 9:8
published 12:7; 14:4;
16:25; 33:19; 65:8; 70:14;
72:24; 122:18; 143:21
pure 90:11
purely 117:5
purposes 102:24
pursue 31:13
pursued 31:23
put 24:19; 41:14; 99:17;
138:1
puts 38:4
Putting 69:13; 139:10
PWP 66:6

Q

qua 69:21
quality 10:2; 21:22, 24;
104:1, 7
quantitative 59:19
quantity 44:8, 16, 19, 24;
45:16, 18; 49:18; 85:24;
86:5; 111:5, 7; 132:9;
154:11
quantity/frequency
83:16
quarter 56:4
quick 51:11; 68:11;
77:16; 78:25; 132:19
quickly 9:18
quiet 95:18, 19
quit 95:24; 96:1; 103:13;
137:8
quite 10:9, 12; 11:5; 32:5;

39:19; 45:18; 66:17;
85:11; 108:2; 110:6;
128:13

R

race 21:10
raise 37:4; 82:1
raised 154:18
raises 112:21
random 18:25
randomized 17:5; 47:22;
53:1; 63:18
range 11:3; 24:1, 2;
46:11, 12; 94:19; 116:8;
153:25
ranging 94:9
ranking 62:9
rate 11:20, 22; 12:3; 15:1,
17, 20; 23:8; 79:8; 106:23,
24; 108:6, 6; 119:14;
128:8; 131:15
rates 24:10; 58:15; 95:25;
102:21; 106:16, 19;
107:20; 124:4; 131:18
rather 26:10, 13; 28:21;
64:19; 69:20; 70:25; 87:2;
89:11; 112:14; 115:2;
120:6; 153:12
rationale 111:23; 115:14,
19, 22
Ray 99:3
Raymond 7:12
reach 33:16
reached 56:14; 70:11;
106:7
read 5:23; 50:20; 81:2;
156:11
reading 139:2
real 14:21; 63:17; 89:23;
91:17, 19; 105:2; 130:11;
141:17; 153:2; 156:22
realistic 43:22; 93:17;
136:9; 154:4
reality 93:12
realize 142:3
really 8:6; 32:12; 47:23;
48:6; 50:15; 58:1, 2; 68:22;
69:6, 7; 70:9; 88:1; 91:6;
95:13; 98:19, 22; 101:8;
102:15; 103:12, 13;
104:20; 105:21; 112:7;
115:14; 116:22; 118:17,
25; 120:8; 123:3, 4, 23;
126:15; 129:21; 130:2, 7,
10; 131:12, 20, 24; 135:16;
138:22; 141:14; 142:25;
147:21; 149:12; 150:8, 10;
154:14, 25; 155:1, 5, 10;
156:22
reanalyzed 68:13
reason 42:21; 47:5, 6;
62:3; 117:14, 15, 15;
130:9; 137:16; 147:5
reasonable 112:7;

118:18; 153:15
reasons 55:3; 95:10;
127:13
recall 107:24; 144:10
receive 7:23; 41:24;
106:11
received 7:22; 27:18;
41:24; 43:8, 12; 44:20;
66:17
receives 11:13
recent 122:17
recently 15:5; 25:14;
26:7; 42:25
Recess 71:20
recidivism 124:4
recidivistic 26:9; 129:18
recognition 89:22;
97:19; 153:23
recognize 27:16; 92:4;
136:12; 137:10, 13
recognizing 91:7
recommend 97:1; 144:2
recommendation 60:2
recommendations 25:9;
85:23
recommended 70:15;
77:9
recommending 96:16
reconstruct 68:18
record 6:3, 15, 21;
150:10; 156:24
recording 98:24
records 101:4; 102:21
recover 58:20
recovering 40:3
recovery 41:3
recruit 94:15; 117:10, 11,
23
recruiting 92:1; 117:24
recurrences 64:8; 84:14
recurrent 63:5, 10; 64:5,
11, 18, 22, 25; 65:5, 22;
66:2, 4, 7, 15, 16; 67:4, 15,
18, 21; 68:13, 19, 23; 69:8;
70:13, 16, 20, 22; 84:7
recurring 62:23, 25
red 19:8; 61:3; 63:23
reduce 23:6; 28:15; 29:1,
9; 31:9; 32:1, 19; 61:7;
83:21; 97:24; 111:20;
138:15, 15, 17; 144:12;
149:23; 151:16, 22
reduced 21:21
reduces 30:13; 135:21;
140:3
reducing 88:14; 133:3;
138:16
reduction 24:14; 26:13;
28:25; 31:6, 13; 32:8; 33:4,
7; 43:7, 13; 44:18; 111:7;
118:8; 153:7
reductions 47:11;
103:23; 146:14
redundant 114:22

refer 64:11
reference 63:4
referred 63:7; 68:24
referring 95:10
refers 30:14; 38:13;
39:11; 71:4, 5
refinement 107:15
reflect 22:3; 136:18
reflected 24:17
reflects 41:13; 143:7
regard 6:2; 78:24; 98:12,
20; 99:3, 8; 107:7; 127:19
regarding 8:8; 25:19;
70:7
regardless 33:10;
104:11; 148:1
registered 4:14
regression 18:25; 56:18;
57:5, 11
regular 61:7; 62:1
regulated 6:7
regulatory 34:11
reimbursing 47:9
reinforcement 152:24
rejected 98:10
relapse 8:24; 17:14; 22:6;
34:22; 41:8, 11; 49:19;
53:19; 54:25; 55:12; 56:7;
61:10; 71:6, 6; 98:3, 6, 6;
119:13; 122:22
relapsed 46:7; 55:9
related 95:11; 98:24
relation 76:12; 107:19;
138:12
relations 23:1, 2; 76:10
relationship 79:2;
111:25
relative 98:14; 107:18;
146:7; 152:22
relatively 19:8; 80:7;
111:15; 112:10; 113:15;
117:22; 121:14
relatives 41:21; 43:12
relevance 86:3; 98:8
relevant 34:15; 59:15;
66:9; 67:6; 84:22
reliable 22:11
reliably 32:7, 10, 17;
81:11
relief 29:25
reluctance 137:25
remained 128:12
remark 123:2
Remarks 27:23
remember 51:3
reminded 137:19
reminding 156:3
remission 22:1
remove 109:5
repeated 64:13; 78:24;
79:18; 84:4; 86:12; 88:20;
142:8, 16, 24
repeatedly 143:8

repertoires 18:8
replacement 138:24;
139:2
replicates 17:10
report 38:15; 39:19;
57:22; 104:13; 105:10;
109:24; 110:6; 145:18
reported 6:7, 17; 22:8;
41:20, 21; 43:13, 15;
53:13; 57:20; 64:13;
105:11; 107:12
reporting 24:9; 48:17
reports 6:23; 7:1; 95:22;
104:16; 107:10, 18; 110:4
represent 49:4
representative 21:6, 9
representatives 25:5
represented 35:14
represents 48:15, 16, 22;
49:3; 54:8, 9, 11, 14, 20;
55:11; 61:4; 156:20
request 78:8
require 30:9; 117:21;
131:12
required 76:23; 154:2
requirement 139:10;
142:1
requires 101:15
rescue 30:4
Research 5:19; 6:8; 9:21;
21:3; 22:16; 23:6, 18;
28:16; 31:22; 34:10; 36:5,
10, 13, 16; 37:24; 38:9;
40:15; 41:7; 42:13; 49:23;
66:15; 102:24; 108:18;
150:2
researcher 24:5
researchers 28:5
researching 27:17
reserved 134:20
resident 149:1
resolve 28:1; 36:2
respect 6:16; 7:5; 155:25
respond 13:8; 78:22;
93:2; 121:19; 138:16, 17;
140:8; 143:5
responders 126:3
response 20:18; 23:8;
51:12; 54:1, 4; 78:12;
94:12; 99:11; 102:21;
108:22; 122:2; 150:6
responses 60:6; 76:1
responsive 151:20
rest 8:21; 62:5; 124:5
restrictive 13:24
result 29:24
results 22:13; 23:4, 11,
20; 24:10; 29:13; 35:3;
44:23; 49:1; 55:18; 109:7;
120:16; 128:11, 18;
141:18
resume 71:21
retain 13:1
retention 10:12; 14:6, 12,
14; 109:3; 146:7

retrieve 58:17
retrieved 58:20
retrospective 107:24
return 125:6
revealing 151:15
reversal 122:14
reversing 152:23
Revia 36:20
Review 5:2; 9:8; 36:19,
23; 55:18; 57:21; 68:17;
72:3; 106:18; 139:5
reviewed 151:9
revised 38:8
revolve 40:2
rheumatoid 50:23
riboflavin 15:5, 6, 10, 14;
99:4, 4, 13, 22, 23; 100:11,
13; 101:6
Richard 5:12; 36:4
rid 74:18
right 12:21; 18:13; 32:15;
50:7, 24; 54:8; 84:25; 85:2;
90:2; 96:20; 112:23;
118:25; 130:20; 141:6
rising 19:11
risk 31:9; 33:12; 47:1;
48:5; 75:11; 77:10; 87:8;
89:19; 92:7; 121:7, 12;
138:5; 149:24; 150:19
Roberts 19:1
Roger 20:24
role 26:25
room 24:21
rotate 155:22
roughly 122:7
routine 73:12
routinely 124:22
run 51:5; 94:14; 103:18;
126:19, 20; 139:8
run-in 33:6
running 67:9

S

safe 153:19
safety 25:11; 53:8;
138:11
sake 102:5
same 9:15; 19:2, 2; 30:18;
35:17, 17, 20, 22; 41:22;
42:13; 43:4; 50:21, 22;
64:8, 24; 70:23; 86:21;
100:13; 107:25; 109:4;
115:5; 120:12; 122:19;
125:13; 133:3; 147:3
sample 21:9; 22:9; 23:9;
97:22; 98:1; 102:22; 152:9
samples 21:5; 92:20
San 38:19
Sanchez 143:20; 144:12;
145:10
satiation 152:25; 153:4
save 150:18; 154:12

saw 105:9
saying 49:22; 91:4;
113:20; 118:15; 119:17,
25; 123:14; 134:12; 138:1,
3; 140:10; 147:19
scale 24:3; 30:4; 85:9
scheduled 67:9; 71:17;
88:18
schema 58:14
scheme 46:3
schizophrenia 137:20;
140:25
schizophrenic 149:3
schizophrenics 106:21
School 5:6, 9
Schuckit 38:18
Science 4:22; 12:6;
105:10; 126:3; 152:20
scientific 38:18; 117:15;
126:8; 154:15
scores 15:12; 23:25;
30:16
Scotland 44:12
screen 73:3
screening 73:10, 11
se 62:20
Second 4:15; 35:20;
50:12; 52:15; 56:24;
62:10; 68:3; 71:7; 74:21;
75:8, 12, 24; 79:3, 12, 14,
21, 23; 80:12, 17; 81:19;
89:15; 90:24; 126:17;
142:19
Secondly 99:1
Secretary 4:10
seeing 28:14; 114:2, 13,
14; 116:2, 5, 7; 137:3
seek 92:22
seeking 143:2
seem 73:5; 94:1
seemed 59:12; 61:19, 23;
90:8
seems 14:7; 25:25;
106:1; 110:22; 118:6;
119:25; 129:12, 14;
141:19; 150:1
seizure 64:19
seizures 64:18
selected 72:9; 139:12
selection 139:14
self 104:12; 109:23;
120:25
self-correcting 37:17
self-help 133:23
self-report 34:3; 98:13;
104:15; 105:1, 14, 16, 21;
109:19, 25; 110:5, 9;
144:22
self-reported 33:6
self-reports 98:14;
104:10; 105:9
send 115:3
sense 17:14; 35:10;
38:14; 76:4; 83:21; 92:9;

106:3; 110:9; 120:22;
121:9; 123:5; 134:18;
142:18; 144:3
sensitive 59:14; 62:25;
64:3; 86:9; 105:6, 21
sensitivity 98:13, 21;
105:14
sensitizing 96:6
sent 72:13
separate 110:17, 23, 24,
25; 129:6
separated 81:11
separately 80:22
series 74:9; 82:20; 89:5
serious 48:24; 150:19
served 6:24
serves 7:2
service 149:11; 156:21,
23
services 23:19; 46:20;
47:10, 20
serving 149:12
session 9:13; 26:20, 21;
37:16
set 27:4; 32:6; 36:3; 75:4;
79:2, 5; 80:5, 7; 140:6;
149:11
setpoint 95:5
sets 17:11; 45:15
setting 93:17; 101:4;
110:7; 124:24; 132:21;
133:16, 21; 145:22;
147:12, 14
settings 11:10; 82:21;
132:18; 133:19; 150:15
seven 45:3; 61:18; 62:2,
3; 79:14; 80:17, 18; 81:2;
83:17; 86:7
Several 15:19; 17:9;
26:6; 37:14; 39:13; 46:2;
62:15; 63:24; 66:11;
72:11; 98:12; 99:1;
118:16, 20; 150:1; 151:2
severe 11:2, 4, 5, 10, 16,
23; 12:24; 13:3, 6, 17;
39:14; 75:16; 76:15;
90:17; 98:6; 106:10;
129:17
severely 26:11; 84:11,
16; 98:16; 108:8
severity 12:12, 15, 18,
22; 14:6, 14; 21:15; 22:24;
24:15; 69:16; 73:18;
75:10, 11, 24; 77:1; 84:3,
18, 21; 93:6; 103:3, 4;
112:24; 142:20, 21; 144:4
severity/history 21:12
sexual 76:6
share 8:7; 20:11; 51:25
sharing 8:1
sharp 71:19
shoot 12:2; 79:6
short 70:9; 72:9
shorter 69:22; 125:15, 17
shouldn't 95:23; 148:20

show 14:2, 16; 18:10;
35:6; 41:15; 59:9; 64:24;
65:5; 67:14, 19; 69:5;
111:24; 122:17; 130:5
showed 42:11; 44:14;
49:20; 56:17, 19; 57:6;
65:13, 14; 145:2; 146:13,
15
showing 18:18; 42:14;
46:4; 82:22; 97:5; 112:4, 5
shown 55:11; 60:24;
63:22, 23, 25; 65:15, 16;
122:20; 147:13
shows 14:4; 18:12;
23:14; 42:1, 13; 45:17;
67:17; 104:18
side 12:1; 93:23; 106:5, 8;
108:24; 109:6, 8, 9; 139:23
sides 123:8
Siegel 70:14, 21
significant 15:20; 22:10;
23:13, 13, 14, 24; 24:13;
30:12, 20; 42:17; 43:7, 13;
48:6; 54:18; 55:16; 56:1;
57:7; 65:16; 67:13, 19, 21;
68:4, 7; 69:7; 79:16; 83:3;
98:19; 114:2; 118:11;
137:13; 146:14, 18;
152:21
significantly 43:16; 91:6
silly 119:7
similar 13:6; 14:6; 16:25;
104:22
Similarly 94:2
simple 83:20; 93:2;
145:1, 2, 7, 12
simply 21:18; 86:17;
95:23; 104:10; 110:18;
111:23; 143:7; 144:5;
151:20
SIMPSON 4:18, 18;
22:16; 93:7, 8; 105:23, 24;
118:13, 14; 119:16, 19;
123:12; 128:5, 6; 141:11
Simpson's 108:23
simultaneously 140:4
sine 69:21
single 41:21
sit 84:25, 25; 132:13, 24
situation 89:12; 97:4;
114:1, 6; 115:3; 125:9;
134:19
situations 11:5; 35:14;
75:20; 77:9; 88:15, 16;
89:19
six 16:7, 8; 17:25; 43:18;
46:12, 17; 48:7, 13, 18;
61:18; 71:8; 78:23; 82:14;
86:2; 89:15, 16, 17; 113:6;
126:10, 14, 20; 145:1, 6,
12
six-month 44:18; 69:19;
70:4; 79:25; 123:20
sixties 149:9
size 12:20; 18:15; 98:1;
113:1; 117:22; 144:13;
152:5, 9, 10; 155:1

sizes 97:22
skeptical 137:23
skepticism 137:24, 25
 13:9; 56:24; 57:1, 4
 als 133:11
skip 47:15
sleep 76:6
Slide 8:14; 9:9, 14; 10:6,
15; 12:10; 13:7; 14:1; 15:2;
16:12, 23; 18:23; 28:3;
29:7, 17; 30:21; 31:21;
32:23; 33:15, 19; 34:17;
35:25; 37:23; 38:2; 40:22;
41:9, 16; 42:8, 24; 43:3,
11, 23; 44:7, 10; 45:10, 25;
47:4, 15, 17; 48:9; 49:5,
20; 51:24; 52:6, 20; 53:6,
24; 55:20; 56:10, 21; 57:8;
58:3; 59:2; 60:11, 12;
62:12; 63:2, 16; 64:4, 21;
65:2, 25; 66:21; 69:16;
70:17, 18, 19; 72:2, 7, 11,
21; 73:9, 22; 74:7, 23;
75:7, 15, 23; 76:14, 25;
77:11, 20; 99:3; 104:17;
114:12
slides 9:16; 16:14; 24:19;
51:4
slight 19:9
slightly 56:19; 103:1
slippery 138:20
slope 19:8, 10, 15, 16, 19;
 9:20
pes 19:6
small 102:23; 116:14;
117:22; 121:14; 156:7
smoke 95:24
smokers 113:6
smoking 41:5, 6; 113:5,
14; 136:12, 16; 137:8
so-called 33:24; 58:5;
61:14
social 22:19; 23:1; 24:15;
40:11; 72:18
Socially 11:11, 11, 16,
23; 87:8
society 13:21; 47:23;
85:16
softwares 66:19
solely 145:7
solid 15:25
somatic 95:3
somebody 11:16, 23;
13:1, 3; 103:17; 116:6;
129:3
somehow 35:5; 135:20
someone 29:1; 84:15;
135:2, 15, 22; 142:7; 143:3
Somers 4:7, 9; 5:23;
24:24
nothing 12:14; 16:13;
16; 93:15, 16; 94:12,
25; 97:16; 101:6, 13;
104:6, 6, 7; 105:4; 112:18;
115:17, 20; 123:3, 7;
127:6; 128:1; 129:11;

143:7; 152:15; 156:21
sometime 19:25
sometimes 63:7; 129:1;
138:3
somewhat 26:14; 37:12;
143:16
sons 38:20, 25
soon 96:9
sophisticated 65:22;
80:3
sorry 103:21; 110:11;
155:22
sort 11:14; 14:21; 17:14;
71:15; 79:17; 101:13;
106:2; 109:24; 111:6;
126:3; 129:24; 138:21;
142:22
sorts 101:23
sound 153:15
sounded 128:13, 14
sounds 89:24
source 72:22
sources 152:9
South 7:13; 8:11
speak 20:16; 37:19, 20;
78:14; 80:11
speaker 6:24; 7:12; 8:2
speakers 20:16; 37:4
specific 25:10, 11; 27:9;
32:24; 58:14; 59:7; 65:23;
105:21; 110:24
Specifically 52:1; 58:7;
61:1; 67:2; 74:1
specimens 41:22
spectrum 84:8
spend 132:20
spending 115:2
spends 35:21
spent 40:2; 156:21
sponsor 26:7, 19; 57:20;
65:10; 97:2, 11
sponsor's 27:12
sponsors 96:17
spontaneous 96:1
spousal 104:16
spouse 95:12
stable 11:11, 24
staff 25:6; 27:3; 78:4
stage 13:13; 27:4; 36:3;
76:15; 97:1
stages 9:8
standard 23:10; 34:11;
40:15; 120:6; 125:1, 2;
126:22; 127:11; 138:10
standardization 49:11,
25
standardized 21:13;
24:3
standing 7:18; 74:8
star 61:4
start 4:7; 52:7; 71:18;
82:3; 92:5; 116:4; 120:22;
123:8

started 91:21; 129:11;
156:16
starting 88:13; 98:4
starts 86:5
State 4:12; 39:12; 99:7
stated 70:22
statement 5:24, 25; 7:21;
39:18; 109:5
States 9:20; 40:24;
136:14
statistical 17:19; 23:12,
16; 27:8; 38:5; 51:3, 6;
52:1, 8, 16; 54:18; 55:18;
57:9; 62:24; 63:3; 65:22;
66:1, 19; 68:8, 16, 17;
69:24; 70:5; 84:20;
102:24; 126:15, 24; 127:1
statistically 23:13;
55:16; 56:1; 69:6; 146:18
statistician 5:4; 19:1;
36:18; 67:23
statistics 35:14; 51:14,
16
status 58:21, 25; 104:22
stay 18:9
stayed 14:10
steadily 19:11
steady 74:17
steal 97:6
step 18:4; 54:11; 73:23;
75:8; 77:2; 103:20; 135:3,
15; 149:10
Stephanie 5:5; 6:22; 79:1
sticks 91:1, 1
still 13:4; 68:6; 69:3;
108:14; 115:5; 126:8;
134:9; 141:19; 151:12
stop 20:10; 28:15; 39:20;
50:3; 76:21; 154:2
stopped 18:12, 19;
19:22; 76:21; 122:19
stopping 39:13; 71:18
stops 122:12
straight 139:18
STRAIN 4:3, 3; 5:21, 21;
7:11, 16; 20:15, 19, 25;
24:24; 25:4; 27:22; 37:6;
50:9; 51:9, 13; 67:8, 23;
68:11; 69:9, 12; 71:13, 21;
78:2, 21; 80:10, 16; 84:1,
23; 86:14, 24; 87:14; 89:7;
90:3, 12; 91:20; 93:7;
94:11; 95:16, 19; 96:14;
98:11; 99:9, 12; 101:10;
102:11; 103:6, 20; 104:9,
16; 105:19, 23; 106:14;
108:20; 109:17, 20; 110:2;
111:13; 112:18; 113:13,
25; 114:23; 115:24;
117:17; 118:13; 119:1, 16;
120:1; 122:25; 124:8;
125:5; 126:5, 13; 127:8,
20, 23; 128:5, 19; 129:9;
130:16, 19, 22; 132:11;
134:1, 10; 140:8, 15, 18;
146:23; 147:18, 25;
149:25; 150:5, 22; 152:1,

12; 154:7; 155:12; 156:24
strategy 83:25; 88:16;
134:24
streams 148:11, 15
strengthen 65:1
strengthens 67:18
stretch 154:14
strikes 123:2; 136:3
stringent 42:18; 60:9
stroke 47:1
strong 68:1, 1
struck 123:23
struggling 69:6; 113:18
studied 26:3; 29:12;
38:21; 49:12; 55:22;
59:15; 90:22; 104:12;
155:6
studies 10:21, 23, 24;
12:7; 20:4; 22:13, 15; 23:3;
30:23; 34:19, 24; 37:22;
38:1, 11, 19; 40:21; 46:4;
49:7, 9, 21; 65:17; 68:13;
82:20; 83:1; 85:6; 90:7;
94:9; 99:25; 108:7;
111:24; 112:20; 113:14,
16; 119:10, 15; 123:12, 13,
19, 24, 25; 124:3; 138:11,
12; 150:3; 151:1, 6, 9, 10;
154:19
study 6:22; 7:4; 8:21; 9:2;
10:12; 14:6; 19:4; 26:5, 9;
27:6; 35:4; 41:17, 18;
42:14, 15; 43:4; 44:11, 12,
12, 14; 47:21, 22, 25;
48:25; 51:4; 52:10; 53:7,
15, 17; 54:21, 24; 55:2, 13;
56:12; 58:7, 12, 13; 61:1;
64:13, 15, 18; 65:9, 18;
66:9; 67:1; 68:23; 70:10,
21; 83:3; 88:18; 91:17, 25;
92:5; 96:18; 97:12, 12, 14;
99:16; 101:2; 107:9;
108:6; 109:7; 113:21, 24;
115:15, 18; 116:17; 117:5,
6, 10, 12, 20; 118:9; 124:6;
130:5; 132:23; 133:1;
144:14, 25; 145:18; 146:6,
8, 17; 151:4, 18, 21; 152:6;
153:10; 154:1, 25
studying 25:14; 38:20;
85:7; 109:1; 112:22;
117:2; 120:9; 129:23
stuff 119:22; 128:15
subgroups 81:7, 19;
93:25; 131:15
subject 35:15, 15
subjects 23:14, 18;
24:16; 33:10; 73:24;
77:16, 19, 22; 94:4; 146:22
submit 120:6; 148:9
submitted 6:5; 72:12
subsequent 39:2; 59:16;
62:15, 20; 64:23; 65:7, 15;
138:6
subset 43:5
subsets 58:10
subside 122:10

substance 13:19; 14:18,
23; 124:7
substantial 36:11;
121:19
substantially 138:23
substantive 8:15
subtypes 92:14
succeed 135:9; 153:25
succeeded 30:16
success 13:14; 29:14;
30:6; 31:1; 40:17, 19; 41:8,
11; 42:20; 49:3; 61:11;
66:23; 81:21; 131:15, 18
successes 55:8; 59:10
successful 24:12; 33:11
succinct 77:24
Sue-Jane 5:4; 36:18;
51:15, 17
suffer 23:3
suffers 100:12, 13
sufficient 40:5; 92:11;
104:13
sufficiently 81:4, 8, 23;
92:10; 98:15
suggest 51:2, 8; 71:14;
72:22; 73:24; 74:5, 20;
75:5, 10; 79:20; 86:15;
92:4; 95:4, 13; 131:1;
134:24
suggested 13:6; 16:6;
88:3
suggesting 16:9; 21:4;
76:18; 87:1; 95:6; 125:23
suggestion 79:1
suggestions 142:9
suggestive 45:6; 75:22
suggests 70:23; 73:10;
75:18; 101:19; 112:23
suitable 31:25
summarize 57:9
summarizing 52:7
superior 24:9; 151:11
supervised 44:19
supply 40:5
support 133:23
supported 8:1, 3, 20;
47:23; 95:22
supportive 56:25; 57:2, 4
Suppose 60:14, 19
sure 29:22; 50:3, 24;
62:11, 16; 80:21; 89:1;
108:4, 9; 126:14; 129:1;
130:17; 131:17; 139:21;
142:23; 147:18
surface 122:24
surrogate 14:5
Survey 116:18, 21
survival 17:14; 22:5;
23:17; 34:21; 42:11, 11;
52:3; 56:17; 57:4
suspect 83:9
sustain 84:12; 124:13
sustained 42:2, 5; 48:15;
124:16

switch 52:9
symptom 40:1
symptoms 38:12; 39:6,
10, 23; 76:18, 22, 22;
82:14; 86:8; 94:17; 95:3;
124:23; 138:4; 153:13
system 22:20; 139:16;
153:3

T

table 68:24; 97:9; 155:10
tailor 108:18; 155:1
tailored 58:13
talk 7:17; 16:14; 29:13,
18; 84:18; 105:24; 111:5;
120:17; 129:11
talked 44:22
talking 9:5; 29:21, 22;
91:14, 25; 102:10; 103:23;
105:7; 107:6; 116:25;
119:9; 123:3, 5; 127:9;
129:1, 2, 8; 133:3; 138:9;
139:11; 154:19, 19, 23
target 58:14; 83:15, 18,
19; 87:12, 23; 91:11;
94:23; 102:16; 103:24, 25;
111:21; 116:24; 124:23;
132:6, 23; 133:1
targeted 84:9, 11
targeting 91:5
taste 138:2
taught 28:17
Team 4:25; 27:14; 59:12;
60:1, 17
teased 62:23
techniques 19:6; 36:21
technologies 98:24
technology 91:19;
102:18; 105:7
telephone 58:24
TEMPLETON-SOMERS
4:9; 6:1; 21:1
temporary 62:7
Ten 87:19
tend 94:18; 111:15; 122:7
tendency 13:21; 18:13
tends 87:10, 10
tenure 123:24
term 17:23; 59:8; 138:11
termed 154:4
terms 22:13; 26:3; 29:19,
21; 49:24; 70:13; 73:16;
75:10; 76:12; 84:15; 87:8;
88:9, 20; 89:3, 20; 91:16;
94:14, 21; 96:18; 98:1, 2,
7, 8; 102:21, 24; 105:8;
107:7, 8, 8, 15; 108:11;
111:3; 124:10, 17; 127:6;
128:22; 130:4; 144:1;
145:23; 152:23
terrific 128:14
test 23:25; 28:5; 29:3, 8;
54:19; 56:18; 57:5, 11, 12,
15, 16, 16; 85:20; 93:15,

16; 134:19
tested 28:10
Texas 4:21
themselves 4:7; 6:13;
10:4; 78:15; 137:3
theoretical 32:4
theoretically 45:4
theory 68:6
therapeutic 23:19; 26:23
therapies 125:13; 142:3;
146:11; 151:3, 12
therapy 9:6; 11:14, 18,
25; 12:4, 23, 25, 25; 17:5;
20:2; 29:25; 56:24, 25;
57:1, 2, 4, 4; 122:8;
124:21; 141:1, 8, 10, 22,
23; 145:17; 146:6, 8, 9, 16,
17; 147:16; 150:24; 151:5,
7
therefore 101:17; 106:7;
141:12; 148:13, 20
Therneau 63:18
thick 33:19
thinking 93:9; 101:19;
103:10; 118:14; 121:10;
124:12; 128:17; 132:6;
143:1, 8; 156:4
third 35:20; 52:15; 55:7;
56:4, 25; 68:3; 71:5; 75:14;
76:15; 77:2; 86:6; 91:3;
127:17
though 82:11; 86:24;
91:4; 92:23; 97:19;
100:12; 103:21; 113:11;
124:4; 137:5; 140:9, 9;
144:24; 152:4
thought 45:22; 66:9;
128:13; 142:13; 148:11;
149:6; 151:18; 155:2;
156:8
thoughts 8:8; 155:15
thousands 47:25
three 9:3; 16:8; 17:24;
18:1, 3; 39:5; 42:17; 44:1,
2; 45:15; 46:25; 48:11, 13;
49:1; 51:8; 61:8; 66:25;
69:2; 70:24; 75:10; 78:23;
86:5; 90:15; 116:21;
118:21; 119:12, 13, 21, 22;
120:10; 124:1; 126:22;
127:2; 128:9; 131:20;
143:22; 155:19
three-month 48:12;
69:15, 20; 70:4; 103:16;
112:15; 120:5; 122:7;
126:6; 127:11, 15
threshold 131:9, 11
throughout 7:20
throw 92:15
throwing 109:22
thunder 97:7
Thus 58:4
tickled 43:10; 104:17
tied 113:9
tier 75:16, 16, 24
tiers 75:10

ties 124:18
timely 88:24
times 35:19; 40:5, 20;
59:17; 63:23; 73:11, 12;
89:15, 16, 17; 96:25;
116:4, 22; 118:16; 137:24
tissue 109:22
TLC 146:1
today 7:25; 8:3; 9:5; 17:1;
25:16; 27:25; 29:5; 36:2;
78:1; 99:21; 119:20;
151:21
together 128:25
token 156:7
told 128:12; 153:12
tolerability 93:23
Tolerance 38:13, 16, 21;
39:1, 4; 106:8; 118:12
tolerate 93:25; 94:2, 4
tolerated 96:13
tool 65:22; 69:4
tools 27:8; 150:14, 15
top 56:24; 114:21; 131:14
topic 101:19; 108:22
topics 70:6
topography 107:23
total 18:16; 66:7
totally 104:20; 121:3;
136:15
touched 92:18
tough 80:4
toward 82:7; 101:22;
123:15; 134:17; 139:15,
17
towards 26:15; 60:17;
91:5
town 85:1; 132:14
trace 58:24
tradition 133:25
traditional 52:3; 63:4;
86:10
traditionally 128:7
training 50:20
transfer 33:23
transferring 91:18
transitory 101:22
transpired 136:14
travel 8:3
treat 8:9; 9:4, 24; 10:5;
13:22; 21:5; 25:20; 58:5;
91:9; 106:16; 137:20;
144:18; 147:22
treated 21:7; 41:19; 54:9;
147:24; 155:6
treating 18:7; 25:21;
115:20; 123:6
Treatment 4:15; 8:24;
10:13; 15:22; 17:8, 15, 20,
21; 18:22; 19:15, 16; 20:7;
21:7, 9, 19, 20, 23; 22:12,
19; 23:5, 7; 24:7, 17;
25:24; 26:1, 12; 27:7; 28:6,
10; 29:4, 10, 10, 18, 24;
30:8, 9, 22, 24; 31:4, 6, 11;

32:12, 13; 34:10; 36:13,
16; 37:22, 24; 38:9; 40:15,
17, 17, 24, 25, 25; 41:2,
14; 42:6, 13, 17; 43:25;
44:2, 3, 18; 48:12, 14;
49:23; 51:22; 52:4, 17, 23;
53:2, 10; 55:5, 6, 8, 10;
56:5, 14, 23; 57:10, 13, 16,
19; 58:5, 8, 59:3, 9, 9, 14;
60:10, 12, 15, 15, 22; 61:3,
7, 11, 14, 16, 21; 62:1, 3, 6,
16, 21; 64:17, 23, 24; 65:1,
4, 6, 6, 14, 18, 24; 66:23;
67:2, 5, 13, 17, 18; 71:2;
72:4, 5, 10; 81:6, 10, 14,
16, 18, 24; 82:4, 18; 83:8;
85:12; 86:13, 20; 90:19,
23, 24, 25; 91:1, 2, 14;
92:20, 22; 94:14; 95:1, 8;
99:20; 104:22; 105:1, 16;
106:4; 107:7; 109:3, 10;
110:24; 111:4, 10; 112:20;
114:5, 16, 19, 21; 115:1, 8;
118:2; 122:11, 12, 19;
124:23; 125:7, 7, 24, 25;
126:3; 132:17, 17; 133:4,
6, 15; 135:5, 6; 139:7;
140:16, 17, 20, 22; 141:9,
12, 13, 14; 143:2, 22;
144:16; 146:7, 19; 147:6,
15; 148:7, 13, 18, 22, 24,
25; 153:7; 154:8
treatments 14:5, 8, 10,
11; 30:23; 36:10; 90:18;
112:25; 114:25; 115:3, 4;
130:6; 131:17; 133:7, 11;
138:13, 24; 142:4, 5;
148:14
tremendous 50:19; 85:2;
145:23
tremens 39:15
tremulousness 39:13
trend 19:18; 55:17; 69:1
trends 69:5
trial 6:24; 7:25; 9:7, 11,
12; 11:15; 13:1, 11; 14:3,
9, 10, 12, 25; 15:4, 4, 9, 21;
16:4, 6, 24; 18:22; 19:2, 4;
23:19; 30:3; 34:23; 35:22;
47:22; 52:17; 54:5, 21;
55:9, 13, 21; 56:6, 22;
58:19, 19, 25; 59:1, 3;
60:14; 61:10; 62:5, 18;
63:19; 64:12, 19; 65:12, -
12, 24; 66:12; 67:2; 68:22;
69:15, 19; 70:7; 72:14;
79:8, 22, 25; 84:19; 85:22;
86:21, 22; 88:5; 98:3;
99:14; 100:21; 101:2, 8;
103:16; 107:2; 108:24;
109:6; 113:7; 120:16, 23;
122:21; 124:13, 20, 25;
125:20; 126:2, 11, 18;
127:3; 128:13; 134:25;
135:13; 141:14; 142:22;
144:5, 17; 145:16, 24;
153:7, 22
trials 7:2, 4; 8:17, 19, 20,
22, 22, 23; 9:10; 10:2, 8,
18, 19; 12:20; 13:20, 25;

16:11; 18:4; 21:4; 25:20;
26:3, 4, 6; 32:7; 36:12, 17,
20; 40:20; 50:1; 51:22;
52:5, 24; 53:1; 58:4, 6;
60:22; 64:6, 10, 15, 20;
66:4, 11; 72:5; 86:17;
91:16; 94:16; 99:20;
103:2; 106:19; 109:12;
117:24; 120:4, 21; 121:4,
7; 122:7; 124:11; 125:16;
128:8; 140:21, 25; 141:4,
7, 9; 143:22; 149:9, 10;
152:19, 20
tricky 111:24; 138:20;
139:5, 14
tried 77:4; 142:11;
143:11; 144:3
trouble 128:10
troubled 35:4
Truax 23:23
true 18:5; 39:18; 45:7;
61:17; 82:16; 84:6; 108:1
truly 65:7; 132:15;
156:16, 22
trusted 143:3
try 12:2; 13:9, 10, 22;
33:6; 34:13; 58:22; 70:19;
80:22; 148:4; 152:14
trying 12:21; 90:25;
96:22, 23, 24; 97:24;
111:7; 116:9; 119:1;
122:21; 136:24; 144:1
tumor 30:4, 13
turn 25:1; 27:13; 80:16;
96:17; 97:1; 148:21, 22
turned 94:17
turns 12:5; 57:3; 69:7
twice 35:20; 56:7; 61:22
two 10:25; 12:12; 14:11;
15:16; 16:14; 21:21;
35:17; 41:23; 43:8, 14;
44:24, 25; 45:1, 2, 3; 46:7,
22, 23; 48:4; 51:8; 52:24;
53:25; 55:4; 58:10; 66:19,
24; 67:11; 69:2; 71:11;
76:1, 16; 77:14; 78:25;
86:22; 98:5; 105:1, 16;
107:1; 116:21; 124:1;
129:14, 20; 130:6, 12, 16;
141:21; 156:6
two-week 44:25
Type 10:19, 20, 25; 11:15,
21, 25; 12:3, 4, 23; 13:6,
10; 14:7, 15, 25; 19:5, 14;
20:5; 24:7; 31:20; 49:16;
62:9; 64:8; 69:17; 77:18;
95:3, 12, 13; 124:19;
152:10
types 9:3; 11:6; 23:16;
54:1; 64:8; 91:23
typical 23:8; 120:11;
124:12, 22
typically 22:18
typologies 93:21

U

21:8; 116:16
UCLA 4:17
ultimately 88:20; 96:6
unable 39:20; 76:20;
135:13
uncertainties 50:13
under 7:4; 26:25; 30:17;
67:21; 88:17; 113:2;
122:11; 153:17
unduly 136:18
unexpected 16:10;
154:24
unhealthy 137:24
unique 79:5; 107:6
unit 44:17
United 9:20; 40:24;
136:14
universally 40:19
University 4:21; 5:6, 8,
11, 15, 17; 7:12; 8:11;
102:19
unless 86:22; 111:16
Unlike 25:8; 44:12
unlikely 41:4; 45:2
unstable 11:11, 17
unsuccessful 77:5;
142:16, 24; 153:21
successfully 142:8
unsympathetic 120:25
unusual 61:25
unworthwhile 98:10
up 12:16, 16, 17; 19:17;
39:25; 51:3; 54:12; 62:25;
65:4; 68:3, 6, 24; 70:17;
71:10; 78:10; 83:8; 88:4;
89:12, 22; 90:4, 13; 99:18;
103:8, 20; 105:4; 111:1, 7,
9; 115:22; 118:16, 24;
119:23; 120:20; 126:4, 24;
127:13, 16; 132:14;
139:15; 147:2; 149:11
upon 7:8; 147:1
upward 19:9
urge 13:13; 18:3
urged 89:15, 17
urinary 15:10, 14; 151:4
urine 99:24; 109:22
use 7:24; 10:1; 13:9; 18:7;
20:2; 21:5, 12, 13, 15;
22:14, 24; 26:13; 28:7;
29:21; 33:22; 38:1; 45:14,
20; 47:12; 49:23; 50:9;
51:2, 22, 22; 52:22; 58:5;
60:13; 64:1; 65:23; 70:15;
77:25; 81:25; 83:2; 85:19;
87:11; 89:5; 90:9; 92:21;
22; 102:15; 107:12;
110:1, 21; 111:3, 4, 5, 7, 8,
12; 112:16, 24; 114:15;
116:6, 8; 119:7, 8; 138:3;
140:6; 148:1, 2
used 15:5; 22:3, 14; 32:7,

15, 18, 25; 34:10, 11;
36:19; 37:21; 38:9; 41:10,
13; 42:23, 25; 44:16;
45:21, 21; 49:10, 16; 51:4;
57:12, 16; 58:16; 63:21;
73:8; 98:18; 99:14, 24, 25;
100:5; 109:15; 142:1;
143:4; 145:10; 147:9
useful 12:11; 13:17; 22:7;
23:17; 27:5; 33:22; 37:15;
64:2; 68:7; 69:24; 77:21,
24, 25; 80:8, 21; 86:11, 12;
90:21; 99:6; 104:8; 105:3
user 130:19
users 26:10, 11; 58:9;
59:5, 6, 7, 10, 11; 90:11;
92:2; 113:22; 114:4, 20
using 18:16, 17, 25; 19:5;
28:12; 34:3; 51:8; 52:13;
56:4; 57:24; 60:17; 63:9;
67:14; 68:13; 70:5, 13;
84:20; 88:6, 15; 89:10, 21;
95:1; 107:10, 11; 108:16;
115:22; 127:11; 128:22;
138:10, 13
usual 46:11
usually 58:17; 76:9;
94:18; 100:12; 151:10
utility 33:23; 52:2
utilization 23:2

V

VA 8:21; 16:6; 36:8; 41:17
Valiant 120:17
valiant 120:17
valid 22:11; 105:9
validate 98:18
validated 86:3
validity 98:13, 22;
105:14; 110:9; 124:22;
144:22
valuable 65:23; 155:24
value 56:2
variability 97:20, 21;
112:6; 127:14
variable 41:13; 42:22, 23;
51:2; 108:12
variables 11:2; 37:21;
41:10; 42:25; 44:16;
45:13; 49:10; 51:5, 8
variation 42:9, 10;
108:15
variations 22:10; 46:3
varies 33:24; 120:8
variety 50:17; 91:23;
99:2; 108:15; 141:2; 145:8
various 33:21; 34:2;
35:3, 14; 55:3
varying 106:2
vast 82:10, 12; 83:8
vehicle 85:10
vein 104:9
Vermont 102:20
version 38:6
versions 100:25

versus 11:2, 11; 15:7;
21:16, 18; 54:17; 55:14;
56:8; 69:7; 78:23; 80:1;
83:6; 88:10; 96:16;
105:12; 125:7; 128:23, 23;
129:3; 131:21; 144:23;
145:11; 152:16
via 105:12
Vice 21:3
videotape 156:25
view 17:19, 23; 18:2;
110:22; 111:2; 136:16;
154:15
viewpoint 38:18
views 136:25
violation 35:8
violence 31:19
visitors 4:6
visual 30:3
Vitamin 44:21
vivid 39:19
vocational 22:19; 24:15
vocational/educational
22:25
Volpicelli 52:24; 54:5;
68:21; 69:4; 70:10
Volpicelli's 56:12; 68:12
volume 34:4; 44:24
vote 94:13
vulnerable 156:3

W

waffling 129:24
waiting 101:11
WANG 5:4, 4; 36:18;
51:15, 17, 17; 67:11, 22,
25; 68:15; 69:10; 70:6
wants 119:2
warrant 81:5, 9, 24;
121:3, 16
wash 65:13
washed 125:4
washout 140:11, 12, 13,
19, 25; 141:20
water 138:2
way 18:24; 19:3; 36:23;
42:3; 74:21; 78:9; 79:17;
80:20; 92:2; 97:8; 109:15;
110:18; 124:6; 127:5;
135:21; 139:14, 19; 141:5;
147:24; 148:25; 149:5;
155:4, 6, 6
ways 16:25; 69:21; 80:6;
84:3; 105:8; 132:5;
133:14; 153:3
week 19:4, 11, 22; 35:22;
45:4; 53:16; 62:4; 74:1;
75:1, 2; 83:18, 19; 88:14;
89:14, 15; 96:25; 97:25;
98:1, 5; 103:11; 108:1;
113:7; 115:2, 4, 4; 116:4,
10; 143:18, 18; 144:10, 10;
156:10
week's 49:6

weekend 35:15; 61:14;
96:24
weekly 61:16, 19, 22;
113:6
weeks 14:11; 20:7; 35:16,
17; 53:3; 62:2, 3; 70:8, 8,
12; 71:8; 79:7; 88:12;
120:10; 126:12, 17;
141:21
Welcome 25:1, 3, 6;
29:21; 80:8
well-structured 9:3
weren't 151:17
Western 36:8
whereas 59:23; 95:9;
123:25; 146:16; 154:22
whets 71:14
white 48:22
whole 79:7; 92:20; 93:20;
108:11; 152:14
wholly 120:25
whose 7:7
widely 41:7
WINCHELL 4:25, 25;
27:14, 21, 24; 37:6, 11;
44:22; 51:19; 127:23, 24;
134:4, 13; 139:11; 140:10;
141:8; 142:6; 144:4, 7, 16,
19; 151:14; 153:5; 155:7
Winchell's 138:19
window 33:25; 69:19, 20;
70:4, 5; 118:10; 119:7, 8;
120:11, 12; 123:20;
127:15
wine 73:25
winnowed 49:8
wish 7:8; 20:16; 78:14;
80:11
wished 26:9
WIT 5:14, 14; 82:2, 3, 16;
89:8, 9, 24; 110:14;
111:19; 114:13; 127:8, 9,
19, 22; 133:2; 155:20;
156:1
Wit's 91:20; 123:2; 130:1
withdrawal 8:22; 39:11,
12; 54:25; 58:15; 76:21;
135:17; 153:13
withdrew 54:21, 24
within 17:15; 79:20;
92:12; 93:18; 122:18;
146:18; 148:11, 15;
150:14; 153:25
within-treatment 18:18
without 26:24; 28:1;
32:20; 41:3; 49:3; 54:22;
63:24; 98:9; 134:15, 16;
137:20; 154:15
WLW 66:10
woman 87:25
women 46:23; 48:19;
53:18; 75:2; 77:15; 83:17;
87:18, 19; 92:7, 8; 94:2;
95:9; 96:24; 108:7; 121:7;
129:16; 130:20, 22; 132:1;
143:18; 144:11

wonder 85:8; 99:12;
122:14; 129:10; 130:14;
146:24
wondered 90:6
wonderful 156:2
wondering 65:18; 70:3
word 43:11; 156:5
words 45:1; 104:12;
115:2
work 11:19; 40:12; 50:13,
16; 70:14; 76:9, 11; 90:23;
93:20, 22; 114:9, 10, 11,
14; 128:24; 145:15;
149:23; 150:4
worked 35:5; 85:8; 90:18,
20; 100:22; 102:23
worker 137:3
working 73:2; 96:17
works 19:1; 30:8; 114:14;
115:21; 119:12; 148:19
Workshop 118:20
world 91:17, 19
worse 24:6
worth 92:13; 97:16;
150:24
Wright 57:22
written 21:2; 80:18
wrong 9:19

Y

Yale 5:6; 17:2
YAROMA 4:14, 14
yeah 97:15; 107:25
year 9:7; 17:25; 23:22;
41:19; 42:2; 44:3; 75:4;
76:2; 122:18; 124:13, 14,
16; 151:2
years 7:20; 8:18; 9:22;
10:18; 14:4; 16:6; 38:7, 23;
39:2; 41:12; 43:18; 48:1;
104:18; 118:7, 7, 8;
119:13; 120:19; 122:9;
124:2; 125:10; 135:10;
136:12; 137:9
yellow 42:1
yes/no 54:1, 4; 60:6;
70:25; 107:14
young 38:21
younger 87:10; 94:4
youth 92:7

Z

zones 114:12
Zyban 123:19

Lawyer's Notes
