

UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DRUG ABUSE ADVISORY COMMITTEE MEETING

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OPEN SESSION

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Tuesday, June 10, 1997

The Committee met in the Versailles Room at the Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, at 9:00 a.m., Eric C. Strain, M.D., Chairman, presiding

PRESENT:

ERIC C. STRAIN, M.D. Chairman
KAREN M. TEMPLETON-SOMERS, Ph.D, Executive Secretary
ANNE C. ANDORN, M.D., member
HARRIET de WIT, M.D., member
ELIZABETH KHURI, M.D., member
LLYN A. LLOYD, R. Ph, member
ROGER E. MEYER, M.D., member
ALICE M. YOUNG, Ph.D., member
DELORES YAROMA, R.N., Consumer Representative
PIPPA M. SIMPSON, Ph.d. Psychopharmacologic Drugs
Advisory Committee
PETER BRIDGE, M.D., NIDA
DEBORAH B. LEIBERMAN, M.D., NIDA
THOMAS PERMUTT, Ph.d. FDA
CELIA JAFFEE WINCHELL, M.D., FDA
CURTIS WRIGHT, M.D., FDA

A-G-E-N-D-A

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1 P-R-O-C-E-E-D-I-N-G-S

2 9:13 a.m.

3 CHAIRMAN STRAIN: If the members of the
4 committee could take their seats, please.

5 Why don't we get started. I'm Eric Strain,
6 I'll be chairing this meeting.

7 I'd like to introduce Karen Templeton-
8 Somers, who will read the conflict of interest
9 statement.

10 EXECUTIVE SECRETARY TEMPLETON-SOMERS: The
11 following announcement addresses the issue of conflict
12 of interest with regard to this meeting and is made a
13 part of the record to preclude even of the appearance
14 of such at this meeting.

15 The purpose of this meeting is to have a
16 general scientific discussion of issues relevant to
17 clinical trial designs for medications used to treat
18 cocaine abuse. Since no questions will be addressed
19 to the committee by the agency on issues dealing with
20 a specific product, IND, NDA or firm it has been
21 determined that all interests and firms regulated by
22 the Center for Drug Evaluation and Research, which
23 have been reported by the participants present no
24 potential for a conflict of interest at this meeting
25 when evaluated against the agenda. However, in the

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

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

11 Thank you.

12 CHAIRMAN STRAIN: Let's take a moment and
13 have the committee introduce itself.

14 Dr. Wright, if we can start at your end.

15 DR. WRIGHT: Dr. Curtis Wright, Deputy
16 Director of the Division of Anesthetics, Critical Care
17 and Addiction Drug Products for the FDA.

18 DR. WINCHELL: Celia Winchell, medical
19 team leader, Addiction Drug Products.

20 DR. PERMUTT: Tom Permutt.

21 DR. LLOYD: Llyn Lloyd, Arizona Board of
22 Pharmacy, member of the committee.

23 DR. SIMPSON: Pippa Simpson, Wayne State
24 University.

25 DR. de WIT: I'm Harriet de Wit,

1 Department of Psychiatry at the University of Chicago
2 and I'm a member of the committee.

3 DR. KHURI: Elizabeth Khuri, member of the
4 committee. Cornell Medical Center, New York City and
5 Rockefeller University.

6 EXECUTIVE SECRETARY TEMPLETON-SOMERS:
7 Karen Somers, Executive Secretary, FDA.

8 CHAIRMAN STRAIN: Eric Strain, I'm from
9 Baltimore, Maryland.

10 DR. ANDORN: I'm Anne Andorn from St.
11 Louis, member of the committee.

12 DR. YOUNG: Alice Young, Wayne State
13 University, member of the committee.

14 DR. JARVIK: Murray Jarvik, UCLA and the
15 West LA VA Hospital.

16 MS. YAROMA: Dolores Yaroma, I'm a
17 registered nurse.

18 DR. BRIDGE: Peter Bridge.

19 CHAIRMAN STRAIN: Thank you.

20 At this point we will hold an open public
21 hearing. Are there any participants attending who
22 would like to speak at the open public hearing? If
23 not, then we will proceed on then and this closes the
24 open public hearing, and we'll move to the FDA
25 introductory remarks by Dr. Curtis Wright.

1 Dr. Wright?

2 DR. WRIGHT: I'd like to set the tone for
3 today's discussion by reviewing a little bit from
4 yesterday.

5 Yesterday we saw that how a simple test,
6 essentially the "quit for a month" test for cigarette
7 smoking evolved into a complex operational standard of
8 success that dominates smoking cessation therapy,
9 defines trial design, describes what a successful
10 outcome is and generally has shaped the face of that
11 therapy. Fortunately, it was a good enough standard
12 to do the job despite it's flaws, and it had flaws.

13 But now we find ourselves having to do the
14 same thing for cocaine addiction. Stripping off the
15 incumbrances of scientific convention and using plain
16 language, as recommended yesterday which resulted in
17 my rewriting my talk last night, the question is this:
18 how do we measure the severity of addiction in the
19 life of an individual and what are the signs that
20 they're on the way back from it? That has to be a
21 very specific question. It has to talk about which
22 addicts, what symptoms, what stage of the illness,
23 what are the objectives of treatment and what's the
24 ultimate treatment goal.

25 Now, over time I describe the ultimate

1 treatment goal, someone looks at me as if I'm daft and
2 says "We want them to stop using cocaine, Dr. Wright,"
3 and I agree with that. But there are, if you will
4 pardon the analogy, ordinary lead bullets and there
5 are silver bullets in addictions treatment.

6 There are drugs that detect use, there are
7 drugs that attempt to deflect someone who is
8 experimenting or abusing a drug from developing
9 addiction and there are drugs that we have in
10 addiction medicine which are used to achieve specific
11 treatment goals. An example would be the use of
12 supervised disulfiram to enable outpatient treatment
13 of alcoholism.

14 Another example would be the use of
15 naltrexone in opioid addicts who are in occupational
16 positions of responsibility and could not be returned
17 to work unless we were very sure that they were not
18 using opioids.

19 Another example that's in common use is
20 the use of antidepressants in treating the dual
21 dependent addict who has a depressive disorder.

22 These nibble at the addiction problem.
23 They take sub populations and specific clinical
24 problems and treat them for the benefit of the
25 patient. I think it's important as we search for the

1 silver bullet not to forget that there are plenty of
2 indications in that area. However, we have a major
3 public health concern and we need something that will
4 hit right in the center of the target that we're
5 dealing with.

6 I think there are three goals of
7 addictions treatment for the population. We would
8 like to reduce or eliminate use, we would like to
9 reduce harm to the individual and to those around them
10 and we would like to modify high risk behaviors
11 because those behaviors have posed a serious problem
12 for our culture. So our targets are morbidity,
13 mortality, use and risk.

14 As will be described in the next
15 presentation, I think it's important to remember that
16 group statistics are made up of individual patient
17 successes. And I think that if we are to claim that
18 we have a real treatment, we need to see sustained
19 significant change.

20 Put in another way, medications claiming
21 efficacy in the treatment of an addiction must show a
22 sustained clinically meaningful effect on morbidity,
23 mortality, drug use and/or high risk behavior at the
24 level of the individual patient when they are
25 administered at the proper dose in a suitably selected

1 group of patients who are in need of such therapy.

2 Sustained is complicated because we
3 discussed yesterday how the cure concept, however
4 attractive it may be in the design of a clinical
5 trial, treat and relapse is not necessarily a valid
6 model for a complex remitting and relapsing disorder.
7 Clinically meaningful is even harder. We're pretty
8 good on what statistical significance is, but how much
9 of a change do we accept as having a real impact on
10 the life of the patient, and we'll talk about that.

11 Morbidity, mortality and high risk
12 behavior I think includes the patient's symptoms. Too
13 often in this business we forget that drug addiction
14 hurts. Certainly the patients try to deny it as part
15 of their denial structure, but the letters that we
16 continue to get from patients begging for treatment to
17 relieve their suffering attest to the fact that in
18 their own private lives this is a miserable disease.

19 I think treatment success at the level of
20 the individual is important. Showing an overall
21 general reduction in some perimeter of addiction or a
22 group of people where no one achieved any individual
23 meaningful success I think would be cruel.

24 Suitably selected groups of patients are
25 always a problem in this area. There are populations

1 that are easy to find and easy to collect and come
2 regular, but may not be at a stage of their illness
3 where they're very treatable anymore. And I think
4 it's critically important in all clinical trials to
5 have a clear vision going in as to exactly what the
6 behaviors, problems, morbidities that you wish to
7 treat are and to insure that the patients have an
8 adequate level of severity so that the trial can
9 possibly succeed.

10 If you're treating, for example,
11 depressive symptoms in addicts and they don't have any
12 depressive symptoms going in, it's very unlikely that
13 you're going to get any significant effect.

14 In preparation for this meeting we looked
15 at the addiction treatments and we looked across the
16 addiction treatments. And we tried to address what a
17 meaningful effect was in terms of our prior
18 experience. There's always some value in that and
19 there's always some cautions that have to be attached
20 to that. So, I'd like to conclude my remarks and have
21 Dr. Permutt to present the material that he's prepared
22 for us today.

23 CHAIRMAN STRAIN: Thank you, Dr. Wright.

24 As Dr. Permutt is coming up, I'd like to
25 introduce Dr. Roger Meyer, who has joined.

1 DR. PERMUTT: Thank you, Mr. Chairman.

2 I'm going to show you data that most of
3 the committee will have seen before, but no one in the
4 agency, at least, had seen it all in one place at the
5 same time. So, I hope that this may be useful to you
6 for that reason.

7 So far as I know, there are six different
8 chemical entities approved in the United States in
9 connection with the treatment of addiction. I'm going
10 to concentrate on the three on the right and say a
11 little bit about the others and why I'm not going to
12 talk about those.

13 Levo-alpha-acetylmethadol or LAAM, was
14 approved fairly recently for the treatment of
15 withdrawal, largely on the basis of comparative trials
16 to methadone. So, that experience was probably
17 relevant. We hope in the near future a second
18 pharmacal therapy for cocaine, but obviously not in
19 the first one.

20 The other three on the left, dysulpher and
21 naltrexone for opulates and methadone were approved
22 quite a long time ago. I don't know very much about
23 the trials on the basis of which they were approved.
24 I think it also may be worth noting that in none of
25 those 3 cases is the drug actually claimed to have an

1 effect on the things that Dr. Wright had just
2 mentioned: use of the drug and you particular. Dr.
3 Curry, I believe, alluded to that with methadone.

4 Methadone is indicated for the treatment
5 of withdrawal symptoms. Dysulpher is claimed, quite
6 rightly, to produce a very nasty reaction when
7 combined with alcohol. And naltrexone is claimed to
8 block some of the reenforcing effects of opiod, but
9 not actually to be effective in preventing their use.

10 Therefore, I'm going to concentrate on
11 three chemical entities; nicotine, which as you well
12 know, has been approved in a variety of dosage forms
13 for prevention of cigarette smoking. Bupropion, which
14 has been approved in between the last meeting of this
15 committee and this, also for cigarette smoking. And
16 naltrexone, which was approved in 1994 efficacy
17 supplement for treatment of alcoholism.

18 Next one, please.

19 So, I have rushed in where Dr. Hughes'
20 nine meta analytic angels feared to tread and here are
21 all of the trials of nicotine products on which
22 approval was based; all the placebo controlled trials
23 anyway. Now there still is ambiguity in the
24 definition of which ones to include. Odd, because
25 there is ambiguity in saying on what approval was

1 based. I think for some of the earlier products there
2 may be studies that were not considered and critical
3 to approval that were left out. But for the nicotine
4 inhaler, for example, I reviewed that and I considered
5 all six of the placebo controlled trials relevant even
6 though some of them were not very successful. But
7 anyway, here's a whole bunch of nicotine trials of a
8 whole bunch of different products.

9 I've marked the reference line at 30
10 percent. What I've plotted here is the success rate
11 in the active treatment group against the success rate
12 in the placebo treatment group. Now you know what the
13 success is from yesterday. Success is 4 weeks of
14 reported and documented complete abstinence usually
15 from the end of the second to the end of the sixth
16 week of treatment.

17 I've marked lines at 30 percent on both
18 axes. Thirty percent is about the lower quartile of
19 the active success rates and about the upper quartile
20 of the placebo success rates. So most of the placebo
21 groups did less than 30 percent and most of the active
22 groups did more than 30 percent; but if I had to do a
23 trial a group in which the success rate was 30 percent
24 and ask you to guess whether that was an active or a
25 placebo group, you'd have a significant chance of

1 making a mistake. It could be a placebo group from a
2 relatively successful trial, as probably one with more
3 other than pharmacological intervention, it could be
4 an active group in a relatively unsuccessful trial.

5 Now, when we talk about percentages and a
6 difference of percentages and percents of percents, I
7 rapidly get confused so I will permit myself some
8 jargon here.

9 I've also drawn a regression line on here,
10 for what it's worth. The slope is just a little more
11 than one. I might have said if hadn't been another
12 statistician in the room that it was not significantly
13 different from one, but I suspect Dr. Simpson would
14 rightly question whether significance testing has any
15 real meaning in this haphazardly selective group of
16 trials.

17 Anyway, I'm going to subtract for each
18 trial the placebo rate from the active rate. So
19 here's a trial in which the active rate was a little
20 more than 30 percent and the placebo rate was about 5
21 percent. I'm going to take 35 minus 5 and get 30. I'm
22 going to call that the attributable success rate. So
23 I estimate that 5 percent of the people in this trial
24 in the active group would have quit even if they're on
25 placebo and I attribute the other 30 percent of their

1 success to the active treatment.

2 May I have the next one?

3 There it is, a little less than 30 percent
4 attributable rate. And here are all the attributable
5 rates. They range from near zero to almost 40
6 percent. They're very weakly correlated with the
7 placebo rates. So if you wanted to believe and
8 additive model of the effect of nicotine substitution
9 in these trials, I think you'd be justified. That is
10 to say, you could believe that there is some
11 underlying rate of success that the patients in these
12 trials are likely to achieve. This is highly variable
13 from trial-to-trial, anywhere from 5 to nearly 45
14 percent. Again, depending we think mainly on the
15 selection of patients and on the nature of other
16 interventions that were provided. But over and above
17 whatever that placebo success rate is there's an
18 attributable success rate, which is highly variable
19 but doesn't vary much to the placebo rate and averages
20 a little less than 20 percent.

21 So, a highly variable rate of underlying
22 success and an extra 20 percent of people who are
23 going to quit if and only if you give them nicotine.

24 Let's have the next one.

25 Of course, you could divide instead of

1 subtracting. If I'd divided all the active success
2 rates by the placebo success rates and call that the
3 relative success rate, it ranges from hardly more than
4 1 to about 5. It's negatively correlated with the
5 placebo success rate. Naturally, you can get a rate
6 as high as -- if you have a placebo rate as low as 7
7 percent, you could get an active rate as high as 5
8 times that. But if you have a placebo rate as high as
9 40 percent, you certainly can't get an active rate as
10 high as 5 times.

11 But I think the multiplicative model on
12 the whole is not quite as good as the additive model.
13 It would look a little bit better, as Dr. Schiffman
14 suggested yesterday, if you stuck odds ratios instead
15 of relative rates; that would move these points on the
16 right up a little bit, leave the ones on the left
17 basically unaffected. I still think the additive
18 model is a little better, but you've paid your money
19 and you takes your choice. And in any case, I think
20 it's both meaningful and fair to say that, again, on
21 the average and subject to wide variation almost twice
22 as many patients of the average 1.8 quit on active
23 treatment as on the placebo in each trial.

24 The next slide, please. That's about all
25 I have to say about nicotine. To summarize it, we

1 have, as you heard yesterday in great detail, insisted
2 on a clinical definition of success or failure for
3 each patient in the trial. We defined it as four
4 weeks of complete abstinence. We could have defined
5 it in other ways. We could have defined it in non
6 binary ways too, as it doesn't have to be a yes or no,
7 we could have had very successful patients moderately
8 successful patients and unsuccessful patients, sort of
9 a number of extensions of that. But notably we're not
10 talking about the number of cigarettes smoked on
11 average by all the patients, we're talking about the
12 number of patients who succeeded in the trail by
13 definition of success.

14 With the definition we have, we had --
15 attributable success rate in some ways is rather
16 bleak. Basically what we're saying is that you've go
17 to go and treat six patients with nicotine to get one
18 success by this criteria. I think this is one of the
19 reasons rather than statistics that the multiplicative
20 model is rather more attractive, it sounds better to
21 say that nicotine is twice as good as placebo, and it
22 is twice as good and that's important when you get
23 people with not a very good chance of success, and
24 give them a much better chance of success although
25 still not a very good one.

1 The next slide please. Now, at the last
2 meeting of this committee you recommended approval of
3 bupropion for smoking cessation. This is the drug
4 substance long known as wellbutrin, an anti-depressant
5 and recently approved under the trade name Zyban for
6 smoking cessation.

7 The designs and studies rather complicate
8 this table. There are three different doses of
9 bupropion to try, there are two different formulations
10 of sustained release and immediate release
11 formulation. In one case nicotine patch and bupropion
12 were tried in combination. But if you focus on the
13 300 milligram dose of bupropion in these two columns,
14 you see numbers that are not too terribly different
15 from those for nicotine. Here we have 37 and 24
16 attributable success rate of 13 percent, relatively
17 about one and a half. 36 and 17, in this case a
18 relative rate of nearly two. And 49 and 23, a little
19 better than two. A little better still with the
20 patch, although I'm not sure it's significantly so.

21 The next slide please. This is the same
22 graph you saw before with the bupropion trials added
23 in. As you see the bigger bupropion -- fall more or
24 less into the same cloud. It looks like at the lower
25 doses there, tending to be towards the bottom of the

1 cloud. And you might say that the combination therapy
2 is showing some signs of peaking out with the -- out
3 of the cloud, although that requires some
4 confirmation. But again what we've seen in cigarette
5 smoking with abstinence defined by this four week
6 criterion is on the whole with wide variations about
7 a 20 percent attributable success rate and about a
8 factor of two relative success rate.

9 The next slide. Now, I'll ask you to
10 shift gears substantially. In 1994 we approved an
11 efficacy supplement for naltrexone in treatment of
12 alcoholism. The course of development of this
13 produce, the efficacy supplement for this product, is
14 rather different from that for, rather less cut and
15 dried than the nicotine trails. We lack experience
16 with successful therapies in this indication. And the
17 indication is after all truly different, alcohol and
18 nicotine may both be addictive drugs, but the process
19 by which alcoholism damages people's lives is rather
20 different from the process of cigarette smoking.

21 So we didn't go in for all these reasons,
22 these trials, with the idea that they had to quit
23 drinking for a month, the investigators and the
24 sponsor and the reviewers all looked at a variety of
25 measures of outcome. There was a complete abstinence

1 measure. The two trials were both of 12 weeks
2 duration, but longer abstinence than the cigarette
3 trials.

4 The sponsors also considered possibly a
5 more primary outcome, if such a thing can be
6 comparative, to be relapsed to heavy drinking defined
7 by the number of drinks taken within a single day.
8 There were some survival analyses submitted. And even
9 a comparison of the total number of drinks taken on
10 average by the patients in the naltrexone group and
11 the placebo group.

12 The next slide. Here are the data on
13 relapsed to heavy drinking from naltrexone. Both the
14 sponsor and the reviewers were interested in heavy
15 drinking for two reasons. One was a thought that
16 heavy drinking was an important, clinically relevant
17 outcome for alcoholics, possibly more so than single
18 drinks, single failures of abstinence, and also partly
19 because of a notion about the possible mechanism of
20 action of naltrexone and alcoholism that rather than
21 preventing taking the first drink, it might make the
22 second one seem less attractive. That hypothesis is
23 not strongly borne out by the data however.

24 In any case, to me what is most striking
25 in these data is that the enormous problem with

1 dropouts. In the first study, for example, 17 people,
2 17 percent of the patients known to have relapsed to
3 heavy drinking on naltrexone, half the patients were
4 known not to have relapsed, but fully a third of the
5 patients dropped out and it was not known whether they
6 relapsed to heavy drinking or not. They had not
7 relapsed at the time that they dropped out of the
8 study. So we had in this case no clear, mutually
9 acceptable A-priority plan for analyzing dropouts.

10 And you could analyze them along the same
11 lines, and I think that there is a good argument that
12 they should be analyzed along much the same lines as
13 the smoking trials with dropouts considered as
14 failures. So you are a success, a clinical success,
15 only if you don't relapse to heavy drinking and you
16 show up for treatments so that that can be verified.
17 And in that case, you see numbers that again will not
18 be terribly out of place in the nicotine graph,
19 although I think it would be pushing it a bit to
20 actually plot them on there. See, that attributable
21 rate of 12 percent, a rather feeble relative rate in
22 the first study, a relative rate of two in the second
23 study.

24 Next slide. Here is 12 weeks of total
25 abstinence from alcohol on naltrexone. Here the

1 numbers, I suppose, are even more like the smoking,
2 almost two to one, a little better than two to one.

3 Let's have the next slide. Now, in one of
4 the studies the naltrexone group took 13 drinks on
5 average over 12 weeks of treatment with a standard
6 deviation of 28 very -- And the placebo group took 38
7 drinks on average, again with a very big standard
8 deviation.

9 I want to show you these data and ask you
10 to think about them for a minute, although I rather
11 expect your response may be so what, and I think that
12 is the point. Actually there is about three different
13 ways as well as combinations that this could happen,
14 right. We've got roughly a third as many drinks on
15 naltrexone as on placebo. Is that because a third as
16 many people are drinking? People who are drinking are
17 drinking on a third as many occasions? Or people who
18 are drinking are drinking on as many occasions and
19 drinking a dose a third as much? Those are all
20 different and, you know, various combinations are also
21 possible.

22 Nevertheless, I'm sort of impressed by 38
23 versus 13 difference in spite of the standard
24 deviations. It's highly statistically significant.
25 I think you could make a case that if you can cut

1 total drinking by a factor of three by any of these
2 mechanisms, you've done something. On the other hand,
3 if it weren't three times, if it were four-fifths as
4 much on naltrexone as on placebo, then I suspect you
5 would worry a lot about whether people were cutting
6 their dose by 20 percent as opposed to 20 percent of
7 people actually abstaining from drinking who otherwise
8 would not have. I think you would probably think the
9 second was a more meaningful outcome.

10 Let's have the next slide. So what can we
11 say about nicotine and bupropion and naltrexone in
12 alcoholism altogether? Obviously nothing really
13 statistical that I would say about those three drugs
14 together would make very much sense to you. But I
15 think there are aspects of the common experience that
16 may be relevant to your deliberations today. One is,
17 we have always felt that we needed to define clinical
18 outcomes for individuals patients, as Dr. Schiffman
19 has said. This is impact a matter of regulation that
20 efficacy evaluations need to be based on clinically
21 relevant, generally recognized measures of success.
22 We need a rational way of dealing with dropouts.

23 Now, possibly not optimal, but I think a
24 very rational way of dealing with dropouts, in trials
25 with binary outcome success or failures, to treat them

1 as failures. If you propose something other than an
2 binary outcome, or something other than success or
3 failure, then you need a rational way of dealing with
4 dropouts, and that becomes a difficult, but not
5 impossible mathematical and statistical problem.

6 I don't think, as I said before, that
7 meaningful and mathematically tractable outcomes
8 necessarily have to be binary outcomes. Again we can
9 measure the degree of clinical success, we can measure
10 the time during which people were clinically
11 successful. On the other hand, I don't think anything
12 goes either. I don't think that in general, unless
13 you get dramatic results, like we saw with naltrexone,
14 that the total consumption of drugs is likely to be
15 seen as useful indication of what's actually going on
16 with the individual patient.

17 I've got nothing again survival analysis,
18 I think it's a good idea. Although it's not as good
19 an idea as has sometimes been proposed. In particular
20 it is not the magic way of dealing with the dropout
21 problem. Also I think it's utility probably depends
22 on the indication, on the nature of the addiction. I
23 think if you said that alcoholics who were treated
24 with naltrexone were going two months between episodes
25 of heavy drinking rather than a week between episodes

1 of heavy drinking, some people might already consider
2 that to be a significant clinical success, whereas if
3 you said that cigarette smokers were undergoing a
4 course of nicotine replacement and were not smoking
5 for two months and then resuming heavy smoking as
6 opposed to not smoking for a week and then going back
7 to their previously habit, you're the experts and not
8 I on this, but I suspect you might interpret that
9 rather differently. So I think that while we're
10 comfortable with the methodology of survival analysis,
11 application needs to be thought out carefully.

12 Let's have the last one. Well, you
13 wouldn't have a statistician talking to you unless
14 someone wanted you to be told numbers, so here's some
15 numbers, which may or may not be relevant. We have
16 never approved a product, recent approvals, with less
17 than about 15 percent attributable success rate in at
18 least one trial, and about a one and a half, factor of
19 one and a half, three to two, relative success rate.
20 Again, where the effect is measured on a binary scale
21 success or failure at 15 percent of people succeeding
22 who otherwise we believe would have failed. Which is
23 a different think than 15 percent reduction in
24 consumption of 15 percent change in something else.
25 Similarly, one and a half, we're talking about one and

1 a half, a factor of one and a half in the number of
2 successes.

3 Now, we haven't approved the drug without
4 seeing this, but there are a lot of reasons for that,
5 and that's not because we went out and told people to
6 bring us a 15 percent attributable success rate, a one
7 and one half times relative success rate, it's because
8 of the size of the trials that we've seen and which
9 results were statistically significant, it's because
10 of the nature of both the addictions and the
11 treatments for them. Frankly even if you consider a
12 15 percent attributable success with nicotine to be
13 fairly bleak, we have believed that nicotine treatment
14 of smokers is a relatively safe treatment and a
15 treatment for a very serious, potentially fatal
16 condition, and we thought that the risks outweighed
17 the benefit. We also made a similar determination
18 with respect to bupropion with a different
19 constellation of side affects. So I would caution you
20 about generalizing too far from the results that we've
21 seen. The decision with respect to any new therapy
22 that we've seen will depend on the risks of that
23 therapy and the benefits. And I don't think that
24 there are general statistical issues, I think there
25 are some statistical issues in the background that try

1 to illuminate for you, but we're asking you for your
2 expert advice on questions that are only dimly related
3 to statistics. And how relevant this all is, is for
4 you to judge, but I'd be happy to help you with it in
5 any way I can.

6 CHAIRMAN STRAIN: Thank you, Dr. Permutt.

7 Are there questions from the committee for
8 Dr. Permutt?

9 Dr. Khuri?

10 DR. KHURI: Dr. Permutt, in your
11 introductory slide you made a small remark about
12 possible exception of methadone, methadone not having
13 an effect on the drug, and I want to understand what
14 you said since you referenced me. I didn't understand
15 what you said, sorry?

16 DR. PERMUTT: I did not mean to say that
17 it did not have an effect, I mean to say that as I
18 understand it that the efficacy claim is not that it
19 has an effect on, it wasn't approved on the basis that
20 it keeps people from taking heroin, it was approved on
21 the basis that it's effective in treating withdrawal
22 symptoms.

23 I may be mistaken, I believe that you made
24 a remark yesterday about not having three months, six
25 months, nine months of abstinence data with respect to

1 methadone, and that was all I was alluding to. I hope
2 that I didn't misrepresent --

3 DR. KHURI: No, I'm glad I asked the
4 question because I didn't say abstinence data
5 yesterday, I simply said that if one were -- I meant
6 to say if one were withdrawn from methadone at three
7 months, six months, nine months, it would not be
8 successful because we do know the relapse rate in
9 opiod addiction is 80, 90 percent. But indeed the
10 success rate in keeping people off methadone, or off
11 heroin, excuse me, or off other opioids is 70 percent,
12 60, 70 percent because it does ablate abstinence
13 syndrome and blocks the high and prevents the
14 euphoria, although it is probably our most successful
15 drug in psychopharmacology, and efficacious and safe.

16 DR. PERMUTT: Thank you for clarifying
17 that. I did misunderstand you yesterday and I'm sorry
18 if I'm giving anyone a wrong impression of what you
19 mean to say.

20 DR. KHURI: Thank you.

21 CHAIRMAN STRAIN: Dr. Meyer?

22 DR. MEYER: Just a couple of points.

23 CHAIRMAN STRAIN: If you could use the
24 mice please. Thank you.

25 DR. MEYER: One of the problems with

1 looking at reduced use is the reliance on self-report,
2 and in the literature in the alcohol field selective
3 serotonin, re-uptake inhibitors produce about an 18
4 percent reduction in self-reported drinks per drinking
5 occasion in moderate, in heavy drinkers, but not in
6 alcoholics. I would regard that as not significant as
7 an effect. Whereas the effect that you report with
8 naltrexone in fact was a significant effect in terms
9 of reduction of drinking in those who resumed drinking
10 during the 12 week period. The dilemma about
11 naltrexone is that anyone who drank during that period
12 was at much greater risk at the end of the study of
13 relapsing after the 12 weeks. So the issue there is
14 a very complicated one.

15 Abstinance is clearly the best predictor
16 of long term outcome, the ability of people, just as
17 in the nicotine studies, to remain abstinent is in
18 fact the best predictor. But it could be related to
19 compliance as much as it could be related to
20 pharmacological effect, except that in this study they
21 looked at the compliers with placebo and with
22 naltrexone and naltrexone was better. Whereas in the
23 VA study with disulfiram compliance was the predictor
24 rather than whether disulfiram was present.

25 The bottom line that I'd like to make on

1 this is that, if naltrexone's effect is to produce and
2 sustain a moderate drinking outcome, and if that
3 effect disappears at the end of 12 weeks, then maybe
4 the issue is long term naltrexone treatment for those
5 people who can't maintain abstinence. That's an issue
6 that the field has to struggle with. Naltrexone, as
7 you know, is not an addictive drug, but one has to
8 begin to look at this.

9 So the first issue is the problems with
10 self-report. The second issue is the whole issue of
11 moderate drinking, which doesn't apply to cocaine, but
12 is an issue in the alcohol field. And the third
13 issue, which I don't think this is the right place,
14 but I do think it's an issue that needs to be
15 addressed by NIDA, is the problem of really a
16 methodology for screening drugs, for cocaine.

17 The animal model literature was developed
18 for looking at the reinforcing properties of drugs,
19 and not useful for necessarily for screening drugs for
20 treatment. And the problem in most areas of
21 pharmacotherapy we do an open trial to see if a drug
22 might be useful. It's a pre-controlled study. And
23 yet open trials in this field are fraught with risk of
24 over-interpretation of the data because anyone who
25 does well may simply be a good complier, and it may

1 not be the pharmacological effect.

2 So I think more than anything else, rather
3 than rushing into studies that are methodologically
4 rigorous and would meet your mathematical criteria, we
5 need to go back to the methodological drawing board
6 and begin to identify those pharmacological properties
7 that we believe may be useful in modifying the course
8 of addiction and see whether the drugs actually
9 achieve those effects, modest though they may be, then
10 to figure out how to incorporate the drug into a long
11 term treatment program. We are really at square
12 kindergarten in this field. We really have not moved
13 far enough, I think, to make the leap to the kind of
14 controlled studies that you could do with methadone.

15 And that was the other point is that
16 methadone was in fact one of the best and well-
17 controlled outcome studies that was done in this
18 field. Vince Dole and Marie Nice want to really set
19 a standard that has unfortunately been met by few
20 others down the road in other studies.

21 CHAIRMAN STRAIN: Thank you.

22 Dr. Young?

23 DR. YOUNG: I have a question about the
24 treatment package that these drugs are part of. If I
25 understand the conditions, the therapeutic approvals

1 for Bupropion, naltrexone, and nicotine, these are all
2 approved as adjuncts to other treatment modalities in
3 the sense that the indications say that there is a --
4 naltrexone is actually approved as an adjunct to
5 psychotherapy for alcoholism, and in the case of the
6 nicotine products, am I correct that they also include
7 a labeling that says they must be combined with
8 appropriate behavioral interventions, and in fact
9 clinical trails included such interventions in all
10 groups?

11 DR. PERMUTT: I believe that is the case
12 in general --

13 DR. YOUNG: It's true, I mean is it the
14 case, how do you assess the importance of the non
15 pharmacological pieces of the package? This was
16 alluded to yesterday in a comment, I believe by Dr.
17 Meyer actually, that how do you assess the
18 effectiveness of the behavioral intervention portions.
19 And I wonder, is there any thinking in those lines, is
20 there any information for the compounds that are
21 currently available that were or were not approved as
22 part of a package of treatments, is there any post-
23 marketing information showing how the post-marketing
24 success rates for the compound is actually used as
25 part of a medical practice compared to the predicted

1 success rates on the basis of the clinical trials data
2 where you actually know that you were delivering those
3 other parts of the package?

4 MR. WRIGHT: I'd like to take that, and
5 we're not going to do many statistical questions. We
6 could let Dr. Purmett sit down if he wants to. We
7 actually have direct clinical trails data on that in
8 that a number of the nicotine replacement products
9 were tested in fairly aggressive intervention, minimal
10 medical intervention, and essentially no medical
11 intervention models using a variety of in-patient,
12 out-patient setting.

13 DR. YOUNG: With the no medical
14 intervention being a, here is a prescription and one
15 of the outcome variables being even whether or not you
16 fill it?

17 DR. WRIGHT: Right.

18 DR. YOUNG: Okay. And nothing other than
19 a brief mention of the problem by the physician?

20 DR. WRIGHT: Well, sometimes it's unclear
21 as to how brief that was, or if it was mentioned at
22 all. One of the studies that was done by one of the
23 sponsors was extremely innovative, I thought, in that
24 they went to a pharmacy, found people who had filled
25 prescriptions and then asked them what the nature of

1 their medical intervention in receiving that
2 prescription was, and those varied from moderate to
3 very low.

4 And the outcome so far is that there is no
5 question that a behavioral intervention program
6 substantially enhances the efficacy of these
7 treatments as reflected by the spread and the placebo
8 success rate in all of the controlled clinical trials.
9 It is for that reason that we only approved these
10 medications as adjunctive treatment and not as sole
11 treatment. I hope that answers your question.

12 CHAIRMAN STRAIN: Dr. Simpson?

13 DR. SIMPSON: Actually I just wanted to
14 address actually Dr. Permutt's closing remarks about
15 statistics and the issues raised here. I think that
16 you know whatever we're talking about here when we're
17 talking about designing trails, we're talking about
18 some sort of testable hypotheses. And when you're
19 formulating a testable hypotheses the clinical issues
20 come into play considerably, but whether it's testable
21 or not is what statistics is basically looking at. So
22 I think that statistics and clinical issues go hand in
23 hand rather than one being predominant. I want to
24 stress that. Obviously I'm biased.

25 CHAIRMAN STRAIN: Dr. De Wit, did you have

1 a question?

2 DR. de WIT: I just have a minor
3 observation. When Dr. Young was talking about the use
4 of the behavioral interventions as a key component of
5 our pharmacological treatments, of course we develop
6 a lot of our models for cocaine pharmacotherapy in
7 animal models, and there's no really an animal
8 counterpart of the behavioral therapy. And it might
9 be something for us to think about, there may be ways
10 to introduce a behavioral constraintion the animals
11 to, for example, not respond to the drug, and then
12 look at that in combination with the drug. It's just
13 an observation. And curiously we haven't developed
14 our nicotine pharmacotherapies based on animal models,
15 it's something that's going to be relatively new
16 that's coming up in the stimulant and cocaine models.

17 CHAIRMAN STRAIN: Dr. Winchell?

18 DR. WINCHELL: I just wanted to comment in
19 response to Dr. Meyer's concerns that although we are
20 in a much more rudimentary phase of research in this
21 area than we are for example in the field of smoking
22 cessation research, we do have commercial sponsors
23 interested in developing products for this indication
24 as well as the activities of the NIDA Medications
25 Development Division that we'd like to support, and we

1 have an urgent need to develop our science of clinical
2 trails design even for phase two and three.

3 So maybe people are putting the cart
4 before the horse, but there are folks out there who
5 are really raring to go in these phase three trials
6 and would like your input on the design of the trials,
7 the choice of the outcomes and everything from soup to
8 nuts. So I hope that they're not rushing ahead
9 blindly, but they seem to have some pre-clinical
10 evidence that these things might work and they're
11 ready to sink a couple of million dollars into it. So
12 let's give them whatever thoughts we have.

13 CHAIRMAN STRAIN: Dr. Meyer?

14 DR. MEYER: Yes, what I'm arguing is that
15 there may be an effect and the effect could be washed
16 out in a well designed clinical trial. Looking simply
17 at behavioral measures of outcome, and that may be
18 other measures of outcome that are important to look
19 at that can be defined as a drug affect, and that
20 maybe the problem then is with the non pharmacological
21 ways that we're approaching the use of the medication,
22 which would mean that we'd have to go back to the
23 drawing board and use it in a different way, and then
24 we're ready to do the clinical trial.

25 The problem is that in the absence of that

1 methodology, you're forced to looking at some of the
2 gross measures that you described, and putting them
3 into essentially a double placebo-controlled trial.
4 When it's done well you have a good documentation of
5 the non pharmacological treatment, but again if you're
6 only left with self-report or biological measures of
7 use, then you may be missing a pharmacological effect
8 that could be significant down the road, and you may
9 be prematurely throwing a drug away. And that's what
10 my concern would be.

11 DR. WINCHELL: Do you have some specific
12 outcomes that you'd like people to consider including
13 apart from measurement of use?

14 DR. MEYER: Well, I do in the alcohol
15 field, and there are some things that people have
16 thought about with regard to cocaine like in terms of
17 the animal model, the changes in stimulation
18 thresholds as a screening device. We don't have the
19 human equivalence of those. I think we need to do in
20 fact better clinical observation of some of our
21 cocaine dependent patients post withdrawal to look at
22 some of the factors that might predict relapse.

23 For example in the alcohol field, insomnia
24 turns out to be a very powerful predictor in two
25 studies of relapse. I'd like to know what

1 characteristics of people post cocaine -- people focus
2 a lot of co-morbidity, it's almost become a mantra,
3 it's certainly become a growth industry, but no one
4 has really looked systematically at the ways in which
5 -- I mean Abe Wikler used the term "sui generis," that
6 these are disorders that are disorders in their right,
7 and I think a lot of the clinical work in the
8 addictions field needs to go back to the earlier
9 observational types of work that were done and
10 describe these characteristics of patients using some
11 of our new technology.

12 DR. JARVIK: Roger, I just want to ask
13 you, do you think that looking at measurements of
14 toxicity rather than measures of efficacy would be
15 another way of looking at outcome? For example, if
16 you had a drug that reduced the toxicity of alcohol,
17 protected the liver let's say, might that be a useful
18 drug to give to alcoholics?

19 DR. MEYER: It might be, if you had data,
20 if you were looking for it. But, if you weren't
21 looking for it, you wouldn't find it. If you were
22 simply looking at whether they drank or not and you
23 weren't looking at liver function as a predicted
24 effect, the drug would be thrown out perhaps. And
25 that's the dilemma.

1 CHAIRMAN STRAIN: Other questions or
2 comments by the committee members?

3 DR. de WIT: Could you just refocus us on
4 what question we're working on right now?

5 CHAIRMAN STRAIN: Well, actually I'm not
6 sure if we have any questions in front of us right
7 now. We are responding to Dr. Permutt's presentation
8 regarding statistical issues related to the design and
9 analysis of clinical trials as far as substance abuse
10 related products.

11 DR. de WIT: I do have one more comment
12 then on Dr. Permutt's presentation. I know this is a
13 fundamental question, but your last slide had, tried,
14 to put a number to percent of success. But of course
15 we might have to define success differently for each
16 class of drugs. Is that so important, I mean our
17 outcomes measures are likely to be quite different for
18 alcohol use, as you pointed out, and for cigarette
19 smoking and for cocaine use. So the likelihood of
20 coming up with any numeric quantitative comparisons
21 across or at least, I guess I can't really set a
22 numeric standard for percent success because we're
23 using different standards of success for each drug
24 class.

25 DR. PERMUTT: Yes, I think that's true to

1 a very great extent. I think potentially it is in
2 fact one of the advantages of a binary kind of
3 analysis, because there at least you do have a
4 standard across all kinds of things. I mean the
5 number of successes, the fraction of successes can be
6 15 percent for one drug and it could be 15 percent for
7 another drug. And those, I think, can be compared to
8 some extent, even though the definition of success may
9 be different, but I think on the whole that you're
10 quite right and it's a very important point to be very
11 careful about comparing numbers across indications
12 where the numbers are not actually measuring the same
13 thing.

14 CHAIRMAN STRAIN: Dr. Simpson?

15 DR. SIMPSON: We've been talking just, you
16 know, about cocaine abuse and cessation or reduction
17 of cocaine abuse. If cocaine abuse is a disease, then
18 one might, and a chronic disease maybe, in some sense
19 or the desire to abuse cocaine is a chronic disease,
20 perhaps there are other measures one could look at,
21 for example the functionality of the person in
22 society, and the improved functionality, this is very
23 broadly, the, you know, as you say the co-morbid
24 conditions or whatever, if you were addressing perhaps
25 a sub population who had some sort of psychiatric

1 condition, the improvement of that psychiatric
2 condition, and so on. So these are possible other
3 outcomes that actually, depending on your sub
4 population, might be your focus rather than the
5 cessation of abuse which might be more difficult to
6 get at. Just a thought.

7 CHAIRMAN STRAIN: It's an interesting
8 idea. I think it would be intriguing if we found a
9 medication that made people function better but didn't
10 make any material difference on their cocaine use.

11 DR. de WIT: Well, I mean just that you
12 wouldn't focus on that --

13 CHAIRMAN STRAIN: Right.

14 DR. de WIT: -- that might be a secondary
15 measure rather than the primary measure.

16 CHAIRMAN STRAIN: Exactly, yes. And I
17 think it's important to acknowledge that in clinical
18 trails I think a lot of the clinical trials have
19 attempted to capture some of that through use of, for
20 example, the addiction severity index where it's
21 looking at functioning in other areas besides simply
22 drug use.

23 DR. WRIGHT: I'd like to comment actually
24 on Dr. de Wit's last statement because it's been
25 interesting to see we can't get off of yesterday's

1 topic I'm afraid.

2 CHAIRMAN STRAIN: It's interesting to see
3 how the repercussions of the decision for four weeks
4 of smoking abstinence has had a ripple effect I think.
5 For example, in cocaine studies where when Steve
6 Higgins went to handle analyze the results from his
7 behavioral therapy interventions what he used was four
8 weeks of continuous abstinence as one of his outcome
9 measures, and the decision used that, was because four
10 weeks had been selected out of the nicotine studies.
11 And now we're starting to see some of the -- clinical
12 trials for example with lam where --- and
13 beofornorfene where people have gone back and reported
14 on four weeks of continuous abstinence as an outcome
15 measure, and again that selection is because four
16 weeks was used in the nicotine study.

17 So, you know, the little pebble that was
18 thrown in the water thinking well it's just going to
19 have an effect on one little thing here, doesn't. It
20 certainly has repercussions that encompass a variety
21 of drug classes, and we need to keep that in mind
22 constantly, constantly reminding ourselves of that.

23 Dr. Wright?

24 DR. WRIGHT: I think that's critical, and
25 I think I'll use an analogy from the alcoholism field.

1 And institution that I matriculated at did a study of
2 forced counseling linked to DWI, and returned a
3 finding that forced counseling was ineffective in
4 preventing the second DWI. And that was absolutely
5 true, but misleading in the sense that the purpose of
6 the forced counseling was hopefully to prevent further
7 social morbidity, but had it's real effect in moving
8 patients from a pre-contemplative phase of treatment
9 to a clear recognition of what the problem was. It's
10 very difficult after going through alcoholism
11 counseling to explain away your second DWI. It
12 becomes very technically difficult and embarrassing.

13 And one of the things that we've not
14 addressed at all that I know of in the cocaine area,
15 except very tentatively, is the stages of change model
16 and the commitment to change model, and whether the
17 patient indeed has any serious intention of complying
18 with treatment. This ties in with the earlier comment
19 that when we cone down to the very gross clinical
20 model of did it work or not, we throw away medications
21 that could work, and we expose the development plan to
22 risks associated with the vagaries of clinical trials.

23 On the other hand I can assure you that
24 the general public viewing a medication that didn't
25 materially reduce cocaine use and didn't materially

1 reduce cocaine use associated morbidity would view it
2 as a fraud. They simply would view that as an attempt
3 by a pharmaceutical industry to make money off of
4 suffering of others without helping them in any
5 material way.

6 So there is a lowest common denominator,
7 and this is where the quip for a month came from where
8 a group like this in desperation said "Well, what's
9 the minimum that we would expect to see?" And what
10 Tom's presentation and a lot of our thinking centers
11 around is there must be a minimum threshold for
12 success. Something meaningful has to happen or you
13 just abandon the attempt.

14 CHAIRMAN STRAIN: Dr. Meyer?

15 DR. MEYER: Yes. I think that there is
16 also a pragmatic issue. These are disorders which
17 have a high non compliance rate, a high dropout rate.
18 And it's not easy to necessarily interest the
19 pharmaceutical industry in supporting large scale
20 clinical trials where you have dropout rates of that
21 magnitude. So that the four week period that was hit
22 upon for nicotine is in fact politically pragmatic.
23 If you look at the literature, one of the most
24 dramatic survival curves that I've seen was the one
25 out a paper by Hunt and Noderov in 1971 in which they

1 compared the relapse rates for nicotine, alcohol and
2 heroin addiction. And it was really the three month
3 period that was the critical, I mean the critical
4 point, and I would argue that clinically it's the
5 first three to six months. But I wouldn't require
6 that in a clinical trial because the dropout rate is
7 horrendous. So four weeks at least gives you some
8 indication that's manageable in the context -- and
9 people drop out for all kinds of reasons. This is a
10 very often an unstable population that may or may not
11 be tied to their addiction, but may be tied to
12 lifestyle issues. So that the four weeks is not a bad
13 handle, but clinically you really are looking at a
14 three to six month window that you really may want to
15 focus treatment around.

16 And the problem I have that followed from
17 the nicotine work was that the four weeks then became
18 essentially a mantra related to six weeks, and that
19 became, well, you go beyond that, you'll become
20 addicted. Whereas it may be that you want to get
21 people through three to six months because that's the
22 period of greatest risk, and I don't know how you move
23 from that four weeks, which is essential to get the
24 pharmaceutical industry interested in studying
25 disorders that are very difficult to study, to how you

1 would really then apply it clinically in an excellent
2 clinical program that focuses on that three to six
3 month period. But I think that's a critical issue and
4 it's very critical as we talk about cocaine.

5 CHAIRMAN STRAIN: Yes, I agree completely
6 with what you're saying, if you look at Darp and Tops
7 and things like that --

8 DR. MEYER: Right.

9 CHAIRMAN STRAIN: -- it fits with your
10 clinical impression, that three to six months is what
11 you really need to get under the belt.

12 DR. ANDORN: Maybe one way to do that is
13 to divide it into different responses, if you will,
14 that the first thing that one month of abstinence is
15 abstinence achievement, initial abstinence
16 achievement, and that is what has been studied for
17 every drug. But then what hasn't been studied is
18 relapse rate subsequent to that. And if some
19 companies have reported that and that was included as
20 part of the deliberation, but that is very crucial and
21 I know if Max were here he'd be saying and that is, it
22 is in gradic to each drug and that quite possibly three
23 to six month relapse rates don't mean as much for
24 nicotine where we need to be looking at a year
25 relapse, right, than as compared to say alcohol or one

1 of the others, and particularly with the delayed
2 withdrawal effects.

3 DR. MEYER: Hunt and Noderov was
4 interesting because the nicotine, alcohol and opioids
5 were superimposed on each other, the curves were
6 absolutely the same, and the most dramatic drop off
7 was at that three month period. But the three to six
8 months should be reasonable for most drugs, but the
9 issue is how you move from what you need, get the
10 clinical trails and get drugs appropriately approved
11 for promise in this initial abstinence phase, and then
12 how you then can apply them in practice so that
13 actually if someone needs to be on nicotine for six
14 months, it's not a sin.

15 DR. ANDORN: Or even for the rest of their
16 life.

17 DR. MEYER: Right.

18 CHAIRMAN STRAIN: Dr. Simpson?

19 DR. SIMPSON: There are two things that I
20 was going to talk about. The four weeks trial or
21 about that period is used a lot in psychopharmacologic
22 drug testing. And there is no illusion that these are
23 going to only be used for four weeks and that's going
24 to cure the problem or whatever, and it's practical.
25 As you brought up, the dropout is a very big problem.

1 When you have dropouts, I mean at the end of the four
2 weeks, you've got to have enough to analyze basically,
3 but apart from anything else the dropout pattern can
4 be indicative in itself.

5 Which brings us back to the survival
6 curves. I haven't seen this paper that's being cited,
7 but when you have dropouts in a survival curve, the
8 survival curves are misleading in the sense that the
9 assumption, with the calculations that are made to
10 calculate, you know, the points on the curve and so on
11 are based on the idea that the dropouts are random.
12 And as we all know in a lot of these drug trials the
13 dropouts are not random, and so the survival curve is
14 misleading. And I'm not saying that the three to six
15 months is the crucial time period, it probably is, but
16 even then that graphic is misleading, and I just
17 wanted to point that out.

18 CHAIRMAN STRAIN: Thank you.

19 DR. ANDORN: I have one kind of naive
20 question for the FDA folks. How did it come about
21 that in the study of nicotine replacement products we
22 didn't apply the same mile that we applied for
23 instance for anti-psychotics where after the initial
24 double blind treatment phase comparing to placebo
25 there is an open label phase because an open label

1 phase would give that relapse data some credence?

2 DR. WRIGHT: A number of the nicotine
3 products did have open label phases extending out to
4 a year. The part of the problem, and it's the one we
5 alluded to yesterday, was at that point in time, and
6 we're talking some years ago, we were concerned that
7 we were addicting people to nicotine, a legitimate
8 concern, and that we had taken people who were using
9 a therapeutic product to get them off of nicotine and
10 maintaining them on it for extended periods of time.

11 We had the question as to whether in the
12 case of some patients that was exactly the right thing
13 to do. But the mentality and mind set of that period
14 was that we wanted to apply the program, it was a cure
15 and relapse model, we were going to apply the program,
16 cure them of smoking, and then they were going to
17 relapse or not. The concept of a chronic remitting
18 disease as the appropriate model for the use had not
19 been well developed. But we do have relapse rates for
20 those products, and the most dramatic relapse is in
21 patients that have been successfully abstinent from
22 cigarettes on nicotine replacement therapy. The most
23 reliable predictor of relapse to smoking is cessation
24 of nicotine replacement therapy.

25 CHAIRMAN STRAIN: Dr. Young?

1 DR. YOUNG: To follow up on that, is the
2 thinking with the cocaine products then to use the
3 open label model? Is the intent to make that
4 suggestion a strong one, that sponsors be encouraged
5 to follow the double blind phase of the trial with an
6 open label phase? And I ask that in part because it
7 seems to me that a fair number of the compounds that
8 may be useful for cocaine treatment may in fact on the
9 basis of the traditional abuse criteria be themselves
10 subject to scheduling.

11 And certainly I read, if I understand the
12 experience of development of compounds like lam and
13 certainly the current clinical patterns of use with
14 lam and methadone, some of the impediments to their
15 use are in fact the scheduling regulations for those
16 compounds. So I wonder what the agency is thinking
17 with respect to the development of clinical trial
18 methodology for a product classification which may
19 include a fair number of compounds which themselves
20 may be schedulable.

21 DR. WRIGHT: The Agency is here and
22 asking. I mean I think I heard behind your question
23 a comment, and the comment was that it is very likely
24 that a successful treatment medication may need to be
25 used for a long period of time, and it is also likely

1 that some agents that may be of use in cocaine
2 dependency may have significant abuse potential.

3 DR. YOUNG: I would endorse both of those
4 potentials.

5 DR. WRIGHT: Is it also your comment that
6 we should not be unduly -- there's a tremendous
7 desire, amounting to almost a passion, to try to
8 develop pharmacotherapies for cocaine dependence that
9 does not involve the administration of a substance
10 that has intrinsic abuse potential. That would be the
11 best outcome in a development program. There is also
12 a realistic possibility that an effective drug may be
13 a drug that has abuse potential. Are you making the
14 suggestion that we need to upfront consider how that
15 will interact with controlled substances laws?

16 DR. YOUNG: And I would also suggest that
17 history with a drug like bupropion would suggest that
18 the formulation in which the compound is available
19 clinically may have an enormous amount of impact in
20 terms of the liability of that compound.

21 I did my post-doctoral training in a
22 laboratory that screened drugs for their reinforcing
23 effects, and one of the first compounds that I was
24 handed as a blind compound was bupropion when it came
25 through the CPPD screen. And the pattern, the

1 predictive pattern that you would have from the self-
2 administration data there actually does not predict
3 the intravenous effects of that compound in an animal
4 self-administrative procedure. Do not predict in fact
5 the clinical profile of the compound as used orally,
6 as used in the formulation with which it is now
7 available, and in fact might not predict the
8 scheduling of the oral formulation of the compound.

9 So I would endorse thinking about these
10 things up front because I guess I think there is a
11 strong possibility that useful compounds may appear in
12 some of the early screenings to have abuse potential.

13 CHAIRMAN STRAIN: Dr. Khuri?

14 DR. KHURI: I'd like to refocus on the
15 fact that our goal in drug treatment is to reduce
16 morbidity and mortality and to restore function.
17 Certainly Methadone is an example of indeed an
18 addictive drug that does those things.

19 Going back to Dr. Wright's comment about
20 the stages of change model and the very weak effect of
21 enforced counseling on DWI. That's a point in time,
22 albeit a few weeks, intervention, it's not a sustained
23 intervention. It doesn't even probably meet a four
24 week criteria. But I find it interesting that there
25 is an aura effect of all drug treatment.

1 In a well run methadone treatment program
2 of use of proper doses, which is albeit rare, 80 to
3 120 milligrams, and good counseling and groups and
4 relapse prevention, you get a decline in cocaine use,
5 and I don't want to get off into a big discussion of
6 why there may also be a pharmacologic effect, but in
7 our hospital clinics 100 percent of those coming in to
8 treatment these days are also using cocaine. But
9 after a year in treatment, not three months, six
10 months, nine months, it goes down to about 30 percent,
11 and that could be, you could call it the aura effect
12 of good drug treatment, plus the fact that you get
13 better pick-ups if your urines are negative, and a lot
14 of other factors. But this is just a point to keep in
15 mind.

16 CHAIRMAN STRAIN: Thank you.

17 Dr. Simpson?

18 DR. SIMPSON: I just wanted to bring up
19 the point about when doing comparisons that we've
20 talked about placebo in the sense of two-arm study
21 with placebo as one arm, placebo in this case I think
22 being understood is a sugar-coated pill, however,
23 there are other ways of doing studies and more
24 difficult often and that is to have the placebo an
25 active compound. And that's a consideration which I

1 think would enter into designing cocaine trails. It
2 could affect the dropout for one thing.

3 CHAIRMAN STRAIN: Thank you.

4 If there are no other questions or
5 comments by the committee at this stage, I'd like to
6 suggest that we go ahead and take a break until 10:45,
7 shall we make it, a 15 minute break.

8 (Whereupon, at 10:35 a.m., off the record
9 until 10:56 a.m.)

10 CHAIRMAN STRAIN: The break is now over.

11 We'll now be hearing from Drs. Deborah
12 Leiderman and Peter Bridge from the National Institute
13 on Drug Abuse who will be presenting a talk entitled
14 "Measurement of cocaine use in clinical trials."

15 Drs. Leiderman and Bridge?

16 DR. BRIDGE: Good morning. It's a
17 pleasure to be here to talk about a topic that's near
18 to our hearts as well as our continued receipt of
19 paychecks.

20 As you know, our Medication Development
21 Division has a pretty straight forward mandate as its
22 primary goal, and that is the identification of a new
23 a new cocaine pharmacotherapy agent. The time frame
24 for that remains a source of some considerable
25 exercise discussion internally. But that said, the

1 goal I think is agreed to by one and all, so what I
2 would like to do this morning is provide a brief
3 introduction bit of background, to the presentation
4 focusing principally on the outcome measures to
5 cocaine pharmacotherapy studies as well as looking at
6 specific considerations that we have given to you,
7 those issues internally.

8 So go ahead and put up the first slide for
9 us. And beyond some background comments by myself,
10 then I'd like to introduce at that point Dr. Deborah
11 Leiderman who is the head of our clinical cocaine
12 program team to talk about issues regarding the
13 current identification of primary and secondary
14 outcome measures in these studies, as well as some of
15 the considerations that surround those both as
16 measures, as instrumentation, as well as questions and
17 issues of clinical trial design.

18 Then I would return to talk about some of
19 the analyses we have done within our division looking
20 at these specific measures, how they relate to each
21 other, and some of the components that have to do with
22 methods and design with regard to their use, as well
23 as looking at future methods development for our
24 program.

25 In terms of a moment, if you will, of

1 history, certainly cocaine pharmacotherapy, as you've
2 heard, has suffered some of the same problems that are
3 addressed by any group that looks at the
4 identification or initial treatment in a clinical
5 context. That is to say that we've got a fairly clear
6 public health imperative that drives our activities.
7 We are absent a pre-clinical animal or cellular model
8 that is validated by known clinical outcome. We
9 certainly have a lot of hypothetically compelling pre-
10 clinical models that are identifying new medications,
11 but don't have any validated and known applications
12 outcome, but we continue to look at many of these
13 simultaneously.

14 Perhaps some of the differences however,
15 the process, let's say AIDS and cancer, is that we
16 operate in the arena where there has been a lot of
17 obvious economic incentives beyond those provided by
18 the government, and we are working in an arena where
19 there have been a number of issues that have minimized
20 the logic of the process and progress, and I think
21 they're probably familiar with most of you, but
22 certainly drug use is replete with issues, and we'll
23 talk about those in terms of the methods for
24 developing new treatments.

25 So in the next overhead, just as a minor

1 comment, I've taken several points from a commentary
2 piece that was done by Drs. Drachman and Leber, whose
3 names are familiar to most of you for a variety of
4 reasons, that appeared in the Medical Journal,
5 referencing a article on a treatment of Alzheimer's
6 controlled clinical trials and they're -- broad
7 ranging discretion of the methods of these sorts of
8 trial designs. However, I want to pull our four
9 questions that he identified because I think they
10 really touch on issues that we struggle with as well.

11 And they raised the utility and -- without
12 utility of end points in the study designs where there
13 is not a single clinical outcome to this measure, but
14 rather a composite end points -- we're going to talk
15 about with regard to our cocaine trail designs. They
16 raised issues of statistical adjusts and the sort of
17 comprehensibility of those as well as the
18 interpretation of them where multiple comparisons
19 exist, where there may be failure of radominization
20 where the targeting of specific patient groups may not
21 be as clear as it might. And again these are issues
22 that we struggle with in our own internal
23 considerations, you know, our internal considerations.

24 There is issues of extensive benefits,
25 exactly where does one draw the line in defining

1 clinical basis for benefiting and statistical and
2 other considerations, as well as asking whether the
3 results are internally consistent, and this is again
4 finally another issue where we've got multiple
5 measures of outcome.

6 A further comment in regard to background
7 is that this is that this is a field that has been
8 relatively newly established, and as you've heard was
9 in part dated by the success consistent with opiod
10 treatment, but at the point in history where
11 medication development for cocaine treatment really
12 became a substantially funded arena. There was not an
13 extant clinical trial community engaged in
14 consideration of these issues, so that among the
15 things, the challenges that faced us beyond the
16 identification an issue was, well, providing
17 standardization to a field and development of clinical
18 trail resources which has been a part of what we have
19 looked at in the first few years and spent
20 considerable energy in, I think we are certainly at a
21 stage where those resources exist, and must of what
22 we're going to be presenting today is a reflection not
23 simply of NIDA staff thinking, but is engagement with
24 a great many of the investigators who now represent a
25 well trained and targeted clinical trial resource for

1 the conduct of these studies.

2 So with that I'd like to introduce Dr.
3 Leiderman who will pick up on some issues about
4 specific end points.

5 DR. LEIDERMAN: Thank you.

6 What I want to do first is briefly review
7 the outcome measures that are currently used in our
8 trials, that have been used in recent past, and that
9 are under consideration at least for future trials.
10 First of all the primary outcome measures among those
11 that have been used in the past are urine
12 benzoylecgonine, which from now on I will refer to as
13 BE, has been looked at in a qualitative way as an
14 outcome, that is the clean/dirty dichotomy. More
15 recently we have focused on the quantitative urine,
16 the E measurements found, the sensitivity to be
17 heightened and the analytic methods -- developed and
18 cost manageable, that this has become our focus in our
19 efforts.

20 Other possible primary outcome measures,
21 and the next two are ones that indeed we have
22 incorporated into our program, our observer which is
23 primarily the principal investigator or clinician in
24 charge of the patient's treatment and trail
25 participating ratings of improvement. These are

1 typically done, again in our program, on a weekly
2 basis and relative to the patient's condition at
3 baseline. We've also looked at severity as well.

4 In addition patient report global
5 information is useful, and again patients rate
6 themselves weekly, and this is again compared to their
7 baseline status. The same can be done with severity,
8 other variables that have been -- looked at. And
9 historically retention has been given a lot of weight,
10 and it is included still in some of our trials. And
11 craving has been used by other investigators, and at
12 least is under exploration within our program.

13 Moving on to other outcome measures that
14 at this point are used more as secondary measures in
15 our program or potential secondary measures, that is
16 not all of these are necessarily incorporated into our
17 current ongoing clinical trials. HIV risk assessment
18 -- behaviors that would be viewed as putting the
19 patients at high risk for contracting HIV,
20 survivorship in a trial as a sort of derivative of
21 retention, addiction severity index, which you all
22 have heard alluded to earlier, and other repeat
23 composite, well we can actually look at composite
24 factors from that, substance abuse and use inventories
25 including both estimates of quantity or volume spent.

1 Also under consideration, not actively in
2 use now, is consideration to obtain observer or
3 informant reports on the patient's actual use
4 patterns. In addition there are some new techniques
5 that Dr. Bridge will show you some examples of this
6 analysis for looking at quantitative urine data and
7 make the inferences about episodes of new use with the
8 available data.

9 I wanted to mention one other set of
10 secondary outcomes, and this actually relates to our
11 interest in sub populations and to design issues. If
12 we target studies for example at a sub population of
13 depressed cocaine dependent individuals, then
14 depression scales would be included in secondary
15 outcome measures. Similarly, we have a trial ongoing
16 now looking at -- attention deficit hyperactivity
17 disorder, effected cocaine dependent adults, and again
18 ADHG outcome measures would be incorporated
19 specifically into the secondary outcomes from that
20 trial.

21 So where are we going in terms of design
22 and whether some of our efforts, concerns? Kind of
23 historically in this field, and it is a short history
24 basically for ten years of cocaine clinical trials,
25 there have been relatively standard design, some

1 variations, but mostly there is some control in the
2 studies. But what was enormously heterogeneous was
3 the selection of target patient populations.
4 Typically these would be sort of all cocaine using
5 comers, and often duly dependent either deliberately
6 selected for because methadone -- the cocaine
7 dependent patients are easy to keep track of, and so
8 for those pragmatic reasons those have been targets of
9 study.

10 All of those clinical trials, and there
11 are at least 25 that we can count, there may be some
12 that were unpublished and that we've not had in our
13 files, were negative. There has been no, nothing that
14 one would even call a real signal, and certainly
15 nothing that clinically or statistically significant.

16 So one of our major efforts in addition to
17 the mandate to find -- or a medication is to improve
18 upon some of these clinical trial design issues, and
19 we are beginning to target, as I mentioned, specific
20 sub populations. For example we are controlling for
21 and even specifically targeting certain patterns of
22 psychiatric -- like depression, like ADD diagnosis.
23 We're also exploring, and this was again alluded to in
24 the discussion earlier, the issue of motivation and
25 readiness for treatment. Now, it hasn't really been

1 looked at systematically heretofore, so we're not at
2 this point not stratifying for those kinds, on that
3 kind of variable, but we are exploring it as a co-
4 variate, and similarly with stages in addiction cycle
5 and severity of illness.

6 We're also trying to more explicitly look
7 at what we are targeting in these trials. Relapse
8 prevention designs which are of great interest to us
9 at the moment may involve for example three to seven
10 days of in-patient detoxification in order to have all
11 patients, all comers sort of at the same point of in
12 fact being withdrawn and not actively using at the
13 time we actually begin treating with the study
14 medication. Hopefully that kind of enhancement may
15 address some of the issues raised this morning about
16 possibly having missed real medication effect because
17 of problems with it inherent to these patient
18 populations as well as to design issues.

19 We are also moving toward standardizing
20 the psychotherapy behavioral treatment component. We
21 remind that all of our medication trials, and I think
22 this is generally true of the field, but certainly in
23 the MDD directed ones, medication is added on to a
24 core of psychosocial behavioral intervention. That is
25 a whole sort of separate topic of what that core

1 should be, but in fact over the past several years
2 NIDA in collaboration with investigators in the field
3 have at least arrived at some working or operational
4 consensus for the moment. And what we are trying to
5 do again is control some of the variants. It may be
6 that some signal was missed because there is so much
7 variability in what counselors and therapists do
8 absolutely apart from the dose of non medication
9 therapy, the nature of what's delivered may in fact be
10 important. So at least again trying to get control
11 over that piece of the treatment and the trial.

12 Another innovation of our's is to
13 introduce what we hope will be more rapid kind of
14 phase two medication screening paradigm in which we
15 study two to three medications in parallel with a
16 single and it would be non matched placebo. But it's
17 an effort at moving more medications through our
18 program, again with control of some of these other
19 variables or sources of variance that I have mentioned
20 and to begin to detect the signal that we're all
21 looking for.

22 Some of the measures that become standard,
23 at least in our program, involve the approach to
24 collection urine. We do collect urine benzoylecgonine
25 three times a week, typically Monday, Wednesday,

1 Fridays, so you're hopefully getting every 48 hour
2 pattern.

3 Other approaches to design measures that
4 we hope will again help us control some of the
5 patient variants and perhaps do things to enhance
6 retention and thus again improve the overall quality
7 of the data that we have at the end of a trial are to
8 require certain things like a one to two week period
9 of essentially baseline, what we call run in or
10 baseline we're not treating with pharmacotherapy, but
11 in fact they are beginning to participate in the non
12 pharmacological treatment program, so getting that
13 attendance at clinic. And then we also get those more
14 measures for example of urine BE for a baseline
15 instead of a line on the one to two single measures
16 that have historically been relied upon in this field.

17 We're also trying to explore such measures
18 as the requisite clean at baseline, this again would
19 be an out-patient study rather than one beginning with
20 in-patients where hopefully they would all be put in
21 the baseline.

22 So again, these are some of the things
23 that we're beginning to explore that will hopefully be
24 of some use in achieving the goal that we're all
25 moving toward. With that I'll turn it back over to

1 Dr. Bridge and then questions or discussion.

2 DR. BRIDGE: As Deborah has indicated this
3 being our probably first, at least to my recall,
4 opportunity to discuss cocaine trials with this group,
5 did in fact inherit the outcome measures for cocaine
6 studies based on the opioid trial experience. And
7 assuming that these systematically apply, but in the
8 face of what has been a fairly compelling negative
9 experience to trials to date, at least at the point we
10 began this consideration about a year and half ago, we
11 really threw, if you will, the door open to
12 considering all components of design as well as the
13 instrumentation for these studies to see whether there
14 are ways that we can refine it. I think Deborah has
15 touched on many of these issues that we perceived
16 without necessary reference to data analysis.

17 So what I'd like to do here at this point
18 is to talk about some of the analysis we have been
19 doing looking at datasets that we have available to
20 us. And we certainly don't want to imply that this is
21 the first time we've actually had some data by any
22 stretch, but really one that focuses on the
23 instrumentation rather than the agent under
24 consideration, as far as initial effort, but that
25 said, it characterizes what the experience has been

1 with these designs, at least with the instruments and
2 the measures that we're looking at in some specific
3 ways.

4 And what I'd like to do is to touch on
5 some of the considerations of urine toxicology as well
6 as experience with global rating both for a self and
7 observer, talk about retention. And you'll notice a
8 shift here in the wording from survivorship to
9 retention. While they may seem to be pretty straight
10 forward, at least synonymous with each other, there is
11 an inference with regard to retention that doesn't
12 necessarily become part of what is particularly viewed
13 as a survival analysis and that is the emphasis on
14 that participation in, i.e., presence at student
15 program for individuals is a benefit to them when they
16 have this disorder. And so therefore retention really
17 refers to and implied that it's part of the provision
18 of this baseline psychosocial treatment that Deborah
19 has mentioned.

20 So we're going to talk about both
21 retention as an issue as well as, as Deborah has
22 identified, a more straight forward analysis, simply
23 a survivorship in the study. And in addition craving,
24 which is not something we inherited from the opioid
25 field, but has been the focus of considerable research

1 in the cocaine arena, and we are giving consideration
2 to the incorporation of this inter-study designs and
3 looking at some of the data that we have so far.

4 We're not as focused on a given study,
5 which is not by any means to imply that it's answered
6 all questions or answers all questions for all
7 situations, nor is it an method analysis, but it
8 really is illustrative of some of the experience we
9 are having at this point.

10 So the next overhead. Questions we have
11 posed to ourselves had to do with issues in terms of
12 urine tox screening. Missing data, it's important --
13 important to this one. We really wanted to get some
14 sense of the extent of the missing data in these
15 studies, where it occurred and the inference about
16 reason. I'm sure you're all aware that where data are
17 missing that something that approximates a random
18 process or whether it's for a reason has a
19 considerable impact on the assumptions for analyses
20 that we need to address these datasets.

21 We also wanted to look at qualitative and
22 quantitative urine benzoylecgonine. I figured the
23 juncture that could be derived between dirty
24 categorical analysis standard, had a clear, compelling
25 understandable inference for purposes of interpreting

1 the results from the study. The quantitative is
2 clearly effecting the qualitative -- as you well know,
3 and -- but like the rest of medicine, we thought that
4 it was relevant that when you have a continuous
5 variable in a quantitative outcome that it means that
6 describing results of clinical trial we'll begin to
7 pursue that. It also gave us something to do while
8 waiting for our data -- to strike us over the head.

9 And as Deborah has mentioned we also
10 looked at potential or are looking at treatments --
11 not past tense, it's present. The potential utility
12 of an approach proposed by Kennedy Preston at the NIDA
13 -- program, looking at the identification of new use
14 episodes based on the quantitative benzoylecgonine
15 data. And when we considered potential incorporation
16 of this as a reported outcome to our trials we
17 certainly want to have some sense of what the baseline
18 characteristics of new use are, just as you want a
19 baseline of use is, and as well as whether or not we
20 need to adjust the scores by some factors such as
21 length of participation in the trial or other factors,
22 and as well some consideration of the utility of using
23 this kind of interpretation of the data.

24 One of the things that we struggle with is
25 an absence of agreement about where quantitative use

1 becomes meaningful. Dr. Korma has suggested that
2 there potentially are statistical means to address
3 this, there are obviously others as well in terms of
4 the clinical assessments.

5 Next one. We also want to get some sense
6 of the global ratings for a self and observer. We
7 used conventionally and in this particular dataset,
8 measures of both severity, there's a statement on
9 that, as well as improvement as -- pardon me, severity
10 -- in terms of -- improvement of comparison between
11 either study entry or to the last visit. We wanted to
12 give some thought in addition to the continued use of
13 retention as an outcome measure. The reason we are
14 giving consideration to that issue, as I said based on
15 the behavioral treatment delivery which now we have
16 looked at, the limited and standardized, is that other
17 research questions that we've done to our assessment
18 were paramount necessarily, again, to consideration
19 and retention. Among them are the provision of, if
20 you will, retention or recruitment carrots, and they
21 are such things as a provision of active drug at the
22 end of trial. Such a design choice corrupts, if you
23 will, what the retention factor will be for any
24 contrast between arms of the study.

25 In addition we have been persuaded there

1 really is a need for more data than we've
2 conventionally obtained with regard to either defining
3 or confirming certain kinds of assumptions.

4 As you will see in this in this particular
5 dataset in a few minutes, patients were
6 administratively discharged when they missed three
7 consecutive visits. And the assumption is by missing
8 a visit that -- missing and -- we've got the data on
9 that, so that we are wishing to gather data for that
10 purpose as well for the safety issues for individuals
11 whether or not they remain on active treatment. And
12 we provide I believe a minimum substraight of support
13 to get those data and make commission for someone to
14 participate by data delivery alone, if you will,
15 rather than actually taking the assigned medication
16 for the investigation study. At least one instance,
17 probably there will be others, to get to the active
18 medication into the study, as well as to provide data.
19 Well, how do we interpret retention in the face of
20 that opportunity?

21 With regard to craving, we have used
22 visual analog scales for the assessment of that. We
23 have looked at the different key words for it; "want,
24 need, afraid." Probably all of us think we know the
25 difference between those. They're not equivalent, but

1 the data seemed to suggest that they probably are for
2 purposes of the way people are reporting it, but we
3 don't really have at this point, at least -- I don't
4 think -- exists to the contrary, at this point it's,
5 as you know, research development, clear constructs on
6 craving or necessarily its relationship to drug use.
7 We think it's got a face validity, obviously, but, you
8 know, beyond that it's not clear.

9 So let's take a look at the data. Here,
10 to address the question about intermittent missing
11 data, and it's in general considered the kinds of data
12 that are missing, this is a somewhat complicated
13 table. It can get worse I assure you, but I will try
14 to keep it somewhat simple.

15 And intermittent data here that is missing
16 is, in other words, an individual has arrived on
17 Monday and on Friday and they failed to show up on
18 Wednesday, so you've got a missing data point
19 bracketed by two actual values.

20 And we looked at this issue for --
21 particular dataset, by whether or not they completed
22 the study, whether or not they didn't complete the
23 study, as well as for the overall study itself. Now,
24 this particular study is an eight week trial of
25 individuals who are primary cocaine users, who are not

1 duly dependent, who had no incentive at the end of the
2 study for continued participation; that is to say they
3 were not going to get active drug in this particular
4 design. And there was a one week single line placebo
5 running. So these are data referring to the point at
6 which randomization occurs.

7 I will show later it also addresses an
8 issue about how a specific design choice can affect
9 the appearance of dropout rates in this particular
10 dataset.

11 And if you look at, under each category,
12 complete or noncomplete and overall at the right under
13 "Adjusted end," what essentially are seen percents of
14 missing data, and those are all below ten percent. So
15 actually in what would be a relatively effort study
16 we're not seeking people to get data from them,
17 tracking them down and encouraging them to come in.
18 We're not providing incentives for their participation
19 either in terms of actual drug use study or a position
20 of sort of assistance, simply providing data. We have
21 a relatively, for this field I think, a low rate of
22 missing data, which is kind of encouraging point of
23 fact, to go on.

24 Shown here, looking at the global ratings
25 for patients versus investigator ratings. And these

1 were categorical -- scale ratings, rating from much
2 better to much worse, and this in contrast to the
3 point of entry. And what we see essentially here is
4 there is a weighted kappa coefficient of about 0.32 by
5 statistical test. Not wonderful, but on the other
6 hand by typical clinical feel, not so bad either.

7 The highlighted boxes simply show the
8 diagonal, the -- patients and investigators with
9 regard to overall rate of improvement in this
10 particular dataset. What you can see in these cells
11 down here is that patients tended to rate themselves
12 more often as doing better than the investigators. We
13 suspect there are reasons for this, but I think it's
14 sufficient to say that typically self-rating and
15 observer rates don't agree perfectly, and so that this
16 was probably very impressive actually from our
17 perspective.

18 Same measure, just looking at last visit
19 instead of at the point of data entry. It's the same
20 issue, approximately the same weighted coefficient,
21 again the same phenomenon of patients seeing
22 themselves as somewhat better in contrast with the
23 investigator's rating.

24 Here what we see is again a correlation,
25 it's quite a correlation of coefficient, between

1 clinical flow rating by the PI and in contrast to
2 urine benzoylecgonine values. Now, the investigator's
3 line is the value at the time these ratings were made.
4 They were performed in a central lab, the values were
5 not made available until the end of the study. So
6 that what's being rated here is either the severity of
7 the drug problem, improvement since last visit or
8 improvement from entry. Without getting into a lot of
9 consideration, in fact these are somewhat different
10 approaches either in terms of rank, order or -- it
11 appears in the -- correlation coefficients. What you
12 see here is that improvement from last visit compared
13 to urine benzoylecgonine when you square this, you get
14 the same thing as explained. We see that this is the
15 baseline particularly.

16 The investigators have a fairly good
17 ability to predict or to correlate with the urine
18 benzoylecgonine value to the extent that one wants to
19 consider that one wants to consider that being a goal
20 standard. And we'll talk about the issue of
21 independence or discreteness of outcome variable in
22 the dataset, and in contrast it varies, it seems to
23 have less of a relationship to the benzoylecgonine for
24 the investigators.

25 Here with communications rating, the same

1 components: varied improvement from last visit
2 improvement from entry, cross data into the study.
3 Again, these are either Pearson correlation
4 coefficients or -- here in rank order. Not probably
5 consistent with the fact that the patients saw
6 themselves as doing better than the investigators and
7 we might speculate, although again this is simply
8 hypothetical, obviously, at this point that the
9 investigators are more cued to an overall assessment
10 that seemed to be consistent with the data from
11 blinded urine benzoylecgonine.

12 With regard to dropout, and this issue has
13 been raised more than once today, this is a field that
14 is saddled with a converse dropout problem with regard
15 to clinical trials. And this looks like the dataset
16 where beginning at this point data zero at
17 randomization individuals have been on a one week
18 single blind, single run in effort on our part to
19 control or reduce some of the dropout problem. And
20 point of fact, for our purposes, it succeeded.

21 Experience in primary cocaine dependent
22 patients studies up to that point, that drop in 4
23 weeks was that there was about a 50 percent dropout
24 rate on average. Here we see it's primary onset, in
25 a sense, so this clearly indicates that we can reduce

1 some of the dropout prior to randomization by such a
2 technique.

3 Another study that we have currently
4 underway we talked about last meeting as naloxone
5 trial, merely an opiate, obviously, but where we have
6 looked at efforts to keep people in the study without
7 prejudice in order to get to active treatment would
8 have been provision of transportation money and the
9 like for provision of data alone and the retention
10 rate in that study is way above what we predicted
11 giving the sighting of it. So, again, it's a point
12 that certain kinds of design can have a consequential
13 impact on dropout issues, but as I said, this is still
14 even by the time we get out at 8 weeks, we're down to
15 a 50 percent dropout.

16 Again, as I indicated earlier, we looked
17 at why people left this particular study. Vast
18 quantities left for administrative discharge -- rather
19 than other reasons for termination from the study,
20 which was data based.

21 This, a look at the correlation between
22 cravings forward, taken each time that the patient
23 visited. The clinic told us 3 times per week with
24 urine benzoylecgonine values. And here one might
25 think that given the fact that the patient knows what

1 they took, they might very well have some sense of
2 what might appear in their urine. There was, by the
3 way, no prejudice for purposes of participation in the
4 study with the presence of positive urine. Some
5 trials have had a contingency to kind of go into it,
6 but this did not. And what we see here is, frankly,
7 a fairly poor -- best words you can get -- correlation
8 between craving scores characterized as craving more
9 and more need and urine benzoylecgonine value as far
10 as supports go in the study.

11 To get some feel for where we think we're
12 going in terms of methodology development for this
13 area, one certainly is consideration of the new use
14 analysis for urine benzoylecgonine. We're fairly
15 convinced at this point, however I haven't presented
16 data for this issue, that the quantitative urine
17 benzoylecgonine value seems pretty consistent with a
18 number of assessments we've done to provide greater
19 sensitivity for a treatment on effect contrasted to a
20 casual variable. This had sort of a straight forward,
21 an intuitive sense to it. You'd expect the category
22 would be less sensitive between the quantitative one.
23 The difficulty, obviously, is that we don't have
24 specific indicators, clinical significant standard
25 quantitative production.

1 The global assessment measures, well, it
2 looks actually somewhat surprising but for our eyes,
3 may nonetheless still be improved. And one of the
4 things we're looking at now is rather than just a
5 straightforward clear inquiry on how severely a
6 diligent patient, how much improved is this patient
7 since last time since study entry, provide anchors or
8 cued perimeters that lead to an assessment performance
9 for both patients and investigators to structure, if
10 you will, how we might be providing a conceived
11 mindset against which then performance would be rated
12 by the individual.

13 Retention is a point, it's an ongoing
14 consideration about the utility of its inclusion. We
15 know in a case-by-case basis that we will eliminate it
16 as an outcome variable where we think the design
17 simply undermines the concept too broad.

18 Craving is a measure that we are looking
19 at, we're giving consideration to. We think that we
20 need further work in clarifying the concept of it and
21 it's independent of the -- well, the relevance to drug
22 use itself. When we look at the fact that we have
23 multiple primary outcome measures, we are pondering,
24 and we don't have answers at this point, with regard
25 to whether it's important that these -- in our case 4,

1 5, 3 determine which list you're referring to, whether
2 these are equivalent measures between -- as such or
3 whether there's a hierarchy established, whether there
4 is one measure that takes priority over the others
5 with regard to strategy or the study design, some
6 other component.

7 As well, we are looking at the issue of
8 whether or not there is a need for overlap -- and I
9 believe we referred to earlier as a consistency of
10 direction of multiple act forms or whether there is an
11 advantage to choose those which are maybe split with--
12 and having an --

13 Just to mention briefly, though you might
14 not be familiar with this, is the means now, as we've
15 talked about a couple of times earlier and as stated
16 to give you a reference article to the very brief
17 summary what Preston has proposed is the assessment of
18 new used based on a number of rules derived from the
19 quantitative theorem schedule, that can be measured.
20 And these are those rules. And they include an
21 increase in urine benzoylecgonine drug, the legally
22 defined standard of use of 300 nanograms per ml. when
23 the required urine value is less than -- a means. A
24 means can be defined as greater than 300 value and
25 either 50 or 25 percent greater than the prior urine--

1 I'm sorry. Less than 50 or 25 percent. It's greater
2 than 50 percent of prior value; 25 percent of the
3 prior value, which is a reduction, so you end up with
4 a negative, but you give it the specific number.

5 An individual who on Monday has a value of
6 30,000; comes in on Wednesday and has a value of
7 15,500, that's a new use under the 50 percent rule.
8 It would not be new use under the -- or it would be
9 also the 25 percent rule. So the 25 percent rule is
10 more stringent.

11 The data analysis examination we have
12 looked at so far, that doesn't appear to be a real
13 concern, but the extension with regard to the use of
14 these two precedents suggest that the 50 percent rule
15 for -- and these are values that add up to 40,000, by
16 the way. And -- but a sample on the study and if
17 there's a prior sample missing, any urine
18 benzoylecgonine counts as new use. So that is the
19 paradigm that is used -- we are, as I said, looking at
20 this as a potentially useful way to strategize the
21 presentation of quantitative urine values. People, I
22 think, have a way of grasping and getting used to the
23 idea that would be meaningful -- wants.

24 So, in summary, Jim, I think what we would
25 like to emphasize is that certainly, as we said, the

1 development of cocaine only for therapeutic benefit --
2 opium and it's particularly a candidate for success
3 and -- finding but I think it's important we recognize
4 that these are discreet pharmacologic agents; they
5 have different characteristics and the approaching use
6 for cocaine treatment should not be limited to those
7 for opium treatment, according to the file design.

8 As well, our tradition has permitted such
9 a broad ranging effort to identify and refine study
10 designs as well as outcome measures or instrumentation
11 and that is clearly focused on an effort to be able to
12 detect more clearly, more accurately or more
13 sensitively the signal of efficacy to give us some
14 greater sense of direction from the field itself as
15 far as the agents. And we recognize this is a highly
16 -- situation, so therefore a design choice -- and as
17 well the knowledge that, you know, this is a work in
18 progress. We don't have, you know, definitive
19 answers. We can't tell you that we know that this is
20 the design. We're looking at a number of things
21 simultaneously and will be back to you in continuing
22 conversation about what our experience has been with
23 that. But that said, as we brought, if you will, the
24 presence of a -- investigator is prepared to do
25 clinical trials, they're also going to need to provide

1 a period where consistency of cross studies will allow
2 us to assess those individual agents but also as well
3 to access the utilities or design to certain
4 instrumentation choices in the assessment that we set.

5 Let me stop there, if I might, and turn
6 the meeting back over to Dr. Strain.

7 CHAIRMAN STRAIN: Thanks you, Drs. Bridge
8 and Leiderman.

9 Dr. Meyer?

10 DR. MEYER: Yes. A few questions and some
11 comments. First of all, based upon the data that's
12 been collected over the last decade, does the field
13 have a sense of what constitutes good and poor
14 prognostic groups, is the first question? What kinds
15 of factors are associated with good prognoses and poor
16 prognoses within the traditional treatment programs?

17 Second, is the craving construct, and it's
18 one that I've given lots of thought and operational
19 concern about. The measure of craving in the absence
20 of context is meaningless, and I think that's one of
21 the problems with measuring the craving, looking at
22 the correlation coefficient between craving and the BE
23 levels in the urine. It's not contemporaneous. But
24 I think there are some interesting methodologies that
25 are being explored. Certainly your funding of Marian

1 Fischman is one very fixed way of looking at a given
2 context and craving in a given context and the
3 possibility of look at pharmacal therapy manipulation.

4 Another is Saul Schiffman's measure of
5 looking at ambient moods in the community. The
6 alcohol field has been looking at this issue in a
7 number of ways using that methodology. Again, it's
8 not something you would want to do on a continuous
9 basis, but if you had, say, a one week window in which
10 the patient was out with the handheld computer and
11 would have to clearly be contingently reenforced for
12 bringing it back, given the population, the issue I
13 think is worth looking at. But actually people have
14 also looked at other things.

15 There's a mail in postcard model that
16 people have looked at.

17 The third issue is contingency management.
18 I think that not enough is being done with that. I'm
19 disheartened to see some of the reports that you use
20 that retention rates did go up, albeit, you know,
21 unclear how valuable. But I think that's an issue
22 both in terms of patient retention and in terms of
23 data reporting and losing dropouts that really needs
24 to be followed.

25 And the last is that there has been work

1 looking at the sweat patch methodology. I'm not sure
2 how that's useful or what value that increases to your
3 quantitative urine data, but it could be of interest,
4 again, in a targeted way. And I guess the bottom line
5 to this is I would like to see, you know, more in the
6 direction that you're talking about; better definition
7 of subpopulations, again the issue of prognoses,
8 targeted studies of craving, of discreet periods were
9 you can get better context measure in the community
10 and more systematic examination of contingency and
11 other ways of retaining the kinds of data that are
12 critically valuable in these kinds of trials,
13 contingency management being one.

14 DR. BRIDGE: You have made a number of
15 important observations and questions. I'm going to
16 try to take them to the extent that I can in sequence.

17 There are things that appear
18 prognostically to relate to beneficial -- that we've
19 observed, among them individuals who arrive with clean
20 urine although documented use pattern prior to that
21 and who stay clean for some time period in the
22 beginning of the study. In this particular dataset,
23 as an example, there were a consequential number of
24 individuals who were clean for the first week. They
25 were far more likely -- to do well in the course of

1 the study generally. There are concerns, obviously,
2 about whether or not they were using an agent which
3 may have reenforcement properties potentially in the
4 face of that kind of behavior. Hypothetically an
5 individually who is given sort of a low level of
6 reenforcement many in fact find that stimulating or
7 likely to lead back to a use and -- the potential
8 outcome. So to say it simply -- way that a good
9 prognostic sign requires the context of whether -- and
10 what the target of your study is.

11 With regard to the issue looking for a
12 variety of focus that are clinical indications,
13 certainly that's, you know, I guess the point where
14 we're striving at at this juncture. And, Deborah, do
15 you want to talk a little bit about direct clinical
16 screening more in terms of how we're going to be using
17 that?

18 DR. LEIBERMAN: Well, as we began to
19 outline for you, the nature was really originally to
20 increase our throughputs, so to speak, medications in
21 outpatient setting. And the efficiency that we
22 hopefully achieved by using a single placebo against
23 several active arms will hopefully allow us to not
24 only look at several medications, but also in a more
25 exploratory kind of phase two way, different kinds of

1 outcomes, maybe even follow up, as we've alluded to
2 earlier, patients at the end of the trial and dropouts
3 with some observational data and to begin to address
4 some of these questions that will then, again, refine
5 what we do as we hopefully are able to take a couple
6 of compounds forward into larger studies.

7 I'm not sure exactly which other aspect of
8 Dr. Meyer's comments or questions --

9 DR. BRIDGE: The issue is -- drugs for a
10 particular population targets so that we can look at,
11 if you will, sort of the greater expansion experience
12 in a preliminary way to address this issue in the area
13 of -- agents that may have relevance to that or not --
14 cousins of each other --

15 DR. LEIBERMAN: I guess that some of,
16 hopefully, insights that we will gain -- I mean, there
17 are assumptions in general in drug development that
18 dropouts, for example, is related to, say, adverse
19 events or lack of efficacy of medication. Well, it
20 appears that this arena may in fact be quite different
21 and that there are lots of other reasons that people
22 drop out of trials in the abuse field that are
23 different from the standard, you know, psychopharm,
24 neuropharm, cardiovascular therapeutics. But, in
25 fact, there isn't much data. I mean, people have lots

1 of assumptions and inferences and there's assumption
2 that people drop out when they're dirty. In fact,
3 various datasets that we've looked at would lead us to
4 conclude the opposite; that dirtiness or cleanness may
5 not be all related to dropping out. But the fact that
6 we will have in parallel several different medications
7 will allow us to at least look at whether medication
8 effect of different kinds of adverse effects profiles
9 is, in fact, potentially a factor or if these really
10 are sort of patient variables that determine such
11 things as retention and dropout.

12 DR. BRIDGE: Just to follow up before we
13 go on. To the issue with regard to how we incorporate
14 what are sometimes rather precise and elegant designs,
15 human pharmacology studies in this much less well
16 controlled world of in clinic studies. In this
17 particular dataset that I was presenting, craving was
18 hypothesized as potentially having an impact with
19 regard to investigational agent under the study. And
20 that said, you know, we're not able to sandwich what
21 was an elegant design by Marian Fischman into this
22 clinic study.

23 The same is true in the precedents board.
24 That's a highly controlled dataset done in a
25 laboratory that she based this method on, and the

1 validation of it. We don't have that kind of
2 elegance. So therefore we -- translating what occurs
3 either in farm labs or even more of it in animal
4 laboratories into the clinic study to get some sense
5 of whether or not we're looking at appropriate models.
6 So recognize that the last bit may have a variety of
7 views for the existence of negative data as an
8 outcome. But that said -- we will need to continue to
9 make our job --

10 CHAIRMAN STRAIN: Dr. Khuri?

11 DR. KHURI: Words are very powerful. They
12 motivate, they reflect attitudes; indeed, they create
13 attitudes and they contribute to prejudice and stigma,
14 which there's a great deal of concern recently
15 regarding particularly the addictive diseases and
16 their treatments.

17 I'd like to make a plea to clean up our
18 language and expunge the clean dirty paradigm from our
19 vocabulary. We don't refer to a plus 4 urine in a
20 diabetic as a dirty urine. We certainly have for a
21 long time used this language in our field. I would
22 suggest we substitute positive/negative or using/not
23 using as just being more useful toward our goal.
24 That's sort of a comment, but I also had a question
25 following up on Dr. Meyer's very good questions.

1 I'm interested in the good prognostic
2 groups and the special groups and how we define them,
3 and I've spent a lot of time thinking about it in my
4 own clinics. Looking at those who continue to use
5 cocaine, despite our best efforts at whatever
6 treatments we use, non-pharmacologic, usually because
7 we don't have anything. We're looking forward to good
8 drugs. And obvious things: should my patients who
9 are dealing drugs be in one group and those who are
10 not dealing drugs but are using cocaine be in another
11 group? Should my suburban Westchester suburban New
12 York City patients be in one group and those living in
13 alphabet city in another? I mean, I'm just wondering
14 what your thinking is about special groups?

15 Of course, the obvious thing is the
16 psychiatric co-morbidity, but I'm interested in the
17 development of your thinking there.

18 DR. BRIDGE: Well, there are several
19 points that reflect the status of our current program
20 as well as how cocaine dependence has evolved over the
21 period of the last 10 years. The appearance of and
22 prevalence of crack cocaine formulation and the
23 existence of our progress in VA based clinic setting,
24 which -- seek out and include nonveterans, but
25 notwithstanding intends to be more in public rather

1 than private patient population progress for
2 improvement. And in compounds, the phenomenon that we
3 don't receive very infrequently the presence of
4 individuals who use inhaled and snorted cocaine as
5 opposed to crack cocaine so that the extent is varied
6 and the cocaine has changed enormously over a period
7 of time.

8 We have not, in point of fact --
9 consideration other than the Westchester patient in
10 our studies using --city, Manhattan, for that purpose.

11 You know, I think whether or not we end up
12 potentially minimizing the generalization of our
13 findings for individuals who don't live in that social
14 context I think is debatable but certainly we're
15 targeting the studies to try to provide some kind of
16 assistance, you know, sometimes specific question --
17 see whether this drug or this set of drugs will be
18 different on any other or, you know, in the
19 alternative contrast meaning whether or not there is
20 some reduction of recidivism, for example -- but
21 probably for the time being -- so many of our trials
22 right now are answering our questions and not
23 necessarily for getting us to a study --

24 CHAIRMAN STRAIN: Dr. Simpson?

25 DR. SIMPSON: I just wanted to come back

1 to what was said a bit before, was the design of the--
2 you know the multi-arm trial. It seems to me that
3 that's got, as you say, many advantages but the thing
4 that bothers me, and I may be wrong, is that you have
5 a relatively small sample size in each arm. And so
6 maybe you won't be able to look at everything that you
7 said you could look at. Is that a possible problem?

8 DR. LEIBERMAN: We certainly can never in
9 any single study answer all the questions. But
10 there's always a sort of compromise between the
11 pragmatics, and I guess this really derived out of the
12 fact that we had to confront we don't have independent
13 of resources. I mean, apart from money that tells the
14 patients and investigators and that we had to begin to
15 somehow prioritize compounds and not everything can
16 just go from preclinical into a phase 3 and 300
17 placebo control for the outpatient trial. We simple
18 can't do that, so we have to begin to figure out ways
19 of deciding what should go into that larger trial. So
20 there's no question, you know, sure we could
21 potentially lose a small signal. We could target the
22 wrong subpopulation. It's no question. I think
23 that's always just kind of a reality we have to
24 contend with and, hopefully, just do the best job of
25 hypothesis generation we can.

1 DR. SIMPSON: Sure. I was really thinking
2 if you comment about, like adverse events and things
3 like that. I doubt if with -- you're really going to
4 get any information about that, are you, unless it's
5 really varied?

6 DR. LEIBERMAN: I'm really sorry. Could
7 you repeat it?

8 DR. SIMPSON: Adverse events or, you know,
9 some of the side issues that you said you could look
10 at, I would find it -- I suspect that all you're going
11 to get is really some sort of very, as you say,
12 something which is pretty obvious and the incidents of
13 adverse events or --

14 DR. LEIBERMAN: Yes, perhaps I failed to
15 communicate. What I was talking about was really sort
16 of looking at sort of maybe gross difference in
17 retention within a study because of different adverse
18 events.

19 DR. SIMPSON: I would think even there you
20 may not pick up much.

21 DR. LEIBERMAN: Yes, but I mean that's why
22 there's always a compromise, it's always better to do
23 a study of 600 rather than --

24 DR. SIMPSON: Oh, sure, but you don't have
25 it.

1 DR. LEIBERMAN: The statisticians always
2 love to have this problem.

3 DR. BRIDGE: -- wrestle it differently --
4 if you will. We're not going to attempt to interpret
5 it -- then hopefully the other studies that we use
6 address design -- try to define sensitivity may help
7 us then do some studies in the future with great
8 precision. And one other comment to that simply is
9 there's a policy internally for us. The outcome of a
10 negative study with a given agent in a specific
11 category -- same area. We'll go on to other agents
12 until we can --

13 CHAIRMAN STRAIN: Dr. Simpson?

14 DR. SIMPSON: The others filing on
15 prognostic factors, you know, people that could be
16 good to include in this study, there's two ways of
17 looking at people that are good to include in a study.
18 One is people who will respond to the treatment and
19 the other is that you want people who will show a
20 significant result. And, you know, one can screen for
21 people that perhaps are severely addicted rather than
22 mildly addicted so that the severely addicted will
23 show some change. And I just wondered about people's
24 thoughts on that.

25 DR. BRIDGE: Well, we've had a little bit

1 of experience using the -- data with regard to that.
2 And I think that it appeared that you had to address
3 that question in the context of the agent under
4 consideration and that one agent could very well
5 appear to be beneficial -- and find a reverse pattern.
6 I think that there are enough studies -- let's only
7 look at -- consequential pathology --

8 DR. LEIBERMAN: One other response. I
9 think that one of the most important conclusions that
10 we've reached looking at various datasets -- and
11 others, is that the important thing to do is to
12 control the patient variance, not so much which end of
13 any spectrum you select, but that in any -- you know,
14 short of a trial with 1500 patients that you control
15 variance in that patient population so that you have
16 a chance of detecting a signal.

17 CHAIRMAN STRAIN: Dr. Meyer and then Dr.
18 Jarvik.

19 DR. MEYER: With regard to that issue of
20 good prognoses, I too am concerned about focusing on
21 the good prognostic group because that's the group
22 that's maybe most responsive to nonpharmacological
23 treatments. Some people have even suggested something
24 I don't agree with, that because of the relative
25 effectiveness of nonpharmacological treatments in some

1 of these populations that you eliminate the
2 nonpharmacological treatment in order to look for a
3 drug effect. I think that would be a serious error.
4 I won't even ask you your thoughts about that. But I
5 do have two questions.

6 One is I am troubles, as Dr. Simpson is,
7 about using the multidrugs against placebo as a
8 screening device. And I'm not sure what you can do as
9 an alternative, it just seems -- it seems expensive
10 and it seems like you may miss a lot because the
11 samples become so small. The open trial is clearly
12 fraught with problems as a screen. Maybe you need
13 investment as a screen in more of the Marian Fischman
14 and other type models that are more experimental. I
15 don't know.

16 It's worrisome to think about throwing all
17 these drugs and looking at the small samples. I think
18 you may miss some things that might be significant and
19 I wonder where you got the model of this as a
20 screening device.

21 I mean, for example, does the NCI do this
22 where you have very good outcome measures, presumably,
23 and they use large numbers of outpatient providers,
24 even, to do some of their clinical trials. How do
25 they deal with some of this issue in terms of small

1 samples and new drugs.

2 And the last issue, which is one that came
3 up yesterday, is I worry about the future of the
4 treatment system in this field under managed care and
5 Medicaid privatization and wonder if you are beginning
6 to hear from any of your grantees about problems that
7 they're having either staying in business or finding
8 patients for these kinds of clinical trials? Because
9 managed care is beginning to impact on the
10 availability of patients for clinical trials in other
11 areas of medicine.

12 DR. LEIBERMAN: Well, very sort of
13 narrowly and selfishly in terms of our actual clinical
14 trials program that we direct, it's done within the VA
15 health care system entirely under an interagency
16 agreement between NIH and Department of Veterans
17 Affairs. So -- now there are real issues there --

18 DR. MEYER: But they're dismantling their
19 system.

20 DR. LEIBERMAN: Well, they are and in fact
21 has in fact begun to impact us and we've spent a lot
22 of time, shall we say, being vocal about the needs for
23 research as well as clinical care. So it has begun to
24 impact. But I have to say I think that that's not
25 really -- that can't be our primary focusing. There

1 are other organized health care agencies you have to
2 address that other fora and can't be a primary focus
3 of any --

4 DR. MEYER: Oh, no, I'm just wondering.
5 That was just a question whether you were having that
6 as a problem.

7 DR. LEIBERMAN: Yes. So we don't directly
8 experience it from our grantees because our program is
9 really quite separate from what grantees are doing.
10 In fact, one could argue that it may push in lots of
11 areas of medicine more people into clinical research
12 because they can't get paid for doing treatments, they
13 may be pushed toward doing more in the way really in
14 terms of treating patients in certain therapy, it's
15 the only way they can treat certain groups of patients
16 is to have clinical trials going on. So I think it's
17 a complicated relationship.

18 And to respond to your earlier concern,
19 there's no question that -- not proposing that this
20 so-called screening paradigm is, you know, an ideal,
21 but as a very, shall we say, modest goal and it's to
22 improve upon what I think is a totally useless
23 paradigm of the open trial. And people have been
24 funded and there's been a lot of dollars down the
25 unmentionable in open, you know, ended 12 to 15 trials

1 that I don't think even asked us whatsoever. So,
2 again, we see this as only an initial effort to
3 improve upon that and that can be refined as it
4 proceeds.

5 DR. BRIDGE: Just briefly, I touch back on
6 the issue about managed care and its impact upon these
7 studies. You know -- in general there has been a
8 philosophy that the availability of a pharmacologic
9 treatment is of great appeal to those who make
10 decisions about managed care. So it just may on the
11 verge work to our advantage in some way, but right now
12 we're not having a great deal of interaction with
13 that.

14 With regards to the issue about the multi-
15 patient significant placebo, there are various designs
16 and the outcome -- where these have been used where
17 you've got a running placebo -- drugs where you've got
18 the large trial of -- reduction in those kinds of
19 thinking.

20 I'm not -- so for our purposes we're going
21 to take a look at this -- initiating it, but as a
22 means of trying to make a minimal --

23 DR. LEIBERMAN: Actually, to answer your
24 question of what other therapeutic areas and, for
25 example, NCI, does; well, I think my understanding of

1 what the -- do again in the early phase two looking
2 for a single, we're talking about small open trials
3 because they've got the advantage of having nice
4 quantitative measures but tumor bulk and they can do
5 their open study, you know, of eight or ten patients
6 and then decide whether to throw out that drug or keep
7 it in and move it into a controlled trial.

8 DR. MEYER: I think what I'm saying is if
9 you had a well characterized system that was ongoing
10 that was a good treatment system, the patients were
11 well characterized, you had a pretty good idea of what
12 dropouts, etc, were and you had a new agent that you
13 wanted to throw into that mix, I'm not sure that I
14 would be as uncomfortable as in some of those open
15 trials that were done in the past. I'm not
16 recommending this as open trial. I'm just a bit
17 worried about this notion of multiple drugs, not even
18 multiple doses of a single drug, but multiple drugs
19 with a placebo as a general screening. I think you
20 may miss something, that's all.

21 I think it's useful to look at it because
22 the other was a mess.

23 DR. BRIDGE: I have finally the comment
24 that as this program is -- this being in development--
25 one of the advantages that would transpire is the

1 availability of agents, which in the beginning are
2 difficult to come by -- probability and therefore we
3 need that time -- we're doing a lot of this while
4 we're waiting for something to pop out -- template --

5 CHAIRMAN STRAIN: Dr. Jarvik?

6 DR. JARVIK: Yes. Although there are a
7 lot of non-pharmacologic issues involved here, I'd
8 like to focus on the pharmacology for a minute and ask
9 what are some of the candidate drugs specifically that
10 have been looked at and have they been chosen on the
11 basis of a rational or an empirical rationale? I
12 think that there was some mention made about opioids
13 and that there is an effective treatment for opioid
14 abuse. I suppose that refers to methadone. Is there
15 anything like methadone that's in the pipeline for
16 cocaine? Is that a possibility?

17 The other kinds of treatments for other
18 drug addictions such as alcohol aren't that
19 terrifically successful, although naltrexone now seems
20 to be one that's worked.

21 One drug that's particularly interesting
22 is bupropion because now we've discovered that that
23 seems to be useful in the treatment of smoking. It
24 was tried in the cocaine trial and apparently there
25 was no result at all. So, there's some kind of a

1 problem there.

2 I'd just like your comments on this.

3 DR. BRIDGE: Let me just state to your
4 opioid comment that were I to respond to your question
5 in specific, my portion would look like -- in
6 principle rather than in specific.

7 We really are looking at the array of
8 neurotransmitter components that are impacted by
9 cocaine and agents that were representative of those
10 both agonist/antagonist fashion. One of the clear
11 mandates we have pharmacologically is to look beyond
12 the -- dogma for agents from other arenas, and we're
13 doing that because of the -- but we certainly can
14 provide a list of those agents where we are able to
15 discuss these publicly.

16 The issue of the bupropion, you're quite
17 right, none of these studies are published and where
18 the result was negative, there was a subsample
19 analysis which suggested perhaps there were some
20 effects for individuals who had mild moderate
21 depression but that was relatively a modest batch.
22 However, when Deborah and I were just speaking
23 beforehand, one of the strategies that are sometimes
24 considered, naltrexone -- because alcohol use is
25 nearly ubiquitous with cocaine and one study -- shows

1 a deduction in cocaine use associated with a reduction
2 in alcohol use, albeit -- toxic interactions -- but
3 again it's strategy to look at two agents that are
4 potentially reenforcement for each other, at least at
5 behavioral conditioned to each other. The
6 interruption point may be -- potentially reduction of
7 smoking behavior in cocaine -- may have some
8 associated benefit --

9 CHAIRMAN STRAIN: Dr. de Wit?

10 DR. de WIT: I just want to get back to
11 your outcome measures. I noticed that neither in your
12 primary nor your secondary measures did you have
13 measures of self reported drug use. And could you
14 tell us a little bit about the benzoylecgonine levels?
15 Could you distinguish between quantity and frequency
16 of use from those urine toxicologies? Could you tell
17 whether there is a change in the amount used per
18 occasion? Yes, tell us a little bit about the
19 kinetics of the metabolite.

20 DR. BRIDGE: One of the things that I
21 think -- reference to was the greater familiarity we
22 have with urine toxicology methodology during the
23 period of time that we're developing a variety of
24 clinical -- it's certainly much more sophisticated I
25 think than we were 5 years ago about how this

1 technology can be used. That said, it has a number of
2 shortcomings; does it conform with -- in the same
3 course of time.

4 It's clear that there's a huge variance in
5 the values that are believed to be reliable reported
6 by this assay quantitatively ranking from 50 to
7 150,000 nannograms -- measure on the assay. That's
8 nearly a 10,000 variance. Statistically that's a
9 nightmare in terms of the data given the samples -- so
10 that some sort of data reduction techniques are
11 necessary.

12 With regard to whether or not we can tell
13 that there is a change in frequency of use, that would
14 rely I believe, although there are others here -- that
15 are more familiar with this than I, you'd have to have
16 -- sampling in able to do that. Potentially a spot
17 urine check rather than 3 or 4 urine -- is also
18 impacted by not necessarily how much they've used but
19 how recently they've used, so you can get large
20 numbers -- are compounded by it.

21 DR. de WIT: Would there be any benefit to
22 getting self report measures to compliment your
23 benzoylecgonine levels?

24 DR. BRIDGE: We do have self report
25 measures. I think one of the comments that was raised

1 earlier is the extent of how much we're going to rely
2 on those given a lot of incentive to under report --

3 DR. de WIT: I understand.

4 DR. BRIDGE: And one of the things we're
5 looking -- is we're looking at these performance
6 studies like they use in Alzheimer's -- reporting of
7 cocaine use or other components of the clinical
8 spectrum by an identified form -- I'm sorry, I
9 thought that was on the list.

10 DR. LEIBERMAN: People have looked at how
11 accurately patients can actually estimate, for
12 example, the quantity of cocaine purchased and used,
13 and it's been shown to be very, very unreliable. I
14 mean, we all have trouble looking at a mass if I were
15 estimating, you know, grams or ounces or looking at
16 grapes in the grocery store. I mean, so it just turns
17 out not to be very valuable. And then there are other
18 problems with dollars expended, there are regional
19 variations and cost, impurity and we have multi-center
20 trials and how do you factor that in.

21 CHAIRMAN STRAIN: Dr. Young?

22 DR. YOUNG: I have two questions. First
23 is I realize you can't talk about the specific agents
24 that you have in trials, but I wondered if you could
25 identify what criteria, objective criteria had been

1 used to pick the doses of the agents that you're
2 comparing in these rapid clinical trials? Because I
3 assume -- I certainly realize these are single dose
4 trials. I assume it's several agents single dose of
5 each agent rather than multiple doses of a common
6 agent in these rapid clinical trial designs?

7 DR. BRIDGE: Again, no single acts fit the
8 entire situation. In part, they may very well relate
9 to what is the available safety data and/or clinical
10 efficacy of an agent in another indication, it may
11 reflect multiple dose rating studies available from
12 the sponsored pharmaceutical company when they provide
13 this -- for cocaine dependents.

14 In parallel to this effort, we do cocaine
15 -- interaction studies -- where we can't get initial
16 dosing information in terms of tolerance -- reasonable
17 dose of cocaine --So I suppose the overall response
18 probably is -- we are launching into this and we're
19 looking for experience -- for a number of factors --

20 DR. YOUNG: But the clinical efficacy may
21 not be related to your primary outcome measures in
22 terms of the criteria you're using to select what is
23 an all important variable, the dose you're using?

24 DR. BRIDGE: I'm not sure I understand
25 your comment.

1 DR. YOUNG: Well, as I understood your
2 comment, it sounds like in many instances what you may
3 have are safety data that -- or currently recommended
4 range, dose and ranges for other indications that may
5 be the driving factors for your dose selection?

6 DR. BRIDGE: And/or -- safety data can
7 conclude, however, testing against cocaine user
8 studies where objective effects are assessed and at
9 the same time adverse effects are observed -- so in
10 that instance we'll get some indication of potential--
11 but beyond that -- and there is concern about how much
12 -- when you don't have safety data to support those.

13 DR. YOUNG: Right.

14 DR. BRIDGE: You have to back in safety
15 data. We don't have a very good example right now
16 of--

17 DR. YOUNG: Let me phrase it -- let me go
18 at it a different way. What sorts of things are you
19 looking for to give a hint that what you're dealing
20 with is not an ineffective compound in a rapid trial,
21 but rather something equivalent to a 40 milligram dose
22 or 60 milligram dose of methadone, which it's an
23 effective drug at a long dose? I mean, what would be
24 your hint to tell the difference between those 2
25 conditions; a drug that we shouldn't go on with and a

1 drug that we need to take now into a dose range and
2 study because we think they're too low?

3 DR. LEIBERMAN: Could I answer that sort
4 of more broadly. I just want to remind everyone that
5 we sometimes are treated like a typical sponsor in our
6 interactions with the FDA division, but in other ways
7 they're not a typical sponsor. That we have a public
8 health mission to, in fact, explore the whole wide
9 range of compounds and to in fact do method and design
10 development. And it's very different from an
11 individual sponsor who is the advocate for a compound
12 or perhaps a couple of compounds and will do
13 everything and gather every bit of possibly relevant
14 data on that particular medication. And perhaps even
15 present it to you.

16 So, you know, you can criticize us for
17 doing some things superficially and my response would
18 be, yes, we need to. But by dint of what we're all
19 about and how we are different from a company sitting
20 in front of you and interacting about their
21 development plan and what may happen next. So, in
22 other words, you're absolutely right; we very well may
23 miss a signal but we couldn't defend as a program
24 spending five years studying in depth 3 medications
25 and have nothing to show at the end. I mean, I think

1 we would have in fact been derelict in our
2 responsibilities.

3 So, that's my general comment.

4 CHAIRMAN STRAIN: Let me just interrupt.
5 I don't think the committee means to be raking you
6 over the coals or anything

7 DR. LEIBERMAN: No, I don't think that.
8 What I'm trying to say is that I feel like this is
9 turning into a program review of what we're doing and
10 not just meeting your goal for your committee. I'd
11 like to ask Dr. Strain and Dr. Winchell is this really
12 the direction you wanted to go, because I'm not sure
13 it's still focused on the outcome question that at
14 least were addressed to us.

15 DR. MEYER: No, but I think her question
16 was.

17 DR. YOUNG: My question was --

18 DR. MEYER: Her question definitely was.
19 You may have the wrong dose and putting it into your
20 screening --

21 DR. YOUNG: My question was. I mean
22 essentially I was asking what your outcome criteria --

23 DR. MEYER: You're putting it into your
24 screening -- you're screening for methadone but you're
25 putting 20 milligrams of methadone into the screen and

1 you haven't effected heroine administration, so you
2 throw methadone out. That's basically her question,
3 and it's not clear how you would pick it up.

4 DR. BRIDGE: Let me try to -- but I think
5 it is an issue that hasn't been given -- and to expand
6 on Deborah's comment, I mean I think our relationship
7 with the agency and this committee is interactive --
8 and, you know, that said it is conceivable -- too low
9 a threshold -- or we're going to pick up a signal
10 that's somewhat stronger from one of those agents.
11 Ideally, we'd love to find -- methadone for this
12 indication, ideally -- but as in fact we're looking at
13 strategies that if we combine multiple agents -- weak
14 signal we can look at subsequent studies of dose
15 modulation, but we've got a lot of agents to look at
16 in terms of --

17 DR. MEYER: But is there any place you're
18 looking before you actually put them into that screen?
19 I mean, classical pharmacology talks about a dose
20 response curve. Is there any place that you're
21 looking at this?

22 CHAIRMAN STRAIN: Let me actually if I
23 can, let me interrupt and throw out, because I think
24 we may be getting stuck on this idea of a screening
25 clinical trial methodology with a single placebo. And

1 so let me try to see if I understand the context of
2 it, which may illuminate things.

3 I believe that the context is that this is
4 one element, a series of steps in a potential product
5 development, and that those steps begin with the
6 animal process, potentially. Move from the animal lab
7 to the human laboratory, which would assess safety and
8 potentially efficacy for interactions with cocaine
9 under very controlled conditions. And then where
10 there a variety of doses may be tested. And then
11 after the human laboratory, which is a small one in
12 subject design study, you're proposing that before
13 moving into the 600 sample size to go into, as it
14 were, a screening clinical trial design where there
15 may be an effort to get some general sense of efficacy
16 in a more naturalistic environment.

17 And then as a final step, moving into a
18 larger clinical trial. Is that true? Is that sort of
19 four step development; animal study, human laboratory
20 study, small clinical trial and then large clinical
21 trial?

22 DR. LEIBERMAN: Absolutely that
23 characterizes the general steps in -- now it doesn't
24 mean that we would ourselves conduct every step of
25 that because remember we are maybe taking -- in fact,

1 that's what we are primarily doing initially is
2 marketed medications for other indications. So that
3 means we don't have to do every bit of animal work,
4 every bit of phase one pharmacokinetics work
5 ourselves. That's available, just as there is an
6 accepted therapeutic dose range for some other
7 indication and perhaps specific safety data that would
8 in fact control and inform our selection of a dose.
9 But in general that does characterize the way we do
10 things. And, again, this particular paradigm is for
11 early phase two and -- drop things out of phase two
12 and may in fact be missing something for all the
13 reasons you've mentioned. It is endemic to looking at
14 our business, so to speak, not unique to our
15 particular paradigm or situation.

16 CHAIRMAN STRAIN: Exactly.

17 DR. YOUNG: Given that, my question was
18 what sort of criteria do you have in place to guard
19 against the possibility of a false negative? I mean
20 it seems to me at this point that given that there
21 isn't anything out there that's effective, the fear is
22 not so much the false positive, but in fact the false
23 negative.

24 DR. BRIDGE: We share your concern, and
25 that's one of the reasons why we have looked --

1 picking up small signals and what we can do to amplify
2 the signal, and certainly dose modulation is an
3 example thereof. But I will also say -- I think that
4 your questions and your comments help us both in the
5 fact that there's an ideal -- characterize every agent
6 that goes through that screen and it's something that
7 we need to look at. Our real focus was in trying to
8 get rid of false positives because it's so much wasted
9 effort in resources going and following those out --

10 CHAIRMAN STRAIN: Dr. Andorn?

11 DR. ANDORN: I'd just like to stress one
12 important thing about a rapid screening design like
13 this, there's a multiple compounds for a given class
14 when a known mechanism are used. So that it does
15 minimize the risk of throwing out a potentially
16 successful class of compounds unless in the
17 extraordinary situation that you mentioned, all the
18 drugs are used at too low a dose. But I kind of got
19 the feeling you were going to use at least 4 from a
20 class, which does minimize that in the rapid
21 screening.

22 CHAIRMAN STRAIN: Dr. Young?

23 DR. YOUNG: I wanted to also following up
24 on an earlier question by Dr. Meyer, which was he
25 mentioned the possibility of using an alternate focus

1 on very well characterized human laboratory models
2 rather than as another alternative for screening. And
3 that was also a recommendation of the IOM committee,
4 which one of the things, in response to your earlier
5 comment, that we pummeled you about was the large
6 scale trials. And we said, go to smaller trials
7 because you're wasting all this money on all these
8 negatives. But one of the other suggestions there was
9 for the potential to suggest that the branch explore
10 the potential of doing some screening in very highly
11 controlled, well characterized human laboratory
12 models. One of the ones mentioned in the IOM report
13 was one of Fischman's models with the idea that the
14 highly controlled nature of those trials might give an
15 opportunity for screening multiple agents in a given
16 class to allow better prediction for going into
17 smaller trials. And I wondered how that idea has been
18 pursued, or if it's been rejected, why so?

19 DR. BRIDGE: It's certainly not rejected.
20 I'll try to be as brief --among the approaches to
21 capitalize on this desire on our part --
22 recommendations -- and what that allows us to do is --
23 in addition to that other methodologies that would
24 have greater or lesser liability to potential efficacy
25 range in a clinical studies. There are -- changes

1 that are being made which will permit the likelihood
2 of funding, grantee applications for screening
3 paradigms that have specific MDD --

4 CHAIRMAN STRAIN: Dr. Winchell?

5 DR. WINCHELL: If I could just comment.
6 I want to reassure you that these suggestions have
7 actually been incorporated by those commercial
8 sponsors who are interested in our input on how to
9 design the next step, which is a clinical trial
10 design. My understanding is that one of the efforts
11 to improve the sensitivity and to avoid the false
12 negative was this reassessment of qualitative urine
13 positive/negative because that was insensitive to
14 intermittent use and the notion that complete
15 abstinence might be an unobtainable goal and therefore
16 to be able to be more sensitive to people who are able
17 to sustain some shorter periods of abstinence or to
18 spread out their episodes of use.

19 But as I looked at the data from the
20 quantitative urine and its correlations with other
21 measure, it occurred to me that perhaps that the
22 somewhat weak correlation spoke to the quantitative
23 urine being of less utility than I would have hoped.
24 It seems that it is sensitive to a variety of reasons
25 for change.

1 I used as much cocaine as I wanted, is one
2 reason a person would stop, or I used as much cocaine
3 as I could afford but still wanted more is another
4 reason a person would stop, and thus the correlation
5 with crave, need, want cocaine would not expect to be
6 especially high. In addition, people use as much as
7 they can on a given occasion, as much as they have
8 access to and then they stop.

9 So the access to cocaine, who is with them
10 in the room, how much they're charging, how much they
11 happen to have on hand and how pure it is would effect
12 that day's BE value.

13 My conclusion, and I'd like to get a sense
14 of the committee's comments on this, is that the
15 utility of the quantitative urine appears to me to be
16 greatest in that it makes it possible to count
17 episodes of use and that trying to make any
18 correlations to the absolute number may not be that
19 useful.

20 And when you commented to Dr. de Wit that
21 it is hard to get self reports that are quantitative,
22 I wondered whether a qualitative self report, I used
23 or I didn't use, is more readily available, more
24 readily verifiable by outside informants and whether
25 we might return to the concept of a qualitative

1 measure use or not use that is improved by the use of
2 quantitative urines to prevent carry over being
3 detected as a positive when in fact the person had not
4 used? I would love to hear the committee comment
5 specifically on their reactions to this quantitative
6 versus qualitative and what we ought to be measuring
7 when we're measuring use.

8 CHAIRMAN STRAIN: Dr. Khuri?

9 DR. KHURI: I want to add to Dr.
10 Winchell's very good list that the obvious thing, the
11 length of time that has elapsed since the last use
12 whether it's one hour or 24 or 36 hours, is certainly
13 a big factor in BE and really makes the quantitative
14 data very questionable and weaker. And I agree with
15 Dr. de Wit when she emphasized the point that the self
16 report is very, very important. I mean, in our clinic
17 we consider the self report more valuable than the
18 urine. In a clinical trial you are able to afford
19 more urines, but in a clinical situation you
20 increasingly have very few urines to go by. So self
21 report is very helpful.

22 CHAIRMAN STRAIN: Dr. Meyer?

23 DR. MEYER: I think the self report is
24 valid depending upon how the context in which you
25 gather the data. And that the urine data and self

1 report are, in fact, complimentary. But I would
2 reiterate that I think you should begin to experiment
3 with targeted one week well basically ongoing self
4 report information. The Schiffman type model or other
5 models that are out there, because that may give you
6 more information on the context questions that Dr.
7 Winchell referred to.

8 The context issues being, you know, I
9 wanted to use, I didn't have any money. Does the guy
10 go to his usual places to buy his drugs or is he
11 better able to avoid those places? Is he feeling no
12 craving in those settings? Again, looking for the
13 signal, which is what the program that you've
14 developed does. I think those targeted examinations
15 may give you more in terms of the signal that you can
16 then begin to utilize.

17 DR. LEIBERMAN: Well, we have seriously
18 considered using currently available satellite
19 technology or attach devices that actually locate
20 patients at all times that's available for your rental
21 car. But levity aside and they actually report where
22 they were and when could be more problematic. But
23 what we are trying to do, we're simply going to count
24 the self report cocaine using days. So this was a 24
25 hour period -- and see if that correlates it better

1 with some of our other measures and be quantitative
2 estimates and dollars reported, dollars spent.

3 DR. BRIDGE: Let me talk a bit about the
4 issues of the effect of quantitative and qualitative
5 urine benzoylecgonine, because it's certainly
6 something that you may have given a fair amount of
7 consideration to and at this point I think that
8 nothing is cast in stone from this point forward.
9 However, certain things -- And up to this point we
10 have not seen an emergence, if you will, between
11 qualitative and quantitative where it appears that
12 quantitative could mean an update positive change
13 whereas the qualitative means negative -- no change --
14 so that there is consistency now -- there is a weak,
15 weak qualitative report and there's been a slight
16 shift for a positive or a negative urine -- so there
17 could be a consistency of sensitivity. I do think
18 that we still have the ultimate -- what it is
19 clinically significant -- But I think if we begin to
20 add in a variety of measures as potentially as --
21 outcome, we --

22 DR. de WIT: Could you clarify for us the
23 craving measure of what was asked? Was it asked how
24 much do you crave right now while they were in a
25 clinic setting or was it a question about how much

1 they craved over the last week or the last 24 hours in
2 a natural setting?

3 DR. BRIDGE: In this particular case, it
4 does not represent all studies by any stretch, asked
5 right now --

6 DR. de WIT: I think Dr. Meyer's comment
7 on that was very appropriate. In fact, some of Dr.
8 Meyer's early studies with heroin indicated that the
9 best indicator of craving or desire for heroin was the
10 availability, the immediate availability in that
11 setting of the drug. So, I think that's something to
12 be very sensitive to; that at least if you ask about
13 craving, you need to ask in a setting where there
14 would be some possibility of use.

15 DR. BRIDGE: Certainly at it's worst at
16 least where we look at this at an in patient setting
17 where that's --

18 CHAIRMAN STRAIN: Our time is about
19 completed. Let me give a couple of thoughts,
20 actually, if I can. This is the value of being the
21 chair, you can give the thoughts and then you can
22 adjourn for lunch.

23 First of all, I want to thank you for a
24 very valuable experience; getting us to be thinking
25 about these issues and topics. It's an exceedingly

1 complex area to study and develop medications and
2 certainly you've just kind of sliced into the tip of
3 the iceberg and there's a lot more that we could be
4 considering here on this.

5 And it's difficult, at times, to I find
6 myself having to remind myself what the big picture is
7 in this whenever I start to look at one small part of
8 it. So, I want to thank you for helping us to keep
9 that in mind.

10 I also want to point out that the
11 committee is very enthusiastic about this topic. I
12 mean, clearly there's a lot of interest and people are
13 intrigued by it. There's lots of ideas and that's fun
14 to hear and watch.

15 I want to leave with just three disparate
16 points, and some have been brought up already, but to
17 reiterate.

18 One that hasn't perhaps explicitly been
19 brought up is that there's been no discussion of the
20 time period for the outcome measures that are being
21 considered. And this comes up, in part, because of
22 yet once again yesterday where we were talking about
23 nicotine products and the 4 weeks that came out there.
24 And at some point with those big clinical trials we
25 need to consider what the window is. We as a

1 committee, perhaps, need to consider what the window
2 is that we'd like to see when a sponsor comes to us
3 with a medication that's effective. So that time
4 period is something we really haven't talked about or
5 addressed here today.

6 The second thing is that we've talked
7 about selecting proper doses of pharmacal therapy, and
8 I think it's important that we keep in mind that
9 proper doses of non-pharmacal therapy need to be
10 addressed as well. That it's certainly possible there
11 are some highly effective behavioral therapies now out
12 there that are being studied and used where up to 50
13 percent response rates occur. And it's conceivable
14 that a proper dose of pharmacal therapy could be
15 selected, but you've given an exceedingly high dose of
16 behavioral therapy; you give people vouchers to stay
17 cocaine clean that have a high monetary value and you
18 don't see any effects of the pharmacal therapy. So
19 the proper selection of behavioral and pharmacal
20 therapy doses both need to be considered.

21 And finally, I'd like to return to the
22 managed care Dr. Meyer brought up. This is because as
23 we were talking about at dinner last night, sometimes
24 I wear a hat as a director of service delivery systems
25 now. And this is something that it's on the horizon,

1 it's a glow on the horizon but the glow is growing
2 stronger I think every day. And the scenario that we
3 may be confronted with is that all patients will be in
4 a managed care organization of some sort, it
5 conceivable, in a metropolitan area or state. The
6 managed care organization will not want that patient
7 in a clinical trial because their utilization review
8 person wants to know outcomes and wants to maximize
9 outcomes. And by maximized outcomes they mean is
10 their urine clean. So that they don't care whether or
11 not we want to look at a very interesting and
12 promising pharmacal therapy. They're going to say "I
13 don't want them in your study. I want them across
14 town in program X because program X is going to give
15 me urine results each week and I'll know what the
16 results are, and if they aren't clean, then we're
17 going to do something about that."

18 We're okay, strangely, in a funny way so
19 long as there are patient populations that are not in
20 managed care organizations. But, that's an era that's
21 probably coming to a close and be that good or bad, it
22 just is.

23 So, we've run past 12:30. I suggest that
24 we break for lunch.

25 Is it possible to come back at 1:30? Yes.

1 Thank you very much.

2

3

4 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

5 1:50 p.m.

6 CHAIRMAN STRAIN: Why don't we get
7 started. We're going to shoot to try to finish by
8 3:00 o'clock. There is a number of people who have
9 flights to catch and whatnot, so that is our goal.

10 Dr. Celia Winchell will now present a
11 preview of guidance development.

12 DR. WINCHELL: One reason I've been
13 hammering so hard on trying to get some specific
14 recommendations out of the committee and some specific
15 responses to specific questions is we are trying to
16 actually write a guidance to industry.

17 And before I begin I'd like to call your
18 attention to the handout on your table which is a
19 revised generic cocaine development plan. It's kind
20 of a table, it's two pages long. You should find the
21 generic cocaine development plan that was mailed to
22 your package and discard it because it is wrong,
23 chiefly in the pre-clinical part which is the result
24 of sending a psychiatrist to a pharmacologist's job,
25 but thanks to Dr. Lucy Jean and her team of

1 pharmacologists, I think it's a lot better although
2 Lucy showed me a couple of ways this morning it could
3 be even better, which I'll add in and send around
4 again.

5 This afternoon I'd like to invite you to
6 assist in our work in developing the guidance
7 document. It will explain current agency thinking on
8 the development and evaluation of drugs to treat
9 cocaine addiction. As you probably know a draft of
10 research guidelines has been floating around for
11 several years. I should have sent you a copy. I
12 thought of it too late, but then Jack Henningfield
13 spared me the trouble, so you actually have a copy.
14 I should thank him.

15 In the past few years FDA has begun an
16 initiative to standardize our approach to developing
17 guidance for industry. And so we would like to begin
18 the process of transferring the information in that
19 1992 draft into a format that meets current agency
20 standards. And in the process we'd like to update the
21 information to reflect the current state of the art.
22 To make the task manageable we're going to address
23 only guidance for developing and evaluation of
24 medications to treat cocaine addiction at this time.
25 This one was a priority for us because there is a

1 great need for research in this area, as we've all
2 heard this morning, and no effective pharmacologic
3 treatment is yet available.

4 Next slide please. Just because I like to
5 do this, here is historical background again. The
6 division has been working on this project in fits and
7 starts for about five years now. A lot of effort was
8 expended in 1992, and really we owe a word of thanks
9 to the committee of members and experts who
10 participated in the process, and particular to George
11 Woody, Laura McNicholas, Frank Vocci, and Jack
12 Henningfield who wrote the 1992 draft. There were a
13 lot of advisory committee meetings devoted to this and
14 a lot of work went into it, but the internal process
15 of finalization was not completed.

16 And in 1995 the Institute of Medicine
17 panel that discussed barriers to drug development in
18 cocaine and also in opiate addiction pointed to the
19 importance of making these guidelines available. So
20 when I came on board to FDA in the summer of '95 one
21 of my first jobs was to figure out how we would
22 complete this process and what the rules were that
23 were incumbent upon us within the agency at that time.

24 Next slide please. So you're asking what
25 the heck is taking you people so long? A few

1 challenges presented themselves. The first was the
2 FDA just begun the process of redefining our practices
3 of guidance development and dissemination through
4 what's called the good guidance practices initiative.
5 And I'll say more about this in a moment.

6 Next, we recognize the need to address an
7 audience outside the pharmaceutical industry because
8 submissions from individual investigators make up a
9 large percentage of our work load, and it's been clear
10 to us that this group would benefit from some
11 guidance. And third, the draft guidance had attempted
12 to address psychoactive substance use disorders and
13 their treatment as a group. And as the state of the
14 art in drug development matured in some areas and not
15 in others, it became apparent to us that we actually
16 had specific advice to offer in some circumstances, in
17 others we had some general principles to outline, and
18 in still others we really had very little to say. So
19 while there were still commonalities, there were a
20 number of differences.

21 Next slide? If you're reading along in my
22 handout you'll probably be distracted by the
23 difference between what I thought I was going to say
24 and what I actually say, so you might want to look
25 just at the slide part.

1 The good guidance practice initiative, let
2 me say a bit about that, mostly I'll read the slide.
3 When complete this process will define how the FDA
4 will develop and use guidance documents. At the
5 moment we're guided by an interim policy which
6 outlines a process to be used in developing writing
7 and disseminating guidance. There is a procedure to
8 be used for obtaining internal comment and for
9 soliciting public comment, as well as a specific
10 format for the document down to the font. Among other
11 things, the policy actually gives us a definition for
12 the term "guidance."

13 Next slide. You remember we used to call
14 this a guideline, but a guidance refers to any written
15 communication that explains the center policy or
16 procedure. Guidance are prepared to establish clarity
17 and consistency in FDA policy, regulatory activities
18 and procedures, and this term replaces "guideline."
19 The term guideline is now used only for guidance
20 documents developed through the ICH and only certain
21 guidance documents at that. So whatever do don't call
22 it a guideline.

23 Next slide. A bit more from our interim
24 policy. Guidance documents contain recommendations on
25 how best to do things, but they are advisory in nature

1 and not legally binding on the FDA or the public.
2 We're advised that our guidance should be complete,
3 concise, easy to understand, accurate and consistent
4 with FDA policies.

5 So of course we'd like as we go through
6 the process of revising our guidance document to
7 follow these procedures outlined in the policy. We're
8 in a very preliminary stage now. We're asking your
9 help so we can shape up this draft that we included in
10 your package so we can actually begin the process of
11 circulating it internally. We haven't even done that
12 yet. And one of the hurdles to overcome is the FDA
13 policies as they're documented really have to be
14 attuned to the state of the art in the research field
15 so your input is essential.

16 Next slide please. Let's say a bit about
17 the audience. Most research guidelines that come out
18 of FDA are clearly aimed at the pharmaceutical
19 industry. However as many people have commented,
20 there is a relative lack of activity in the industry
21 although I'll remind you there is not no activity,
22 there is some. It's very reassuring. There is a
23 relative lack of activity in the industry aimed at
24 drug development for substance abuse disorders. On the
25 other hand we receive a large volume of submissions

1 from individual investigators. Often these are trails
2 where they are looking to explore the utility of
3 already marketed drugs for the indication of treatment
4 of cocaine addiction.

5 Last year in fact I took a look at our
6 numbers and three quarters of our new INDs were
7 received from individual investigators as well as a
8 significant number of new protocols submitted to the
9 existing INDs, and actually it's way more than three
10 quarters because of the other quarter that were
11 commercial, only about half of those were for drug
12 addiction, because our group has responsibility for
13 narcotic analgesics as well. And when you take that
14 half that was drug addiction, a really good number of
15 those were for smoking cessation products. So we're
16 down to an itchy-bitsy number of INDs, commercial INDs
17 for addiction disorders other than tobacco dependence.
18 And quite a large volume from sponsor investigators,
19 many of which do deal with cocaine.

20 It's been clear to us that some of the
21 sponsor investigators would benefit from the
22 availability of a guidance as well. So in drafting a
23 version that we distributed we tried first to address
24 both academic researchers in the pharmaceutical
25 industry, but this is really very hard. The level of

1 basic knowledge of the drug development process, the
2 FDA review process, pre-clinical requirements,
3 chemistry requirements, and the panoply of things that
4 go into knowing what to do with a guidance really
5 varies dramatically between the industry groups and
6 the academic groups, and of course within the academic
7 community as well.

8 Next slide. The most significant change
9 we made in preparing this draft was the decision to
10 issue separate guidance for the treatment of different
11 addictive disorders. This is the basic splitter
12 versus lumbers issue.

13 As we went through the 1992 draft we could
14 see that although there was overlap there were
15 differences and indication in outcome measures across
16 disorders. And a previous draft handled this with a
17 common introductory section, and then it marched
18 through one section on indication, outcome and design
19 issues for each of the various disorders. Which is a
20 reasonable way to do it, but because there was a lot
21 known about some disorders and much less about others,
22 we had some very long sections that were quite
23 prescriptive, we know how to do this, we want you to
24 do it this way, and others that were thin and rather
25 vague. And we thought we might be able to provide

1 more clarity and specificity in the introductory
2 section as well as more detail in the later sections
3 if we just address one disorder at a time. Although
4 obviously there will be plenty of cutting and pasting
5 to be done.

6 In addition we hoped that this would let
7 us shorten the time needed to finalize the cocaine
8 guidelines, because we consider this text separately
9 from the rest of it, and we really feel there is an
10 urgent need to get this out to people who would like
11 to use it. On the other hand I know that this might
12 be an area of concern because there are plenty of
13 people who think that addiction is a disease and
14 general approaches are appropriate. So we'd like your
15 input on this.

16 Next slide. So the points for discussion
17 include the four I've identified here, because the
18 guidance document when complete will identify
19 indications appropriate for the drugs that will guide
20 sponsors in planning the studies necessary for drug
21 development. It will help both commercial sponsors
22 and academic researchers understand FDA's current
23 thinking on clinical trial design and outcome measures
24 in cocaine treatment research. However, we need to
25 get a clearer picture of the state of the art for each

1 of these matters before we can produce a helpful
2 guidance document.

3 This morning we began our discussion with
4 a topic of indications for medications treatments, and
5 we addressed some issues of outcome measures, but this
6 is a topic that needs further exploration. We've also
7 touched on some aspects of trial design.

8 I want to mention some specific things
9 that I've heard said this morning that I would like to
10 ask you to respond to directly. They're not on a
11 slide or on a hand-out sheet. I heard Dr. Wright say
12 that outcome should be measured at the level of the
13 individual patient. I haven't heard anyone dispute
14 that. I'd just like to clarify that the committee
15 endorses that view.

16 We heard some discussion that measurement
17 of the amount of use per occasion either by
18 benzoylecgonine or self-report is fraught with
19 complexity. And that the measurement of the amount of
20 use per occasion may be of questionable clinical
21 utility. I'd like to hear some response to that.

22 I heard that the duration of studies
23 should be sufficient to capture changes in use, but
24 not so long as to deter interest in development,
25 although long term data should be collected. So some

1 guidance as to the length of the study would be
2 helpful.

3 I would also like to solicit any further
4 comments you have on the various issues and
5 particularly as they relate to our draft guidance
6 document. And to broaden our focus to the spectrum of
7 the drug development process which may address some of
8 the concerns raised this morning about the necessity
9 of marching through, in an orderly fashion,
10 establishing the potential utility of a compound.
11 Those are outlined in the generic development plan,
12 the revised one that I handed out today.

13 Next slide. So this is the question, what
14 suggestions do you have for our draft guidance
15 industry? And I indulge myself in one clip art , with
16 apologies to Dr. Kramer who thinks that clip art makes
17 us look like people with too much time on our hands,
18 but I don't know if I have to tell you what this guy
19 is doing, but just please help us to avoid reinventing
20 the wheel.

21 CHAIRMAN STRAIN: Thank you, Dr. Winchell.

22 So Dr. Winchell has presented us with some
23 specific, somewhat specific, questions that may be
24 useful for at least starting our discussion. I heard
25 her ask about whether we endorsed the idea of out come

1 measures at the level of the individual patient, that
2 how to look at the amount of use to occasion, and is
3 this a useful outcome measure, as well the duration of
4 studies, and the issues regarding long terms data
5 acquisition. And then a more general question about
6 guidance for their guidance as it were.

7 Maybe we could begin at least, because
8 perhaps this could be easy to knock off, with getting
9 a sense of the committee, whether Dr. Wright's
10 statement about outcomes measure being measured at the
11 level of the individual patient is something that we
12 do consider to be important or not.

13 Dr. de Wit?

14 DR. de WIT: Could we get a little
15 clarification on that?

16 CHAIRMAN STRAIN: Yes.

17 DR. de WIT: Is it that you don't want a--
18 just clarify?

19 DR. WRIGHT: That in the evaluation of the
20 outcome of the -- I'll try to tone it down, in the
21 evaluation of the outcome of the trial, it should be
22 possible to determine how many patients as individuals
23 improved their clinical outcome as a result of the
24 treatment. That's always necessary in a controlled
25 clinical trial done for the FDA.

1 But it specifically suggests that
2 aggregate measures of how this group used ten percent
3 less cocaine than that group wouldn't be convincing by
4 themselves unless you could show that that represented
5 ten percent of the patients who really used a whole
6 lot less cocaine, or they have ten percent less
7 episodes in which they were out in a shooting gallery,
8 or some other individual patient clinical outcome
9 rather than we studied two group, this group had a
10 little bit different use than that group, that's
11 success.

12 DR. de WIT: I'd certainly be in support
13 of that. I'm not sure exactly how to articulate it in
14 a direction study, the nature of the outcome as you
15 say. You don't to group together, quantity and
16 frequency for different individuals basically.

17 CHAIRMAN STRAIN: Dr. Khuri?

18 DR. KHURI: I heartily endorse Dr.
19 Wright's statement. As a clinician of course I
20 scarcely can understand any other way of doing it, but
21 I know that there do exist other ways. But that's
22 what our research is all about, how to improve a
23 treatment, research of all kinds, how to improve the
24 outcomes of the individual patient regarding their
25 drug use.

1 A question that hasn't been raised, which
2 sort of is related to the second question of amount
3 and quantity and qualitative versus quantitative is
4 the whole issue of binge pattern use of cocaine. As
5 everybody who has worked with cocaine addicts knows,
6 the most common form of use is a binge pattern, and
7 that is repeated use within a limited period of time
8 to almost to collapse. I mean you could use 20, 30
9 times within a time period of less than 24 hours, is
10 that counted as one use as compared to someone who is
11 using it three times a week, but in a \$10.00, \$20.00
12 bag amount, a single administration.

13 It's just something we should consider.
14 I'm not sure how we measure it because we've already
15 cast some doubt on our quantitative measures and
16 whether quantitative BEs would capture that. So it's
17 really in the form of a question as well as a comment,
18 but it certainly is the most usual form of cocaine
19 use. You could have one binge a month where you
20 consume much more cocaine than someone who used
21 regularly three times a week.

22 CHAIRMAN STRAIN: Dr. Lloyd?

23 DR. LLOYD: As a non clinician, the
24 thought occurred to me, and this is directed to Dr.
25 Khuri, is the term "episode" applicable rather than

1 use, is that a term --

2 DR. KHURI: It could be a cocaine episode,
3 could be. But we have to define our terms and agree
4 on it across the board, across the field. An episode
5 could be a binge, sort of a lost weekend, except that
6 interestingly enough it's not a weekend, it's usually
7 period of time because the patient, the person
8 collapses, just crashes or whatever. But it could be
9 a cocaine episode in which a great deal of cocaine is
10 used.

11 CHAIRMAN STRAIN: Dr. Simpson?

12 DR. SIMPSON: The situation you're
13 describing seems to me in some ways similar to, you
14 know, alcohol patterns when you're looking for example
15 at the effect on the fetus, you know, the maternal
16 fetal alcohol syndrome. There are some people who
17 would say that the binge is what is the crucial thing,
18 others would say the amount, if it exceeds a certain
19 amount, and so on. And I guess that that's something,
20 I mean that's something that addresses the outcomes,
21 and maybe initially at least, information should be
22 collected on all of those. It seems to me you are
23 limited to self-report probably just as you are with
24 alcohol studies, with all the attendant problems.

25 CHAIRMAN STRAIN: Let me throw something

1 out on this point, which is an assumption I think
2 that's been made that we as a committee may want to
3 consider rethinking. The assumption is that we would
4 be willing to look at a medication that decreased use,
5 but didn't result in total abstinence. If we said we
6 could argue conversely for a moment that we would only
7 be interested in seeing medication that produced
8 abstinence, in which case whether patterns of use or
9 amounts varied doesn't matter. I mean it doesn't
10 matter of they cut back by 50 percent, they're still
11 using.

12 So maybe need to stop for a moment and
13 consider where we've fallen. Are we agreeing that a
14 relative decrease in use by a medication is an
15 acceptable goal, in which case then we've got to get
16 to the issue of whether we've gotten -- what kind of
17 outcome measures would be sufficiently sensitive to
18 detect that.

19 DR. KHURI: I would heartily endorse such
20 a question for such a medication, if you use cocaine
21 one in some way, you lost your craving for the second,
22 fifth and tenth use would be counted as one use, but
23 not 20 consecutive other intravenous administrations
24 or crack uses or whatever form the cocaine was, and
25 yet it's not total abstinence.

1 CHAIRMAN STRAIN: Well, but if we think of
2 the smoking cessation idea for a moment, what if we've
3 got a medication that we say somebody starts on for
4 the first two weeks, you know, all right there may be
5 some sampling of cocaine while they're stabilizing on
6 the medication, but then we're going to look as a
7 committee at weeks three through six and we'll define
8 abstinence as no cocaine use during that four week
9 period of time as the primary outcome measure. I'm
10 just saying it because it's something we're very
11 familiar with.

12 So, yes, there might be a medication where
13 somebody tries cocaine once during those first couple
14 of weeks as nothing happened, doesn't use it ever
15 again.

16 DR. KHURI: Or something happened but they
17 got turned off for further administration, and maybe
18 used once instead of 20 times the next three to six
19 weeks. But I don't like the idea of lumping that as
20 a failure because they use once or twice, whereas
21 before they'd use 30 to 60 times.

22 CHAIRMAN STRAIN: That's my question. So
23 would we say somebody who between weeks three and six
24 uses once a week as opposed to previously using three
25 times a day, do we want to consider that as a possible

1 effective medication?

2 DR. KHURI: I would say yes, but I may
3 have people who disagree.

4 DR. JARVIK: I have a feeling that we may
5 be losing something by having a very stringent
6 criterion, like a four week criterion for smoking.
7 With smoking you can get away with it because people
8 generally don't smoke in binges, but cocaine, the fact
9 that the pattern of use is so irregular means that
10 we're more likely to miss something by having a very
11 stringent criterion.

12 DR. KHURI: And add to that we don't have
13 such a stringent criterion for either alcohol or
14 opiate -- I think nicotine is the only one that we
15 have as total abstinence for four weeks. And given
16 that we don't have any effective treatments for
17 cocaine right now that would be, it would be working
18 against ourselves to start out with -- I would agree
19 with any reduction in use, substantial reduction in
20 use --

21 DR. YOUNG: I think it would be important
22 to have the data collected in a way so that you could
23 speak to the reduction in use by each individual in a
24 trail rather than taking an aggregate number of
25 reduction and use and dividing it by the number of

1 patients and coming up with some reduction because
2 that gets you right back to the problem that you don't
3 know if a small number of patients stopped their use
4 enormously, whereas the goal might be to have each
5 patient showing some criterion level of drop of use,
6 drop in use.

7 But I think the discussion suggests that
8 it's way premature to decide what that criterion level
9 would need. The data are going to have to be
10 collected in a way that you can go back and
11 reconstruct the criterion. So I am endorsing Curtis'
12 discussion, having the data available at the level of
13 the individual patient even if you go to a reduction
14 in use rather than an abstinence.

15 DR. WRIGHT: Here is the trouble we have,
16 and it's a problem of the agency's own making and in
17 a structure of clinical research. We tell people that
18 they need to have a priori hypothesis, a data
19 collection plan, a protocol, an analytical plan, and
20 if they have all those things lined up and they do
21 their study, they roll the dice, they get a result,
22 and if it's okay, it's okay.

23 Then we have an advisory committee where
24 we sit and tell them well, I'm not sure what the
25 outcome is as it should be, what do you think, Newt?

1 And we struggle and wrestle because we don't have what
2 we need, which is one good successful drug. But then
3 there is the question of how do you get that first
4 successful drug.

5 So, you know, the one concept is to ensure
6 that you're thinking in terms of your criterion in
7 terms of individual patients so that you can do the
8 kind of analysis that you just discussed. And the
9 other is to make sure that you don't set up your
10 selection and entry criteria so that you're biased
11 against yourself.

12 I haven't heard much discussion since I
13 last spoke of it about high risk behavior. I saw it
14 in one NIDA slide, and I heard it mentioned once, but
15 the problem with law enforcement data is that you
16 drive (x) number of times before you get the DWI, and
17 you break into (y) number of houses before you
18 actually get arrested or shot by an irate homeowner,
19 and yet we know that in our clinical trials in this
20 area we see significant mortality in the longer run
21 trials. Certainly you would see it in an open labeled
22 extension.

23 What kind of high risk behavior are we
24 concerned about with cocaine addicts? What do we
25 worry about for them? Is it sort of the generic I use

1 paraneural drugs problems? Is it being in the wrong
2 place at the wrong time? Is it dealing in
3 criminality? What kills these people?

4 DR. KHURI: Well, it's the things that you
5 mentioned, plus it's cardiovascular accidents. It's
6 heart attacks, strokes, particularly in young men in
7 their 30s or 40s as well as the other behaviors.
8 There's a constant risk of death aside from the use of
9 -- with any form of cocaine, I'm not talking about
10 dirty needles, it's a dangerous behavior and it does
11 kill. And certainly a binge, I believe, is, I don't
12 know if there are good studies on this though, a binge
13 is more likely to kill, I would believe, than a single
14 use. But it not be true if you're a 58 year old
15 overweight male, I don't know.

16 CHAIRMAN STRAIN: Dr. Simpson?

17 DR. SIMPSON: I think that, if you were to
18 go with reduction, you would also have to look at the
19 other behaviors. For example, if they are drug
20 addicts and they're also alcoholics, if you reduce
21 their cocaine intake but the alcohol intake went up,
22 so you would have the problem that, if you just look
23 for a reduction in cocaine, you would have to look at
24 their other behaviors, wouldn't you? I mean I'm not
25 the clinician, but I would have thought that that

1 would be the case.

2 Also, to address the other point about the
3 four weeks, I just wanted to reiterate that the
4 problem, if you have a longer term study, you're going
5 to have more drop-outs for one thing. You're also
6 going to be limited in a sense that, almost in a
7 sense, that you have to have an active drug as an
8 alternative, the longer the trial, if you want to keep
9 patients, I would think again, so that you have to
10 balance those two. And I guess that the expense then
11 also is another issue if you're trying to get the
12 pharmaceutical companies to sponsor these drug trials.

13 CHAIRMAN STRAIN: Let me intervene again.
14 I think that what Curtis and Dr. Simpson and Dr. Khuri
15 are all skating around perhaps is an issue regarding
16 primary versus secondary outcome measures. And that
17 certainly there are secondary outcome measures that
18 are important such as associated drug use, morbidity
19 and mortality, you know, high risk behavior,
20 cardiovascular morbidity or mortality. But I suspect
21 for our purposes what we need to consider is what's
22 number one, and we can have a few number ones that we
23 in our minds think of as primary outcome measures.
24 And then what are the number twos, what are the
25 secondary outcome measures? And it would seem to me

1 that we want a medication that decreases cocaine use.

2 I mean it would be great if associated
3 with that there is decreased risk of cardiovascular
4 events or medical morbidity in general, increased pro
5 social behavior, you know, whiter teeth, fresher
6 breath, and so on. But I think ultimately what I'd
7 like to throw at least to the committee is that what
8 we want is to decrease cocaine use.

9 DR. KHURI: Are we not all agreed on that?

10 CHAIRMAN STRAIN: Yes. Well --

11 DR. KHURI: For starters?

12 CHAIRMAN STRAIN: -- but do we want to
13 consider other things as primary outcome measures?
14 And maybe Dr. Simpson's point just now is the most
15 appropriate, do we want to say that we don't want,
16 that we're not going to endorse a medication that
17 decreases cocaine use, but decreases it in the context
18 of increased alcohol use. Or would we say decrease
19 cocaine use, that's fine, we're not going to worry
20 about these other things because we've got other
21 interventions. If alcohol use does go up, we've got
22 other ways that we can manage that, you know, but them
23 on Antibus or naltrexone or whatever. And I don't
24 know what this means --

25 DR. KHURI: Well, they are separate

1 conditions. I think we're here to discuss cocaine
2 medications. We have to focus on cocaine use
3 outcomes, just as in the early days of methadone
4 research, the focus was on heroin use. We didn't have
5 cocaine then, but now it's well known that all
6 methadone patients or all clinics, I won't say all
7 patients, are plagued by this epidemic of cocaine, as
8 well as a fairly consistent 30 percent at least
9 steady, serious alcoholism problem. And methadone
10 scarcely touches those.

11 I've alluded to, I believe, it does touch
12 the cocaine, but less the alcohol. But you have to
13 focus on a single variable I think, and it should be
14 cocaine in this case, cocaine use or diminishment of
15 use.

16 CHAIRMAN STRAIN: So let me, so if a
17 medication came to us that decreased cocaine use, but
18 there was a consistent increase in alcohol use by
19 patients in the pivotal studies, would you say that's
20 okay?

21 DR. KHURI: Yes. People said at the
22 beginning of methadone maintenance, oh everybody is
23 turning to alcohol, it's increased alcohol use to get
24 the high. There may be temporarily in some patients
25 exactly that, or turning to cocaine to get the high.

1 But it doesn't, for me, diminish the effectiveness of
2 methadone for that use. That's the way I'd answer
3 that.

4 CHAIRMAN STRAIN: Yes.

5 DR. KHURI: But I wouldn't want to turn
6 everybody 100 percent into alcoholics, but I can't
7 conceive of such medicine, but it might exist.

8 CHAIRMAN STRAIN: Dr. Andorn?

9 DR. ANDORN: I have a question. In the
10 guidance can you list the primary outcome, is it okay
11 for you to list it that way and then sort of a Chinese
12 menu of secondary outcomes that can be evaluated and
13 also can be entertained as part of the review of the
14 drug, or is that too loose a guidance?

15 DR. WRIGHT: We can write guidance in
16 complexity ranging from simple to Byzantine. And in
17 fact even if we try to write one that's simple, we may
18 end up with one that's Byzantine.

19 But I think you need to wrestle, or at
20 least I would hope that you would wrestle a little bit
21 with the question of is it really, what are you saying
22 when you say cocaine use. If you're saying cocaine
23 use is a pretty good surrogate for high risk behavior,
24 if you're saying cocaine use is a pretty good
25 surrogate for illicit activities, and you say cocaine

1 use is a pretty, you know, if you think that's why,
2 that because this is an illegal drug, because this is
3 a drug that you don't obtain through a safe mechanism,
4 because this is a drug that costs a lot of money or
5 can cost a lot of money especially in a binge pattern,
6 that you've already got your surrogate for all of the
7 other dimensions of this person's life. I think you
8 need to say that explicitly.

9 In many areas of substance abuse, the use
10 of the substance is not what distresses the individual
11 and the family and the culture, it's the behavior
12 consequences of the substance use that tears the place
13 up. We let people drink all day long, and in most
14 places even on Sunday, but we sure don't like people
15 displaying alcoholic behavior. So it's important to
16 recognize that from our perspective with some of our
17 drugs, you know, it's illegal, it's dangerous to get,
18 it's expensive, it chews up your life, you get
19 yourself in the wrong part of town at the wrong time
20 of night, and the drug use itself is a good surrogate
21 for that, for all of those risk behaviors and all of
22 those social harms. For others you go down to the
23 lobby.

24 CHAIRMAN STRAIN: Dr. Young?

25 DR. YOUNG: Well, Dr. Wright just made the

1 main point I wanted to make. Let me raise, coming to
2 a more concrete example or an alternate example of
3 switching from one drug to another. It is the example
4 of if had an opiate treatment product, at what point
5 do you consider the problems with alcohol, increases
6 in alcohol use as a indication that you may have a
7 treatment development product problem.

8 But it seems to me that there is at least
9 one suggested cocaine product, treatment product, the
10 one that attacks the enzyme system, where you might
11 predict that what the patient might do is shift over
12 to another stimulant very quickly, and so move from a
13 cocaine use pattern to a meth, methamphetamine use
14 pattern or a -- pattern or a methamphetamine use
15 pattern, and I wonder if there is any difference if
16 the increased drug use is increased drug use within
17 the same class or increased drug use of a similarly
18 illicit substance, would that change the thinking
19 about the importance of changes in other drug use
20 patterns as outcome variables?

21 DR. de WIT: Can't we look at other drug
22 use as another adverse effect or side effect and
23 consider it in a separate category and look at the
24 severity of that adverse effect or side effect and
25 keep that separate from our primary goal of looking at

1 a reduction in the drug that we're interested in. It
2 would seem to me that's more like a risk or it's like
3 that toxicity, it's like another event --

4 DR. YOUNG: But isn't it important to know
5 what type of drug it is that captures the behavioral
6 repertoire? I mean if in fact you had an antibody or
7 some way that you were changing the activity of the
8 enzyme that degrades cocaine, or you developed a
9 cocaine vaccine for example, would it be of one type
10 of concern if the population was simply shifting to
11 another rapid onset CNS stimulant versus moving to a
12 different kind of drug class? I mean would you want
13 to separate the type of drug use?

14 DR. de WIT: It seems to me it's kind of
15 hypothetical at this point. We don't have that many
16 other fast onsets.

17 CHAIRMAN STRAIN: Dr. Jarvik?

18 DR. JARVIK: I just want to say something
19 about that. We don't have to necessarily assume that
20 there will be compensation, but as a hydraulic model
21 where one goes down and the other one is going to go
22 up. As a matter of fact Steve Shote who I work with
23 is giving a paper to the CPDD on a little study that
24 he did with cocaine use in methadone treated patients
25 who were treated for cigarette smoking, and he's going

1 to report that those who reduced their cigarette
2 smoking also reduced their cocaine intake. So
3 sometimes it goes -- and maybe that's an aura effect
4 of some kind.

5 CHAIRMAN STRAIN: Dr. Simpson?

6 DR. SIMPSON: I was just going to say I
7 think that the way of treating the perhaps increase,
8 or perhaps other use or whatever as an adverse event
9 would deal with that, because that deals with the
10 risk, you know, the benefit risk ratio of approving a
11 drug. And so, if you have a severe adverse event that
12 everybody who is using cocaine now uses heroin, then
13 you wouldn't approve the drug. So I think that that
14 would deal with it, if you dealt with it that way.

15 CHAIRMAN STRAIN: Good.

16 DR. ANDORN: I would endorse that as an
17 adverse event. The only thing is you have to make
18 sure that you ask specifically about it, you can
19 design a study in which adverse events are simply
20 spontaneously reported versus solicited, and I think
21 we would have to make a recommendation that other drug
22 use has to be an elicited questionnaire adverse event
23 type questionnaire.

24 CHAIRMAN STRAIN: Dr. Khuri?

25 DR. KHURI: Yes, Dr. Andorn just said much

1 of my remark. It's important that these events be
2 noted and the questions asked, that's the important
3 thing. I've already reported earlier today on the
4 fact that cocaine use does diminish automatically in
5 a good methadone program. And there is that aura
6 effect, it isn't a, I love the word "hydraulic model"
7 that one goes down per force, all junkies have to use
8 something, and the other goes up. But I'm always
9 reminded our patients are not like Dr. Holstead who
10 operated regularly and well on morphine/heroin
11 stabilized in medical fashion and sterile fashion and
12 was supposedly cured by putting him on cocaine, except
13 that he wasn't. But that's not the model we want.

14 CHAIRMAN STRAIN: We have -- oh, Dr. de
15 Wit?

16 DR. de WIT: I would just like to get back
17 to Dr. Wright's question, risky behaviors or the
18 consequences of the cocaine use, whether that should
19 be our dependent measure or whether it should be the
20 use of the drug. It seems to me that the high risk
21 behaviors are very difficult to measure and quantify
22 and identify, and they're going to be very variable,
23 so just from the point of view of manageability that
24 the drug use itself would seem to me to be our best
25 indicator, our best target behavior.

1 There was another point that you brought
2 up, I thought that we probably aren't so interested in
3 targeting any use of the cocaine because it's an
4 illegal drug, but rather we'll be targeting people who
5 are seeking treatment, for whom the problem of the use
6 has been identified, so I'm not sure that we have to
7 focus our efforts on any drug use and treatment of any
8 drug use at this point.

9 DR. SIMPSON: I guess I'd like to point
10 out that if we are talking about decrease of cocaine
11 use, that is not actually a very rigorously defined
12 thing yet.

13 And I also wanted to say there are some
14 situations now where the idea of having more than one
15 primary outcome and analyzing it as multiple primary
16 outcomes is a possibility and it's something to
17 consider. The pros for that is that in this case you
18 could use definitions for decreased cocaine use. The
19 pro is that you could use several related outcome
20 measures if you can't decide which one is best. The
21 con is that, if you do get a significant result, you
22 don't know really what is significant. So I just
23 wanted to throw that out.

24 CHAIRMAN STRAIN: Thank you.

25 I want to go back to Dr. de Wit's comments

1 just a moment ago, because I think she did respond
2 directly -- you read my mind, I was going to bring up
3 Curtis' question.

4 And I wonder if the committee agrees with
5 what Dr. de Wit said and whether we then responded to
6 Curtis' question on this point, do you want to hear
7 Dr. de Wit's comment again?

8 DR. KHURI: Yes.

9 CHAIRMAN STRAIN: Okay, can you do it
10 again?

11 DR. de WIT: I'm not sure I understand
12 Curtis' point earlier, but I took it to mean that you
13 were interested in identifying the consequences of
14 abuse as a target for outcome.

15 DR. WRIGHT: I'll tell you what, why don't
16 I sharpen up my comment --

17 DR. de WIT: Okay.

18 DR. WRIGHT: -- and you could sharpen up
19 your comment, and then the rest of the committee can
20 discuss it. My comment is not terribly sophisticated.
21 It is based on a belief that if, that what the
22 expectation of effective treatment for cocaine
23 dependency would be by the general public are that
24 people use less cocaine, hopefully use no cocaine, and
25 stop living like addicts. So their morbidity goes

1 down, the mortality goes down and they're engaging in
2 high risk behavior that leads to A and B should also
3 go down. High risk behavior occurs more frequently
4 than high risk behavior consequences. And you can ask
5 people about high risk behavior, and we do on the ASI.

6 But I haven't yet seen a protocol come
7 through that asks questions like how frequently, how
8 many times last week did you have sex for money, you
9 know, how many times last week were you breaking and
10 entering. I think that's because we're dignified
11 people and don't want to ask questions that might
12 embarrass our clients. But in a number of clinics
13 we're dealing with people who are engaging in very
14 high risk behavior that's very destructive to them and
15 destructive to other people, and I think one of the
16 reasons for the stigma that we struggle with in
17 treating our patients is they're doing stuff that the
18 rest of society doesn't think very much of. And if
19 treatment is to be successful, the rest of the culture
20 is going to want to see our patients not doing that no
21 more. And I think we're foolish if we don't face that
22 fearlessly and decide how important that is.

23 DR. de WIT: I appreciate your point, but
24 I don't think there is a perfect relationship between
25 drug use and all those risky behaviors that you've

1 noted. So it's going to be enormously difficult to
2 use that as an outcome measure for decreased -- I mean
3 I think our only, the only feasible measure for us is
4 decreasing the drug use and then if we think there is
5 a strong link to drug use and the other behaviors,
6 than those will by definition go down.

7 CHAIRMAN STRAIN: Dr. Winchell?

8 DR. WINCHELL: I hear the committee
9 endorsing the primacy of documenting a reduction of
10 cocaine use as an outcome. Would anyone venture to
11 offer an opinion on the following: How much reduction
12 should be a criterion for success?

13 CHAIRMAN STRAIN: Can I interrupt you
14 there? So does the committee -- can we put closure to
15 this point, Curtis' point, because you're moving into
16 new territory now, so Curtis' point, Dr. de Wit's
17 response, does the committee in general endorse this?

18 DR. KHURI: I agree absolutely.

19 CHAIRMAN STRAIN: Okay, great.

20 DR. KHURI: And you could include chest
21 pain, but that usually motivates people to stop.

22 CHAIRMAN STRAIN: Okay. New territory, go
23 ahead.

24 DR. WINCHELL: So that we may
25 operationalize the committee's wish that we focus on

1 finding drugs that would reduce cocaine use. I'd like
2 to be able to translate this into choice of concrete
3 outcome. We heard this morning the pros and cons of
4 categorical outcomes, success versus failure, and
5 there are certainly other options available. But I
6 would like someone to take the bull by the horns and
7 just say what is your opinion, how much should people
8 reduce their use, and should it be a reduction in
9 occasions of use, amount of use per occasion? Just
10 tossing it out there once again.

11 CHAIRMAN STRAIN: Dr. Jarvik?

12 DR. JARVIK: Well, we have to have some
13 means of measuring cocaine use, and we can do it by
14 report, by verbal report, but what about
15 benzoylecgonine in urine, I mean that's a very
16 objective measure, but we have to be able to get the
17 urine. And I don't know quite how much we would
18 decide we need to reduce it by, but presumably we
19 start out with a certain level of this metabolite, you
20 could even say over four weeks, and then we want it to
21 be reduced perhaps to zero. But is this something for
22 us to discuss, I think?

23 DR. de WIT: Could we get a comment from
24 Dr. Bridge on a possible outcome criteria?

25 DR. BRIDGE: I'd be happy to respond and

1 suggest here, I think we have declined, if you will,
2 implicitly a requirement -- that we have hunted after
3 discussions with investigators and clinicians in the
4 field with regard to definitions of magnitude of
5 quantitative reductions -- clinical consequence. So
6 that the preference for the clinical really suggested
7 preference with the quantitative measure really based
8 on the apparent sensitivity of that particular
9 approach versus the categorical with regard to the
10 magnitude of resources necessary -- to detect a signal
11 and --.

12 I think that at some point there's going
13 to have to be consideration of whether or not a
14 reduction of 10,000 nanograms per ml, for example in
15 a sample of individuals who on average across an
16 interview period used 40,000 nanograms per ml
17 equivalence -- detected in urine, and the
18 consequential change for a sample. Would you
19 characterize that for the series of parameters
20 thereafter, to wit those in a sample, 10 would be
21 placebo -- showed reduction of use to abstinence,
22 whereas 15 in the treatment are -- I mean they all we
23 suggest would probably fit together. But in terms of
24 the -- statistically at this point, that is the target
25 knowledge we don't have, although we have attempted in

1 consideration -- structure reductions of 25 percent,
2 or consequential there is simply not that level of
3 knowledge available that we have detected.

4 CHAIRMAN STRAIN: Dr. Lloyd?

5 DR. LLOYD: Have we agreed or are we not
6 going to agree on what the ultimate goal is? It seems
7 to me like we've got a starting point which is not
8 fixed, because if we use the BE levels, they're going
9 to vary. So we've got a starting point that's
10 variable, but we've got an end point, if we could
11 agree on it, we've got an end point that's fixed, then
12 we can come up with a percentage that's acceptable.

13 DR. WINCHELL: I just want to clarify, I
14 mean even though there's variables, certain points of
15 variable ending points, let me make sure that we're
16 talking about the same thing. If I use \$100.00 worth
17 of cocaine a day and I enter your trial, if at the end
18 the trial I'm using \$75.00 worth of cocaine, a 25
19 percent reduction in my cocaine use, do you care? You
20 don't think I'm a success? That's what we're talking
21 about. So these are the specific questions.

22 DR. LLOYD: The market price hasn't
23 changed?

24 DR. WINCHELL: Well, the market price may
25 have changed, but also, you know, if I had 10,000

1 nannograms per ml. of benzoylecgonine a day and now I
2 only have 7,500 --

3 DR. ANDORN: Can I maybe turn that
4 question around and give it to the clinicians who deal
5 with cocaine dependent patients all the time, what do
6 your patients measure as success? Anybody identifies
7 themselves as a problem, come in for treatment, what's
8 their measure?

9 DR. KHURI: they would certainly be proud
10 of themselves if there were a decline in use. I was
11 following Dr. Jarvik's remark, you have to have, and
12 also Dr. Wright, every person, look at every
13 individual patient and each patient has their own
14 baseline. I have patients that use \$200.00 a day of
15 cocaine, I have patients that use \$10.00 three times
16 a week, and they, if these two people want to come
17 into some kind of treatment, I would say the decline
18 in use, again we're looking then at the next question,
19 and I don't want to fully take up now, what is the
20 length of time of your trial. But you might get
21 someone indeed coming in and reducing 25 percent or 50
22 percent and be very proud of themselves. And I would
23 look at that as a good outcome, and hopefully
24 continuing, if that were true after four weeks, maybe
25 eight weeks even a further decline. But the person

1 using only \$30.00 a week, I would perhaps look toward
2 total abstinence for that patient as a clinition, or
3 going down to once a week at a party when they're mad
4 at their mother in law or something.

5 CHAIRMAN STRAIN: Well, it's their mother.

6 DR. KHURI: Yes. Just kidding.

7 CHAIRMAN STRAIN: Dr. Simpson?

8 DR. SIMPSON: I think the two examples you
9 gave would be examples where you wouldn't want to mix
10 those two people in the same study anyway, would you?

11 DR. KHURI: That's a question that we're
12 dealing with, that I was trying to get at this
13 morning, how do you select the patients.

14 DR. SIMPSON: Yes, if you divided them up,
15 then you could use different reduction criteria.

16 DR. KHURI: Yes, different patterns of
17 use. It gets back to the binge pattern, my \$10.00 a
18 day, \$10.20 maybe, three times a week would be in a
19 different pile than my binge user who used \$200-
20 \$300.00 on a weekend or within a few hours on the
21 weekend, less than 24.

22 CHAIRMAN STRAIN: Let me try --

23 DR. WRIGHT: Try?

24 CHAIRMAN STRAIN: -- try throwing out a
25 comments on this. First of all, before though let me

1 say this, what we've decided implicitly is that we're
2 assigning a priority to objective measures of cocaine
3 use rather than subjective measures of cocaine use.
4 That is that we're going to look at urine results for
5 BE for example rather than self-reports of drug use.
6 At least that's what I believe has been implicit in
7 the conversation.

8 And let me throw out, Celia, to get right
9 to, that we say that we want to see a 50 percent
10 reduction.

11 DR. LLOYD: In a time frame?

12 CHAIRMAN STRAIN: Pardon me?

13 DR. LLOYD: In a time frame?

14 CHAIRMAN STRAIN: Gee, I didn't think --

15 DR. WINCHELL: Yes, 50 percent reduction,
16 and a individual subject's weekly, mean
17 benzoylecgonine score, or 50 percent reduction in a
18 patient's monthly uses of cocaine?

19 CHAIRMAN STRAIN: Well, let me say this --

20 DR. WINCHELL: I'm backing you into a
21 corner.

22 CHAIRMAN STRAIN: -- well, yes. I think
23 one of the dilemmas we have is that the semi-
24 quantitative urine results is in its infancy and there
25 is insufficient experience I believe at this point by

1 the scientific community to know just, to fully
2 appreciate the parameters of using semi-qualitative
3 urine results. I mean Kensey Preston has done it at
4 NIKDA ARC, Steve Bodke has done some stuff out on the
5 West Coast, and I'm not sure, I mean I'm sure there
6 will be some stuff next week at CPDD on it, but I'm
7 not sure if there is really been that much use.

8 Dr. Bridge, has there?

9 DR. BRIDGE: Well --

10 CHAIRMAN STRAIN: Have we got a lot of
11 experience with it yet?

12 DR. BRIDGE: At this point we've had two
13 trials completely -- quantitative -- it really is not
14 a consequential add-on to the studies -- I think that
15 Steve Bodke is the one -- brought this to our
16 attention -- that too -- move forward, but it is
17 consistent -- again that the practice exists across a
18 number of other medical -- urine toxicology --
19 something that is a objective and reasonably
20 continuous variables, and this is.

21 DR. ANDORN: Can I ask a question of our
22 FDA folks, since analgesics are also in this category?
23 Are you still using sort of Dr. Schraeder's scale, 0
24 to 10, how's your pain relief been on this particular,
25 is that still a standard that's used for analgesic,

1 could that be a standard that could be applied in this
2 case in some way, letting each patient serve as his or
3 her own control?

4 DR. WRIGHT: There are answers, sure, but
5 part of the overhead of science was validating those
6 scores showing that you could send two different
7 nurses in and ask the question and get a similar VAS
8 pain rating scale.

9 You know, part of, the part of this that's
10 hard is not the math and the statistics, although we
11 can make them hard, if we try, the part that's hard is
12 the quantitative valuation of clinical outcomes that
13 everybody has shown a remarkable reluctance except for
14 our intrepid chairman to step into. If somebody, to
15 use the analogy, who is smoking two packs of
16 cigarettes a day, cuts down to one pack of cigarettes
17 a day, is that clinically meaningful at all. If they
18 cut down to a few cigarettes a day, is that a major
19 accomplishment. And if they're completely abstinent,
20 does that have additional prognostic value. Well --

21 DR. ANDORN: That's what I was getting at
22 with the ruler that then, if we set a point of 50
23 percent reduction, it becomes easier to quantify than
24 using all these qualify of life outcome measures that
25 really add to the cost of the study and may not give

1 us the information we need.

2 DR. WRIGHT: The other question I have is
3 that you're going to have to decide, give us some clue
4 for cocaine, you know, how much reduction would
5 represent a good clinical outcome? You'd be happy,
6 you'd go home happy that day when you saw that
7 patient, how much would be a real good clinical
8 outcome and how long a period of abstinence? Because
9 with binge cocaine use patterns people will routinely
10 go until the next payday before they're using cocaine
11 again. What kind of matrix can we use here, and what
12 is the meaningful difference?

13 CHAIRMAN STRAIN: Dr. Khuri?

14 DR. KHURI: You know, it's hard, we're all
15 wrestling with this for good reason. I would go home
16 happy for a few weeks if my big binger cut 50 percent,
17 but I wouldn't be happy for the entire year, if he
18 just kept it up because he still could stroke out and
19 get arrested and all those other things, worrying
20 about him as a clinician.

21 But backing up a little, I really have a
22 lot of trouble using the BE objective measure because
23 we have to have a column for self-report. I mean you
24 can criticize it all you want, but my binger, because
25 it depends on when you get the urine, my binger could

1 binge Friday night and come in and get the urine
2 Monday afternoon and could have little significance,
3 it could have just faded out or even be zero depending
4 on how much he used, and his own metabolism, which is
5 also very individual, so that's another reason a
6 person has to be their own control. But I don't think
7 -- I think your comment was to the point, we don't
8 really have the technology and we're not following
9 them around 24 hours a day and they're not in a
10 clinical research center where we're observing all the
11 time.

12 CHAIRMAN STRAIN: Dr. Simpson?

13 DR. SIMPSON: I was just going to put it
14 that maybe coming up with one criteria, again, might
15 be appropriate. I mean for a study where you're
16 looking at binge cocaine addicts, you might want in a
17 month to have a 50 percent reduction, that would be
18 reasonable. For when you're looking at mildly
19 addicted, you have only 10, I don't know if that's the
20 right term for them, but he only uses a small amount
21 several times a week or whatever, you might expect
22 total abstinence, and so your criteria might be
23 different as long as you could justify it medically.
24 And it seems to me that that's what Dr. Khuri is
25 saying, is that, you know, given different illnesses

1 in a sense you want different outcome issues.

2 DR. WINCHELL: We're asking you to go out
3 on a limb, pick one group and tell us what you think
4 the outcome should be. It doesn't have to be the same
5 outcome for everybody.

6 DR. ANDORN: I think you're asking us to
7 do in 15 minutes what we were very uncomfortable
8 living with yesterday, and that's why you're seeing
9 some reluctance. Maybe this is going to take another
10 session.

11 DR. WRIGHT: Well, there's another way
12 out.

13 DR. ANDORN: But --

14 DR. WRIGHT: I'm sorry.

15 DR. ANDORN: Oh, sorry, go ahead.

16 DR. KHURI: Well, I thought Dr. Simpson
17 did lay it out fairly clearly, that you have an
18 outcome for the heavy user and another outcome for the
19 light user. But I might add sadly that the light user
20 would often use more if they had the money.

21 DR. WRIGHT: I mean one of the strategies
22 that's not a terribly, this is the strategy that will
23 drive the NIDA medications development group wild
24 because one of the strategies is to say that you
25 should define for a patient in your protocol what you

1 think as the researcher for this particular project
2 you think success is. Now, we've done that in some
3 pain studies where the technology was new and we
4 weren't really sure what dorsal column stimulators
5 injecting implanted cobra venom would actually
6 produce, so part of one strategy is to take a more
7 general strategy and to say, if you want to do this
8 research, you're going to have to come up with some
9 description of how much is enough and we'll respond to
10 that.

11 But that's a much harder regulatory
12 developmental problem than a fixed number no matter
13 how vague, which is why they quit for a month carried
14 the day back in 1986.

15 DR. YOUNG: It was my impression they quit
16 for a month carried the day because there was some
17 research literature that suggested that there were
18 agents that might get there.

19 DR. WRIGHT: No, the quit for a month
20 occurred in the context of an OTC advisory committee
21 which was trying to set up a standard to get worthless
22 products off the market.

23 DR. YOUNG: Okay.

24 DR. WRIGHT: And they said you ought to be
25 able to quit for a month, and that was it.

1 DR. YOUNG: I see what you mean.

2 CHAIRMAN STRAIN: Let me once again wander
3 into this dark cave. First of all, let me propose
4 that, but I agree with Dr. Khuri on the importance of
5 self-reports, I vitally agree with that, strongly
6 agree with it, and it worries me not to put self-
7 reports in there, so I'm heartened to hear you say
8 that.

9 It strikes me that in considering self-
10 reports, let's think about that for a moment, we want
11 to look at occasions of use. The reason I would
12 propose occasions of use is because we do have
13 something in the works, looks hopeful on the objective
14 side with new uses, which ties into occasions of use
15 nicely. There may be some way that we can at some
16 point be able to pull those two together. I'm just
17 thinking out loud almost, I mean so don't hold me to
18 this, don't hold my feet to the fire on this one.

19 What if we said that over a four week
20 period we want to look at the proportion of patients
21 who have a reduction of at least 50 percent in their
22 occasions of use by self-report as one possibility.
23 And then kind of, in correlation with that, or we
24 could make it conjunctive, we could say "and they have
25 a 50 percent reduction in urine positives for

1 cocaine."

2 DR. de WIT: Number of urine qualitative
3 positives.

4 CHAIRMAN STRAIN: Qualitative positives.
5 I'm just a little leery of the BE levels right now
6 just because I don't -- I mean I know that there's --
7 I mean we're doing it in our clinical trail, but
8 there's not a lot out there in the published peer
9 review literature, and there may be something in a
10 year or two, we're saying okay this is, we need --

11 DR. WINCHELL: We could in the future
12 replace that with a well-developed --

13 CHAIRMAN STRAIN: Right.

14 DR. WINCHELL: -- new use rule that --

15 CHAIRMAN STRAIN: Right, right.

16 DR. WINCHELL: -- to these.

17 CHAIRMAN STRAIN: Right.

18 DR. WINCHELL: Do people think -- I'd like
19 to hear the committee's response to that suggestion,
20 and particularly the duration, is four weeks long
21 enough to capture a change in use in a typical use
22 pattern of your cocaine addict?

23 CHAIRMAN STRAIN: Yes.

24 DR. KHURI: I would say a little longer,
25 six to eight.

1 DR. WINCHELL: I think Dr. Bridge's trials
2 are generally 12 weeks.

3 DR. KHURI: Well, that's even better, but
4 trying to be parcamoneous. Dr. Bridge would love us
5 to tell him to stop after four weeks, but I like 12
6 better.

7 DR. BRIDGE: Let me say that
8 hypothetically we considered something that
9 characterized a binge episode as being in the range of
10 three to seven days under typical kinds of portrayals
11 and who wanted to lead the opportunity for certainly
12 more than one of those episodes, perhaps multiple
13 episodes.

14 When we look at the data we have so far,
15 and looking at the placebo conditions in specific, the
16 presence of episodic cocaine use just has not emerged.
17 These folks are on it, they use it, and they stay on
18 it. We're not talking about people who are duly
19 dependent, we're talking about people who are primary
20 cocaine users. So while, you know, I have heard it
21 and everybody discusses it, but for whatever sets of
22 reasons, I can't give you any specific identifiers
23 for, we don't see episodic binges within these studies
24 -- often are on repeated, you know, multiple
25 assessments of positive urines three times a week,

1 week after week.

2 CHAIRMAN STRAIN: Dr. de Wit?

3 DR. de WIT: I guess I'm getting a little
4 bit confused about new use then. If you're saying
5 they use drugs all the time and you're definition of
6 new use is essentially pattern of use within a binge
7 or --

8 DR. BRIDGE: Well, I'm saying two things,
9 that it does cloud the issue. We're talking about the
10 new use, if applied to those criteria, and we have
11 done at this point one analysis of one study we're
12 looking at. We have to go back and do, but this is,
13 you know, presented as a direction that we're moving
14 in without any defense of it yet that is a solid point
15 for staking a claim of episode quantity.

16 The alternative comment simply is that
17 when we look at the data of urine benzoylecgonine
18 values independent, whether they go up or down, it's
19 that they up in a range of substantial use that it's
20 present sample after sample, you could still have
21 hypothetically somebody, you know, who starts on
22 Monday at 150K, gets to 140K on Wednesday, 120K on
23 Friday, etcetera and, you know, yes it may or may not
24 drift down by those rules, but it's still heavy use.

25 DR. de WIT: Okay, it might be --

1 DR. BRIDGE: Versus in a period where
2 it's--

3 DR. de WIT: Right. It might be useful
4 for us at some time if we reconsider is to get a
5 better look at the pattern of use based on your data
6 with the BE levels. I guess one concern I have about
7 using the criterion of number of occasions of use is
8 that there may be a treatment that decreases the
9 amount used and doesn't change the number of occasions
10 used and we would miss that. But I think we need a
11 little bit more information about how long the levels,
12 the BE levels, stay high and what the individual
13 variability is. Whether a person for example could
14 shift his or her use to a longer period before the
15 clinic visit in order to decrease their apparent
16 indicators of use.

17 So I think that if we could make a more
18 informed judgement about this with more information
19 about the BE levels, and it sounds like you're just
20 beginning, those are just beginning to be collected,
21 so chances are we can't make the best and most
22 informed decision based on what we know now.

23 DR. KHURI: I heartily agree. That's the
24 point I was trying to get at, and you put it well.
25 Also the question of someone who is using, and I

1 realize we can't use dollar amounts because they may
2 vary from one part of the country to the other, but in
3 New York we tend to use dollar amounts to measure use,
4 and we have someone who said gee, I used to use
5 \$1,000.00 a month in let's say four different
6 episodes, but now I'm using, well hypothetically, only
7 \$300.00 a month, but I'm using more often than four
8 times. Some drug could conceivably change a pattern
9 of use.

10 CHAIRMAN STRAIN: Dr. Wright?

11 DR. WRIGHT: Back into the corner, Mr.
12 Chairman.

13 I'd just like to sort of see a show of
14 hands from the committee as to how many people, all
15 other issues being equal, you know, appropriate
16 patients, right dose, right analysis, missing data
17 handled in an appropriate way, all that other stuff,
18 somebody comes forward with the drug where the
19 criteria for success for a patient is that the patient
20 has reduced their total cocaine use for the eight week
21 or 12 week trial period by half, how many of you think
22 that patient has had been successful in that trail?
23 Okay, thank you.

24 If somebody reduces the number of
25 occasions on which he goes out to buy cocaine, or she

1 goes out to buy cocaine by half, how many of you think
2 that patient has been successful?

3 CHAIRMAN STRAIN: Reduce --

4 DR. WRIGHT: The number of occasions that
5 they go out to buy. Somebody comes in and shows the
6 analytical results and does an integration of the
7 urinary benzoylecgonine and says this patient has used
8 half as much cocaine as they did at baseline
9 throughout the period of drug dosing, has that patient
10 been successful?

11 DR. KHURI: In four weeks again?

12 PROFESSOR WARREN: Eight weeks.

13 DR. KHURI: Eight weeks. Yes.

14 DR. WRIGHT: Okay.

15 So what I'm getting is that the kind of
16 magnitude for an individual that you would want to see
17 is at least half that much or more, it could not be a
18 ten percent drop, it wouldn't be a 15.8 percent drop,
19 it couldn't be a 32 percent drop, you want to see half
20 or better?

21 Would you differentially weight somebody
22 who became totally abstinent from somebody who cut
23 their use in half, would you declare one a partial
24 success and the other a complete success?

25 DR. KHURI: Yes.

1 DR. WRIGHT: Okay.

2 For the rest of it when you're comparing
3 two groups, if you're doing a patient by patient
4 categorical assessment of outcome by whatever
5 technique you're using, would ordinary chi square kind
6 of statistics or whatever is the appropriate analysis
7 for categorical outcome convince you if one group had
8 33 percent of the patients who were rated as partially
9 successful or completely successful in the eight week
10 period and the other group 27 percent were rated as,
11 a placebo group, 27 percent were rated as successful,
12 would that be convincing to you, assuming that it met
13 the appropriate, because that's the next step. You
14 know, once you've decided whether a patient is
15 successful or not, then you're going to have to decide
16 how much of a magnitude of a difference between the
17 groups is convincing to you.

18 DR. de WIT: I think it would
19 statistically -- I have to accept it.

20 DR. WRIGHT: So your clinical validity is
21 dependent upon the assignment of an appropriate
22 clinical state change for the individual patient,
23 that's where you put in your clinical validity as to
24 whether this person has been successful or not?

25 DR. KHURI: Yes. But that's also assuming

1 other things remain constant, that we're avoiding
2 here, namely the adverse effects, but also the
3 behavioral treatments, the relapse prevention, all
4 those other things. It's very important that they
5 remain constant --

6 DR. WRIGHT: Sure.

7 DR. KHURI: -- because they could -- also
8 a medication in one clinic might be more effective
9 than in another clinic without change of any other
10 variables. This is just one problem with the
11 research, it has to do with the nature of the clinic,
12 the milieu, the friendliness of the staff, the
13 support. I mean this is well know, I don't want to
14 stir that murkiness up again.

15 DR. WRIGHT: We have never been accused of
16 being overly generous on the matter of concomitant
17 variables and in our analysis of trials, so I don't
18 think you have to worry about that.

19 CHAIRMAN STRAIN: Let me -- I'm well aware
20 of the time because we have several members of the
21 committee who are going to need to shot out the door
22 here any moment. And I'm wondering if we could put
23 closure to this, or if perhaps you put closure to it
24 with questions that you have posed to us, Curtis?

25 DR. WRIGHT: Well, let me synthesize what

1 I heard.

2 CHAIRMAN STRAIN: Okay.

3 DR. WRIGHT: What I heard you say was that
4 because of the deficiencies of our state of knowledge,
5 it is not possible to define as a group with unanimity
6 today what constitutes an adequate magnitude of a
7 treatment effect in all --. That your suggestion, a
8 suggestion that's been raised most frequently is that
9 the individual conducting the trial or the sponsor for
10 the trial sits down and figures out, using the outcome
11 measures that have been described centering around
12 cocaine use, what will be considered a clinical
13 success, either partial or whole, and what magnitude
14 of reduction is associated with each. That a
15 meaningful reduction, a partial response, is a
16 reduction of at least 50 percent in a meaningful
17 parameter of cocaine use. That you can't do a
18 categorical analysis by patient, and do ordinary
19 statistical tests on that. Did I get it right?

20 CHAIRMAN STRAIN: Yes.

21 DR. KHURI: Yes.

22 DR. ANDORN: The only thing I don't want
23 us to lose sight of is that open labeled the relapse
24 portion that we did feel was kind of left out for
25 nicotine and got us in the pickle we're in with some

1 of the nicotine products clinically.

2 DR. WRIGHT: Okay. Now, that's another
3 issue that I believe you are communicating you believe
4 this to be a chronic collapsing disorder.

5 DR. KHURI: Right.

6 DR. WRIGHT: Where extended duration of
7 treatment may be required. And the development
8 portfolio for the drug should include some evaluation
9 of the safety of chronic treatment?

10 CHAIRMAN STRAIN: Yes.

11 DR. ANDORN: Yes.

12 DR. YOUNG: And I would add that the
13 treatment agents themselves may exert the effects in
14 the, of the euphoric type, that there is existing --
15 we have to take into consideration the possibility
16 that the treatment agents may be agents that exert
17 pharmacological, marked pharmacological effects.

18 DR. WRIGHT: Let me drill a little further
19 on that. Are you saying that we should not treat
20 psychopharmacological effects from the treatment drug
21 as adverse reactions by definition as we did with
22 nicotine in the early days?

23 DR. YOUNG: I would not use them as a
24 categorical rejection variable.

25 CHAIRMAN STRAIN: Are there other

1 concluding comments that people would like to make
2 regarding this topic?

3 Yes, Dr. Khuri?

4 DR. KHURI: Real quick comment. I really
5 want to compliment the hard work of the group laboring
6 in this field. This is a very touch problem. Cocaine
7 is a very highly reinforcing drug, and it ain't easy.

8 CHAIRMAN STRAIN: Yes. Thank you.

9 Doctor?

10 DR. WRIGHT: Sorry to get after you again,
11 Mr. Chairman.

12 Is the committee willing to accept modest
13 variations from sponsor to sponsor, trial to trial in
14 the categorical tests used to determine success for an
15 individual patient until we gain more experience?

16 DR. KHURI: Can you define modest
17 variation?

18 CHAIRMAN STRAIN: Let me put it this way,
19 this is something that needs to be fluid. I think
20 that we need to recognize that if somebody comes in
21 with an agent that's 45 percent, we're not going to
22 thumb our nose at it, I don't think. I mean I think,
23 you know, a sponsor should continue. I think that
24 somebody who comes in with a hot new outcome measure
25 that seems very useful, a patch, a skin patch. Again,

1 we want to consider --

2 DR. WRIGHT: I wasn't thinking of that so
3 much as somebody might decide that the best thing to
4 do is the integrated benzoylecgonine over the month,
5 and somebody else might decide that the inter-usage
6 interval is the appropriate thing, and somebody else
7 might decide the quantity, frequency quotient is, you
8 know --

9 CHAIRMAN STRAIN: Right.

10 DR. WRIGHT: -- but they're all, we look
11 at it and they're all face valid, reflecting about a
12 50 percent reduction in use or better --

13 CHAIRMAN STRAIN: Yes.

14 DR. WRIGHT: -- that's okay?

15 CHAIRMAN STRAIN: Yes.

16 DR. KHURI: Before I take the BE very
17 seriously, I really appreciate just one reference,
18 good reference, on the benzoylecgonine, the drop off
19 after certain amounts of use and the individual
20 variation because I think we are ignorant about a lot
21 of this -- and also knowledge --

22 DR. ANDORN: I think it's coming in
23 addition shortly.

24 DR. KHURI: Okay, and the frequency of
25 taking of the urines too is important to remain

1 constant. But I'd accept very modest improvements
2 personally, clinically.

3 DR. WRIGHT: Let me just say we have a
4 collection of papers and studies. We reviewed this
5 about six months with in the NIDA program and we'd be
6 happy to give that collection of data to you all.

7 DR. KHURI: Thank you.

8 CHAIRMAN STRAIN: So I'd be willing to
9 take a motion for adjournment?

10 DR. KHURI: So moved.

11 CHAIRMAN STRAIN: All those in favor say
12 aye?

13 CHORUS: Aye.

14 (Whereupon, the motion was unanimously
15 carried.)

16 CHAIRMAN STRAIN: Thank you very much to
17 the committee. Thank you to NIDA/MDD for their help
18 and assistance over the course of today. And thanks
19 to the FDA staff as always.

20 Have a good trip.

21 DR. KHURI: Thank you.

22 (Whereupon, at 3:15 p.m., the meeting was
23 adjourned.)

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