

ACTION
Measures of Outcome for Stimulant Trials (MOST)

March 26, 2015

A Matter of Record
(301) 890-4188

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1 DR. STRAIN: Rhonda Beale is not able to be
2 here this morning, so She won't be delivering the
3 first of this session's papers.
4 DR. MONTOYA: So the first speaker is Keith
5 Isenberg?
6 Presentation – Keith Isenberg
7 DR. ISENBERG: Good morning. I appreciate
8 the opportunity to be here. My name is Keith
9 Isenberg. I'm a medical director for Anthem Health
10 Plans. That gives me a particular perspective. As
11 you can see, I change things a little bit. I'm
12 going to try to talk about health plans in as
13 general a fashion as possible. In particular, I am
14 going to try to talk about some of what goes into
15 formulary decisions. And I'd be happy to answer
16 questions to try to address your concerns as best I
17 can.
18 So what do health plans do? Well, we sell
19 insurance. And that seems like a straightforward
20 sort of proposition. But this slide should reveal
21 that it is not a straightforward proposition, and
22 the thing I want you to take away from this is that

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1 the characteristics of the people to whom we sell
2 the product has an influence on what the benefits
3 are.
4 So as you all know, because you have jobs,
5 most insurance is sold through employers. It's
6 probably marketed to you as a benefit. It's
7 something that comes -- it's a perk, something that
8 you get because you're employed. That
9 distinguishes the U.S. healthcare system in a
10 substantial way from other healthcare systems.
11 There's a history to that. I won't go into
12 that. But I think the other important point to
13 make about that is that may be changing as a result
14 of the Affordable Care Act. And I will try to come
15 back to that. Nevertheless, the bulk of insurance
16 sold in the United States is still sold through
17 employers. Employers come in sizes, small and
18 large.
19 On average, small employers will tend to be
20 more concerned about cost. If you think about what
21 you've read about the Affordable Care Act, you're
22 aware of that. A small employer is very concerned

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1 about the mandates and their effect on their
2 viability. Large employers tend to be more
3 concerned about persuading you that you're getting
4 a benefit, that this is something that's a good
5 deal, that you want to continue to work here
6 because the insurance is good, and it's going to be
7 good for you when things go south.
8 Now, these are tendencies because the
9 countertendencies are for large employers to try to
10 shift some of the cost back to you. You probably
11 have noticed that.
12 In addition, some small employers really are
13 interested in perks. So how does that work? Well,
14 think about professional firms, architects,
15 lawyers, and whatnot. They may be interested in
16 really having gold-plated insurance with the caveat
17 that, again, the Affordable Care Act comes in there
18 with some surcharges, excise taxes on those type of
19 plans. Complicated.
20 States. We manage Medicaid plans. The
21 states tend to have very specific ideas about
22 benefits. They contract with us with those ideas

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1 in mind. They can be very specific, and from a
2 formulary perspective, tend to be more aggressive
3 about stipulating rules about how the benefit is to
4 be managed.
5 If you doubt that, you should be attentive
6 to the developing story about hepatitis C treatment
7 because, I assure you, as a rule of thumb, the
8 states have been more particular about how those
9 treatments are to be administered. Sometimes our
10 contracts often spell out exactly what we're
11 supposed to do in these matters.
12 The federal government is a contract. We
13 have contracting relations with the federal
14 government. Those contracting relationships
15 include Medicare, which as you know is a plan for
16 the elderly and for this group, the disabled, lots
17 of disabled folks.
18 However, in addition to Medicare, the
19 federal government has employees. I believe we
20 have some of them here in the audience today. I
21 assure you that the population insured by the
22 federal employees' plan is different than the

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1 Medicare plan, and I will also assure you that the
2 benefits have some very important differences. And
3 the population health matters are obviously
4 different.
5 Finally, the federal government has military
6 personnel in their dependence. This is a different
7 population yet again. It'll tend to be younger
8 than the two populations and will have different
9 health issues.
10 We also sell policies to individuals, and
11 that was changed by the Affordable Care Act. I am
12 not going to dwell on some of the politics that
13 have transpired. My job is just to tell you that
14 the Affordable Care Act changed the individual
15 health plan market substantially. And it has also
16 familiarized you folks to some extent with the idea
17 of purchasing insurance on exchanges.
18 In addition, there is a movement for
19 employers to do the same thing. So you in the
20 future may be purchasing your insurance off of some
21 exchange vehicle in that annual, however that plays
22 out for the particular employer, process. In other

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1 words, you'll get online, look at the benefits, be
2 confused, pick something, and move on.
3 I'd be the first to tell you that part of
4 the challenge with managing insurance benefits is
5 the complexity. So start with this idea that these
6 populations are different, and they have different
7 healthcare needs. And then that has implications
8 for formulary development.
9 Next concept is, healthcare management is
10 predicated on the concept of medical necessity. I
11 will generally keep my talk to public sources and
12 this is a very public and well-known source about
13 what the definition of medical necessity is. Our
14 definition, the Anthem definition, is not
15 proprietary. It's a little different. It also
16 depends to some extent on the health plans.
17 So back to those states and the federal
18 employees, those health plans have definitions that
19 are different than we use in other places for our
20 commercial insurance. All of the other definitions
21 of medical necessity that I am aware of spend a lot
22 of time on this concept of accepted standard of

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1 medicine.
2 That is a little vague there. Try to
3 sharpen that. But in general, what that means is,
4 we tried to examine a variety of sources to
5 determine just what the practice of medicine
6 involves.
7 So what does that mean for pharmacy
8 management? Well, first of all, FDA approval,
9 which supports the concept that a drug is safe and
10 effective is necessary. In addition, we mine the
11 prescribing information for the characteristics of
12 that approval.
13 We want to support the prescription of
14 medications as is believed to be the best way, and
15 the place you start with that is the prescribing
16 information. I have listed a variety of elements
17 from the prescribing information that are looked at
18 to try to figure out how are you supposed to
19 prescribe a drug.
20 We also examine the peer-reviewed
21 literature, a couple of reasons for that. One is,
22 published information about trials sometimes

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1 contains information that elucidates or explains a
2 little bit more about how the drug is supposed to
3 be used.
4 Finally, that last one, authoritative body
5 guidance. What does that mean? That sounds vague,
6 doesn't it? Well, I have already alluded to the
7 role of states in the defining of benefits.
8 They're authoritative. And we manage things by
9 contract, regardless. We're obligated to do that.
10 However, there are other authoritative bodies that
11 we look at.
12 I suspect everyone in the room is aware of
13 the Substance Abuse and Mental Health Service
14 Administration's guidance on treatment. They have
15 published a variety of extensive information about
16 what you're supposed to do, which is not always
17 congruent with the prescribing information. But be
18 that as it may, we're supposed to look at that.
19 Finally, professional societies offer advice about
20 how to manage medications, and we look at that.
21 So we take all this information and try to
22 make decisions about how medications are to be made

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1 available for use.

2 Nevertheless, whatever work you good folks

3 do in terms of trials, and devising tools, and all

4 the rest of that, it's going to be different when

5 it gets out in the community, guaranteed.

6 So the concept that we're paying attention

7 to how drugs are used after they're on the market

8 is very important. It is relevant to safety, and

9 there are continuing efforts to try to use claims

10 data to become more knowledgeable about the adverse

11 effect of drugs and devices.

12 This is a complex and contentious area.

13 Some of you may be aware of the medical device

14 issues going on about identifying particular

15 medical devices by type. If you're not, you might

16 want to look into that. That's kind of

17 interesting.

18 So what happens to drugs after they're on

19 the market should have some implications for how

20 they're used. And the Food and Drug Administration

21 of course is involved in that. But we also try to

22 pay attention to how the drugs are used.

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1 When we put in place formulary interventions

2 like prior authorizations, quantity limits, step

3 therapy, all the rest of that good stuff, we try to

4 look and see how that plays out over the passage of

5 time to determine whether or not the management

6 that we're trying to put in place is reasonable,

7 always subject to some debate as to exactly what

8 that means.

9 So in the end, what I do, or what I'm

10 interested in, or what health plans we're

11 interested in is defining what the standard of care

12 is; what should people be receiving. The

13 conversations of yesterday were very interesting to

14 me, that you folks are trying to determine where

15 we're going. I'm trying to figure out where we're

16 at and trying to make that as consistent and as

17 effective as possible.

18 I am a believer in what I would say is a

19 Medicare or CMS principle, which is that people,

20 regardless of where they are, should have access to

21 treatment that is as fairly available as we can

22 make it.

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1 There will be, inevitably, inequities. I've

2 forgotten which conversation I was in yesterday

3 where people talked about -- where there's a

4 discussion about how different the American

5 landscape is because of its diversity, as opposed

6 to some of the other countries in the world, where

7 there's a bit more homogeneity. So it's going to

8 be more complex here in the United States.

9 From the perspective of a pharmacy, the

10 question of a formulary is, what is the place of a

11 drug and treatment? You folks are informing me

12 that, for stimulus-use disorders, not so much a

13 drug. But then the alternative becomes the

14 therapies that are available, contingency

15 management and cognitive behavioral therapy.

16 If you think trying to support prudent and

17 sensible use of medications is a challenge -- and

18 it is -- how therapy is administered in the larger

19 community, I would offer the opinion that it's a

20 greater challenge.

21 Then I just have some general comments to

22 reflect on what I've heard over the past couple of

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1 days, and these are related to the standard of

2 care.

3 The standard of care now is abstinence. I

4 understand that there are reasons to move beyond

5 that. But I would encourage you to be mindful of

6 the fact that the patients, their families, and

7 significant others, employers, states, and the

8 criminal justice system are going to cling to

9 abstinence.

10 So if there are treatments devised that are

11 based on other parameters -- and abstinence was not

12 looking all that bad yesterday. I understood from

13 the data that was available, maybe the patients who

14 have stimulus-use disorders are not so interested

15 in that. But nevertheless, that may still be the

16 most relevant measure.

17 Regardless, the good news is, the concept

18 that abstinence is a goal is widely accepted. You

19 all are familiar with who is arguably the most

20 famous stimulant user. That would be -- Raye's

21 heard me give part of this talk before, so I'm

22 probably boring. The most famous stimulant user is

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1 a fellow on TV by the name of Sherlock Holmes.
2 So if you use that as a context for your
3 thought about what the standard of care is
4 today -- and you can argue about that. But if you
5 use that as a context, you can see that abstinence
6 is thought to be widely accepted. Why would they
7 weave into a cotton-picking TV show if it wasn't?
8 Another issue is that the provider community
9 that you're proposing to change has consistently
10 demonstrated itself reluctant to change. The
11 penetration of drugs into the substance-use
12 disorder treatment domain is arguably dismal.
13 From my perspective, as a person who looks
14 at cases -- and I'm going to look only at the cases
15 where things are bad and where failure is not going
16 well -- it mystifies me that doing the same thing
17 over, and over, and over is expected in
18 substance-use disorders and not so much in the rest
19 of medicine.
20 Another complex issue is how is
21 substance-use disorder treatment moved into the
22 mainstream of medical care. You all are probably

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1 familiar with the current mania about -- and that's
2 what it seems to be sometimes -- behavioral health
3 and primary care integration. This is a great
4 idea, unquestionably. But if you consider for just
5 a moment the status, look at the literature, and
6 consider the status of things, there's a lot of
7 data, a lot of effort defining, if you have a
8 myocardial infarction, you're at risk of
9 depression, that should be treated or not, so on
10 and so forth.
11 The penetration of substance-use disorder
12 treatment in outside of behavioral health remains
13 relatively poor, I would argue. Now, that's not
14 for one of some changes. The SPERT codes, for
15 example, are a venue for making those kind of
16 changes.
17 Another issue about substance-use disorder
18 treatment is regulation. And here, I would only
19 suggest that you bear in mind the peculiar
20 circumstances surrounding the use of methadone for
21 opioid dependence. It's just odd. It just
22 strikes -- it just seems so peculiar.

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1 Nevertheless, it is festooned with
2 regulations and is indicative of a variety of other
3 issues that I think are substantial barriers to the
4 inclusion of substance-use disorder treatment in
5 the mainstream.
6 Speaking as a representative of a health
7 plan, health plans in general are interested in
8 getting the right treatment to the right person at
9 the right time. And for many individuals, primary
10 care settings are going to be the right place.
11 Having said that, there's another challenge
12 here, and that has to do with population
13 prevalence. The rarer a disorder is, the less
14 likely you are to have the people on the frontline
15 able to be capable of treating it.
16 Now, doctors understand drugs, so having a
17 drug that alters the course of the disorder becomes
18 a tool for making that change. So there is some
19 usefulness to your efforts from that perspective.
20 But as was pointed out yesterday, making it
21 complicated, that dog won't hunt.
22 The electronic records will help

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1 substantially with cueing people in primary care
2 settings what to do. However, the more complicated
3 you make the effort, the less likely it is to be
4 executed. That's just a reality when you're
5 looking at a 10-minute visit. And I realize that
6 I'm responsible for all those 10 visits. I take
7 that responsibility with a great deal of pride.
8 That was a joke. I am expected to look like Darth
9 Vader, I've been told.
10 DSM-V. For better or for worse, DSM-V is
11 what it is. And I understand the limitations for
12 DSM-V. I was a professor for many years at
13 Washington University School of Medicine, and I
14 heard tell that there was some concern about
15 diagnosis there at one time. But once you have a
16 tool like that, you should be using it.
17 The advance in concept that severity of
18 illness is something you do even as simply as by
19 symptom count is worthwhile. I understand the
20 skepticism that that's going to pan out as a truly
21 useful measure. But if you go back to the problem
22 of trying to, "Okay. I've made the diagnosis; now

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1 what do I do? I'm going to count symptoms."
2 When we talk about diagnosis, there was
3 discussion yesterday about how drugs could be
4 useful for withdrawal and for treatment of the
5 disorder. We should also bear in mind that drugs
6 may have a usefulness for intoxication.
7 In addition -- and this can be a real issue
8 for stimulant-use disorders; you all can tell me
9 probably better than I can tell you. But
10 certainly, runs of use, binge use, and intoxication
11 is a big deal. In addition, I think it's obvious,
12 but it's worth stating regardless, that a drug may
13 be useful for intoxication and not useful for
14 withdrawal or for the disorder, and then every
15 other combination that you can think of. And we
16 know there are examples of that.
17 That does not make a drug, for example, that
18 is useful for intoxication useless. It just makes
19 the challenge of trying to figure out how to fit a
20 medication into the scheme of things a challenge.
21 The other issue that comes with some of
22 these measures, we talked about disease models.

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1 And abstinence of course is a cure, and that's one
2 of the attractions to patients, and especially, I
3 think, to their families and significant others.
4 However, we talked about stimulus-use disorders as
5 relapsing remitting disorders.
6 I would suggest to you that, if you develop
7 a drug that alters the use patterns, you run the
8 risk of turning it into a chronic disorder where
9 people are on the medication indefinitely. Now,
10 that's not a bad model. That beats some of the
11 consequences of continued use. But the flip side
12 of that is, that's not exactly a good model,
13 either.
14 I want you to pay attention to abstinence
15 when you think about your measures because I do not
16 see for the foreseeable future the provider
17 community or the public moving readily away from
18 that concept. And I always try to remember the
19 rule of thumb is that it takes 20 years for the
20 practice of medicine to change. I know, in the
21 electronic age, it's going to happen a lot faster.
22 So given that perspective, I appreciate the

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1 opportunity to be here, to listen to the thoughts
2 about how to move things forward. I hope the
3 comments that I made here at the end give you some
4 perspective in whatever I need to do next. Thank
5 you.
6 (Applause.)
7 DR. WOODY: This is a comment. George
8 Woody. I think it's important to keep in mind that
9 there is a paradigm shift happening in addiction
10 treatment. And it is somewhat comparable to what
11 happened in psychiatry. I remember hearing a talk
12 from a psychiatrist from Uruguay, which is the
13 hotbed of psychoanalysis -- and this was within the
14 last 10 years -- who adamantly said that if you
15 have as schizophrenic patient, you should not put
16 them on medication because it interferes with the
17 psychotherapeutic process, and the person really
18 believed that.
19 I heard those comments when I was a resident
20 in medical school, actually, in the early '60s.
21 You had a shift with the development of
22 psychosocial treatments and the development of

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1 medications, a shift away from that. And it seems
2 to me the same sort of a process is happening in
3 psychiatry, but it takes a long time. And it's
4 driven to a large extent, I think, by HIV, in harm
5 reduction, showing to have health benefits and
6 method on maintenance, where people improve even
7 without abstinence.
8 So I would just sort of throw that point
9 out, that what you get from the general -- these
10 feelings, these attitudes that you're describing
11 are old. They're part of history. But we're in a
12 period where history is sort of changing, and it
13 doesn't happen right away.
14 DR. ISENBERG: No, unquestionably. But my
15 job at times over the course of the rest of the
16 day, and tomorrow, will be to administer health
17 benefits as they exist today. So it's of no use
18 for me to advise, say, a provider who's taking care
19 of our one of our members that, "You're out of
20 touch." That just doesn't go well.
21 So I am very interested in seeing the
22 practice of medicine in general, substance-use

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1 disorder treatment in particular improve. I
2 believe that's what I share with you folks. And I
3 believe that the challenge that you're confronting
4 is, okay, how we use data to guess where we need to
5 go next.
6 The asks are to be mindful of what the
7 standard of care is now because, as challenging as
8 it is to determine what we should be measuring and
9 what are the disease concepts we should be
10 addressing -- and those are challenging -- moving
11 the field and getting out of this 20-year interval
12 is widely accepted as something that ought to
13 happen.
14 If my memory serves, I believe the President
15 of the United States has expressed an opinion of
16 that sort. And for anybody that's interested,
17 there's an article in the Wall Street Journal from
18 this morning, and probably other papers as well, so
19 you don't have to choose that one -- that's the one
20 I picked up at the front desk -- that says we
21 should be paying for quality. So there's a lot of
22 interest in mechanisms to shorten this time

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1 interval.
2 Having said that, it's going to be tough.
3 The other burden, I think, for the substance-use
4 disorder treatment is the regulations. I just used
5 methadone as an example, as something that's been
6 around a long time and is still just burdened with
7 regulatory and other approaches that leave it
8 outside of the practice of medicine in many ways,
9 and I don't think that's right.
10 I mean, I've used the drug. I know enough
11 about the drug to tell you that it shouldn't be
12 outside the practice of medicine. If I were a
13 primary care doctor or other specialist, I would
14 want to know about this.
15 How do you make that happen? I'm just
16 saying, that's the nature of the -- if you think
17 about it from that perspective, that's the nature
18 of the problem.
19 DR. MONTOYA: I'm also concerned about the
20 time.
21 DR. ISENBERG: Sorry. Thank you very much.
22 DR. MONTOYA: Sorry about that, but we need

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1 to move on. Thank you so much, excellent
2 presentation. Very interesting.
3 So the next speaker is Amy Duhig. Amy?
4 DR. DUHIG: It's a hard one. I'm sorry. I
5 used to be Smith. Now I'm not.
6 DR. MONTOYA: That would be much easier.
7 Presentation -- Amy Duhig
8 DR. DUHIG: Well, I want to take a minute to
9 thank you for the invitation. And actually, when I
10 got this invitation a couple months ago, I thought,
11 "My gosh, is my boss going to let me do this? I
12 don't get paid for this. It's not billable hours."
13 But I sent along the e-mail and he graciously said,
14 "Go for it." And so thank you for the invite.
15 Then I thought, "Boy, now what am I going to
16 say? I don't really know too much about stimulant
17 addiction. I know alcohol. Thanks, Raye Litten,
18 for getting me into this." One of the things that
19 we do -- I work for a company called Xcenda. And
20 we work for a broader company called
21 AmerisourceBergen, which is a pharmacy distributor.
22 So Xcenda is a scientific and commercial

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1 consulting company. And with that comes the
2 opportunity to actually reach out to payers, to
3 providers, to understand kind of the unmet need and
4 what their thoughts are. So I thought, "Well,
5 maybe I can get my boss to pay these guys to fill
6 out this survey," and he said yes.
7 So I actually do have data for you guys.
8 And it's not a huge end. We do have this survey
9 called PayerPulse, that once a month, we send out
10 forms usually from pharma companies and questions
11 that they want real quick feedback on, on specific
12 items.
13 So we have about 150 people in our managed-
14 care network, that we call it at Xcenda. And this
15 thing fielded on Friday. And I just got data
16 yesterday and, last night, I'm working on Excel
17 sheets, and graphs, and stuff. And I ended up with
18 a response of 34. But the nice thing is that it's
19 pretty heterogeneous in terms of the messages that
20 I got back, so I think it might be useful. And
21 then they had some open fields that they could then
22 also provide some information.

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1 So we have this double-blinded online survey
2 that was conducted in five days. And again, it was
3 sent through our PayerPulse survey. When I added
4 up the number of covered lives by these payers, on
5 the low end it's about 70 million. We do have a
6 range, though. They had little buckets that they
7 could pick, how many lives are in their plan.
8 So I would estimate probably, not
9 conservatively, about 100 million. So we had a
10 pretty good split between pharmacy directors and
11 medical directors. And actually, the national
12 versus regional plans was split down the middle.
13 So that was also pretty nice.
14 Now, because of the small ends but mostly
15 because of the time that I had, I didn't go down
16 and dig and cut data by pharmacy and medical
17 directors or national and regional plans. And
18 also, we're still fielding this, so I should get
19 some more data in that I'm happy to compile and
20 then update you guys if anything changes.
21 So the majority of advisers or payers that
22 responded were from managed-care organizations.

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1 And you can see NCO with integrated health delivery
2 systems and PBMs. So just looking at pharmacy
3 benefits only, or the PBMs, were equal.
4 So who were these folks and what kind of
5 business did they actually run? The majority had
6 commercial Medicare and managed Medicaid. And then
7 the others just kind of trickle down. So what did
8 I find? Well, do you want to know what I asked?
9 The questions are actually on the bottom of
10 the slides. So the first question I asked was just
11 to get a broad idea of what they thought about the
12 unmet need for stimulant addiction treatment. And I
13 defined it as -- I said cocaine and I had some
14 other examples. And when I went back and I looked
15 at their open-ended responses, a lot of them went
16 straight to stimulant abuse in terms of Ritalin and
17 other things like that.
18 So, yes. So there were a few mentions of
19 cocaine, but for the most part, I think maybe
20 because they deal with medications all the time,
21 they were thinking, "Oh, my gosh. This stimulant
22 abuse is ridiculous."

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1 So to put this kind of in context, payers
2 will usually tell us -- we run advisory boards and
3 we run these types of surveys and telephone
4 interviews for companies. And the likelihood of
5 them saying that something is a high unmet need, it
6 just doesn't happen, especially in fields where
7 there's a lot of generics and a really established
8 disease state.
9 So frankly, their response kind of surprised
10 me, even though this is something that there aren't
11 any available treatments for, but they usually
12 would just kind of be lukewarm. So this is
13 positive, I think, for the field in terms of what
14 they view is needed.
15 So here's some quotes. And I think it just
16 gives you a feel of the kind of things that they're
17 thinking about. These folks are difficult to
18 engage. There's a large gap between need and
19 solution. There is inadequate support, inadequate
20 guidelines for diagnosis and treatment. And this
21 is not everyone. I selected some of the sexy
22 quotes, but there are some other ones like, "I

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1 don't know much about this," or things like that.
2 So then I asked how important is it for new
3 pharmacotherapies to come out. And you see pretty
4 similar -- some of the comments, though, were, "A
5 pharmacotherapy is not going to solve this problem
6 alone. We need behavioral therapies." And I
7 immediately thought that Kathy would be happy to
8 hear that. So some of them that were a little more
9 sophisticated said, "A pill isn't going to fix
10 this."
11 So then I asked about what do you know about
12 it just in general. So stepping back from stimulant
13 use, what do they know about addiction in clinical -- I'm
14 sorry, in addiction treatment? I thought, "Well,
15 they might know something about alcohol and they
16 might be familiar with opioid treatments."
17 So there were some folks on the tails, but
18 this isn't bad. At least you have some people who
19 have done a little bit of work in this space and
20 have some sort of familiarity.
21 So then I asked the endpoint question, what
22 would you value? So from no value at all to

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1 extremely valuable, how important are these
2 concepts in terms of the value to your formulary
3 decision-making process? So when they look at the
4 data, what are the different endpoints that they
5 would think are important?
6 Well, of course, you see the resource use up
7 there, but abstinence was number one. But if you
8 look at reduction in use right above it, that's not
9 too bad. And I thought, well, usually, they hate
10 quality of life. That's the worst thing for them.
11 And if they're not an employer-based plan, they're
12 usually not concerned about work productivity. But
13 I thought they were pretty generous in this space.
14 And again, it is 34 folks, but that's probably more
15 folks than we've talked to, period about this.
16 So then I asked about credibility of
17 endpoints. The lower rating -- the least credible
18 sources are patient-reported sources of
19 information. And that's usually around the
20 efficacy endpoint, not so much about -- I think
21 yesterday we were talking about feel and function.
22 I mean, those things obviously need to come from

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1 patient in most cases.
2 But in terms of improvement reported by
3 another person, that was kind of just on par with
4 patient-reported outcomes, but, really, they
5 believe that they wanted those biological measures.
6 And I said non-biological testing. I gave them
7 examples of neuropsych assessment. And they
8 believe in things that are standardized, that are
9 measurable, and that they can kind of hang their
10 hat on.
11 So here are some quotes about the endpoints.
12 I like the idea of -- I'm truly -- I guess I'm
13 patient-centric first, then caregiver, then
14 observer. The best way would be to use a
15 collection of these measures as a means of
16 cross-validation. And it really goes back to what
17 we were talking about yesterday in terms of
18 cross-validation of measures.
19 So again, there were some that said, "I
20 don't trust anything that comes from a patient."
21 So it was all over the place, but I thought these
22 were kind of more enlightened responses. And

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1 that's all I have.
2 So again, I am happy to go back and look at
3 this a little more systematically, especially if I
4 get more information.
5 (Applause.)
6 DR. ISENBERG: Keith Isenberg. Your survey
7 was of pharmacy managers and health plan managers?
8 DR. DUHIG: Pharmacy directors, yes. We
9 have MDs and PharmDs and so forth. Yes.
10 DR. ISENBERG: Sure. The reason for focus
11 on prescribed drugs is the concern about diversion.
12 That would be why you would worry about prescribed
13 drugs as opposed to cocaine. And as you probably
14 are aware, there have been some recent events in
15 Florida that would make you kind of sensitive to
16 those kind of concerns.
17 DR. DUHIG: Yes. If I had, I think, more
18 time and more questions -- I only have a certain
19 amount of questions that I could ask. It's
20 definitely worth diving in a little bit more to
21 that.
22 DR. MONTOYA: Okay. Thank you so much.

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1 Do you have a question?
2 DR. STRAIN: Yes. Could you go back to
3 probably around your fourth slide back? I just
4 wanted to kind of digest this. It was a great
5 talk, by the way, really, yes. And it's
6 interesting. So what they're saying is they would
7 rate abstinence as the most valuable of all in
8 these.
9 DR. DUHIG: Yes. And you can see I clumped
10 them by -- I split them by 1 to 3 is not valuable.
11 So this is kind of crude. I think it's a
12 low-hanging fruit, but it doesn't mean that other
13 things aren't acceptable as supportive evidence or
14 as a primary. And I think it gets back to what you
15 were saying about what is standard of care.
16 I don't know if payers really know what the
17 SoC is, not saying people that don't specialize,
18 but someone who doesn't pay much to this, pay much
19 attention to addiction, they're really not going to
20 know what the standard of care is in making
21 decisions without digging in and really finding
22 out.

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1 DR. STRAIN: I realize this is kind of pie
2 in the sky sort of, but it would be interesting to
3 administer a questionnaire like this to this sort
4 of population, then the same question, or some very
5 similar questionnaire to a patient population and
6 to a family population --
7 DR. DUHIG: Yes.
8 DR. STRAIN: -- to be able to compare --
9 DR. MONTOYA: Priorities.
10 DR. STRAIN: -- yes, the priorities across
11 the different stakeholder groups.
12 DR. DUHIG: Right. And so you're getting
13 back to yesterday with the patient-reported
14 outcomes. And I think it just depends on who is
15 your customer, so to speak. Is it the patient? Is
16 it the family? Is it the payer? Is it the
17 physician? Everybody's going to have different
18 things that they value.
19 DR. STRAIN: Yes.
20 DR. DUHIG: So what evidence do you need to
21 bring to each group. Absolutely? You should be a
22 marketer.

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1 DR. MONTOYA: Thank you so much. Excellent.
2 Connie Weisner is the last speaker.
3 Presentation – Connie Weisner
4 DR. WEISNER: Good morning. I'm going to be
5 presenting some similar data from a slightly
6 different perspective from the previous two
7 speakers, and then a few more things. I'm going to
8 talk about the health plan context from where I'm
9 coming from at Kaiser Permanente and going then to
10 look at what the population looks like of
11 stimulant-abuse and dependent people on this health
12 plan, things about stakeholders, and then a little
13 bit of a glimpse at outcomes and endpoints.
14 So previous speakers, Keith and Amy have
15 really said a whole lot about this. I am not going
16 to say a lot, except I do just have to kind of
17 reiterate what I said yesterday. This is a time in
18 history that we're not going to have again. I've
19 been doing this a long time, and I have never seen
20 such a sea change in how healthcare is looking at
21 alcohol and drug abuse.
22 We really need to take advantage of it.

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1 It's really a time to push for development of
2 medications and other treatments and really, really
3 get going.
4 Part of it has not to do with the Affordable
5 Care Act. Part of it has to do with the huge
6 problem of prescription drug abuse, opioids, and
7 with marijuana. That itself has gotten attention,
8 but the circumstance of this happening right with
9 health reform and parity legislation is a big deal.
10 So I just want to reiterate what's changed.
11 First of all, we went from something that often was
12 not covered in healthcare to being one of 10
13 essential benefits, meaning medical necessity and
14 everything as Keith talked about.
15 It also moves treatment from not just
16 specialty treatment programs, but the whole gamut,
17 from primary care through specialty care. And it
18 can put behavioral health specialists into primary
19 care to help those physicians with some treatments
20 right there as well as referring people to
21 treatment. And it addresses the whole spectrum of
22 use, and abuse, and dependence, not just

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1 dependence. So even though we don't use abuse
2 anymore, I think it's going to take our clinicians
3 a long time to stop using that.
4 Anyway, it really is a point in time where
5 we really have to seize the opportunity. We have
6 employer-based healthcare, as has been discussed.
7 And that brings in multiple stakeholders. I think
8 it's more extensive. It brings in more complexity
9 to what we were talking about yesterday in terms of
10 patient outcomes or patient function, and feelings,
11 and so forth because our providers are often
12 between a rock and a hard place, where the
13 employers want abstinence. You got a Teamster
14 driving a truck, they're going to get drug tested
15 and alcohol tested all the time.
16 So we're often faulting our alcohol and drug
17 treatment programs for not being open to harm
18 reduction. They maybe are as clinicians, but
19 they're really being held responsible for different
20 outcomes. I do think, just as happened with
21 alcohol, that the more they see some benefits from
22 less use and so forth, that that paradigm is going

<p style="text-align: right;">Page 41</p> <p>1 to be changing a little bit. And then treatment 2 entry and the implications for outcome. 3 So I talked a little bit about this 4 yesterday in the question/answer period. I'm not 5 going to go into it very much. But in all of our 6 studies that you're going to see today, we have 7 asked all the addiction severity questions. And at 8 the end of each domain -- alcohol, employment, 9 legal, family, mental health, drug, medical 10 problems -- we say how important to you now is 11 treatment for these problems, one by one? 12 As I said yesterday, the reason that people 13 came to treatment, that's what they say extremely 14 important for. So you can have somebody say, "It's 15 extremely important for me to get my job back," or, 16 "To not have this trial I've got for interpersonal 17 violence coming up go well. But it's not at all 18 important for me to stop using." I mean, that 19 truly happens. 20 So a lot of our questions that we do in our 21 studies about readiness for change and everything, 22 that just focus on that, are kind of missing the</p>	<p style="text-align: right;">Page 43</p> <p>1 of formulary issues and everything from what Keith 2 has talked about and Amy, but not big enough to go 3 into that. I think, on the whole, we're facing the 4 very same issues that they talked about. I would 5 say also that many of the federally qualified 6 health centers in our counties and states are 7 moving towards this model and finding ways to 8 integrate their alcohol, and drug, and mental 9 health programs. 10 So what do patients with stimulant disorder 11 diagnoses look like in this health plan? There 12 were, in 2014, 7400 people on the whole. Sixty 13 percent were men, pretty good age distribution up 14 until age 65, and about 57 percent white. 15 What about for cocaine disorders? Here, 16 it's a little different. The gender difference is 17 pretty much the same. I think the major difference 18 is where there was a larger percentage of white 19 stimulant disorder diagnoses. 20 Here, there's much more of a difference. In 21 fact, I think I have that number wrong. The 22 African-American population is larger. I'm very</p>
<p style="text-align: right;">Page 42</p> <p>1 boat. And again, we do have more people whose 2 their own personal treatment goal is not 3 abstinence, but that is still what they're being 4 held to. 5 Also, as I mentioned yesterday -- I think 6 I'm realizing how much I talked in the question- 7 and-answer period now -- the reasons for people 8 coming to treatment are very diverse. And we 9 really see that the non-alcohol and drug outcomes 10 are really related to those reasons. 11 So I am going to present a little bit of 12 data from another kind of health plan. This is 13 Kaiser Permanente. It's an integrated health plan 14 where alcohol, drug, psychiatric services are run 15 in a staff model. Everyone is employed by the same 16 healthcare system. Northern California has about 17 3.7 million members. And we have data with the 18 other Kaisers and also 14 other health plans that 19 are harmonized. If there's time at the end, I want 20 to talk about that a little bit in terms of 21 opportunities for research. 22 This raises some slight differences in terms</p>	<p style="text-align: right;">Page 44</p> <p>1 sorry. I made a mistake there. 2 MALE SPEAKER: Is this the subpopulation of 3 the [inaudible -- off mic]? 4 DR. WEISNER: No. Because of, really, some 5 patient differences, we have coded stimulant 6 amphetamine disorders separate from cocaine, so 7 it's a separate population. And if I forget to say 8 later, there's about an 8 percent overlap in our 9 treatment samples. 10 Now, I guess the point I want to make that I 11 think bears on medications, something we've talked 12 about with alcohol findings as well, is that these 13 patients are complex patients. They have a lot of 14 health problems and a lot of mental health 15 problems. Here, I'm just looking at the mental 16 health diagnoses are among the membership of people 17 who are stimulant dependent. 18 As you can see, it's high. And it probably 19 isn't a surprise to you, but it's always an issue 20 when our clinicians want to give medications. And 21 in case I forget to say this later, one of the 22 things I don't think Raye mentioned yesterday in</p>

<p style="text-align: right;">Page 45</p> <p>1 the data that we looked at is that the low-risk 2 drinking outcomes were robust when we controlled 3 for medical and mental health diagnoses and other 4 drug diagnoses, but I don't know that would happen 5 here. And for those who met dependence-disorder 6 diagnoses, again, for cocaine, we have, again, a 7 high rate of other mental health disorders. 8 So I'm going to present just a little bit of 9 data on what the patients look like in their 10 outcomes in several treatment studies. Now, these 11 are all randomized studies, but they're pragmatic 12 trials, and so they were studying models of care. 13 The first two studies are the ones that we 14 used for the work with Raye and Dan. One was 15 randomizing patients to getting their healthcare 16 right in the clinic, the substance abuse clinic. 17 The other one was two different levels of 18 treatment. And then the third study is a new one 19 just finished, actually, I should say, 213, that 20 was a medical home study. So patients were 21 randomized to a patient activation intervention 22 while they were in treatment. So they kind of span</p>	<p style="text-align: right;">Page 47</p> <p>1 been using for less than a year. 2 By the way, I think I'll show this later, 3 but this is about 28 percent of the sample: 26 4 were dependent; 2 percent were meeting abuse 5 criteria. In terms of looking at cocaine 6 dependence, here we had, again, only 12 percent who 7 had used it for less than a year. 8 What about their medical and psychiatric 9 conditions? Fifty percent of them had either 10 medical or psychiatric; 34 percent a medical 11 condition and 31 percent a psychiatric condition. 12 And for the cocaine-dependent patients, very 13 similar, about half had one or the other, and 14 38 percent medical and 24 percent psychiatric. 15 So here now, I'm trying to take a first 16 little preliminary look at outcomes. So this is 17 measuring 30 days before the 6-month and 30 days 18 before the 12-month follow-ups. So those who were 19 stimulant dependent at intake, those who used no 20 stimulants at 6 months, 95 percent of them were not 21 using stimulants at 12 months; 3 percent were using 22 them 1 to 4 days, those who were using.</p>
<p style="text-align: right;">Page 46</p> <p>1 locations and time. 2 This is what treatment looks like in this 3 health plan. Detoxification is mainly ambulatory. 4 It's all mostly group based, abstinence based. The 5 main part of treatment, the intense part of 6 treatment, is the first two or three weeks, where 7 it's like a day treatment, which is recommended for 8 most people, and then lesser treatment the next 9 three weeks, and then aftercare up to a year, 10 although very few people avail themselves of that. 11 There is regular drug testing of all 12 patients and increasingly use of medications in the 13 specialty treatment programs, the ones below being 14 used, although disulfiram isn't used very much 15 anymore. 16 So here is what the stimulant-dependent 17 patients look like. And what we asked patients 18 when we did the dependence interview was 19 have -- amphetamine or speed, crank, meth, ice. 20 This is the years of regular stimulant use, that 21 those who were dependent or abuse, who met that 22 criteria, showed. So very few of them only had</p>	<p style="text-align: right;">Page 48</p> <p>1 So I did this -- just looked at the 2 frequencies and tried to mimic what we did with the 3 alcohol a little bit in terms of saying zero days, 4 1 to 4 days, or 5 or more days. So again, of those 5 using stimulants 1 to 4 days at 6 months, 6 77 percent of them were not using at 12 months and 7 18 percent. We did urine tests with these studies, 8 by the way. And as you can see, those who were 9 using 5 or more days in the last 30 days did not do 10 so well. 11 So what about for cocaine? Here, those who 12 did not use any cocaine at 6 months, 95 percent of 13 them were not using at 12 months. And of those 14 using 1 to 4 days at 6 months, there's a pretty 15 even spread. Only 66 percent could meet that kind 16 of no-harm, whatever, if you wanted to call it 17 that, and again, those people who were using 5 or 18 more days. 19 One thing I have to say, these are pragmatic 20 trials. They are in the course of treatment, 21 real-life programs. So sometimes these patients 22 have gone back to treatment, all of that. I can</p>

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1 look at if this is interesting, the samples are
2 large enough.
3 This is a recent study in San Francisco, so
4 it's a smaller sample size. Here is a breakdown of
5 the medical conditions that we found in this
6 sample. Again, two-thirds had a psychiatric
7 condition. About 52 percent had a medical
8 condition, and they're listed there.
9 Here's where we see hep C coming into the
10 picture. This is a big issue in the health plan,
11 especially for alcohol. They are coming to us and
12 saying, "All of these people are drinkers. These
13 are the sins of the '60s and they're still
14 drinkers. We need to do some intervention in the
15 hep C clinics," because, as you know, those
16 treatments are very costly. When we looked at
17 medical conditions for the cocaine-dependent
18 patients, we found even really higher rates of
19 medical and psychiatric conditions.
20 In this sample, I accidentally asked for the
21 wrong ones here, so I don't have years of regular
22 use here. But it's how often were they using

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1 amphetamines in the year before treatment entry,
2 and 45 percent were using them 4 or more times a
3 week, 17 percent, 2 or 3 times a week. And over
4 the past year, those using cocaine in the year
5 before treatment, 28 percent, 4 or more times a
6 week, 27 percent.
7 So we don't have a sample like 90 percent of
8 people are using it every day or anything, but they
9 do have severity characteristics with medical and
10 mental health issues.
11 In terms of the prescription stimulants, our
12 providers haven't found that to be as big of a
13 deal. They're also really on top -- they
14 say -- now of addressing ADHD in adults much more
15 than they have in the past in the treatment
16 programs, so I don't know how much this is. But
17 this is before treatment.
18 So when we look at this sample now and we
19 look at stimulant use in the 30 days before the
20 12-month interview based on 30 days before the
21 6-month interview, there are some similarities and
22 some differences. I think the biggest

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1 difference -- I won't walk you through again, but I
2 think the biggest difference is that when we looked
3 at the old Sacramento study, we found that
4 1 to 4 days group was 33 percent, 33 percent,
5 33 percent.
6 So it looks like -- I hope that in the last
7 15 years, the treatment has improved a lot and that
8 could be why. But it's also a different population
9 in San Francisco than it is in Sacramento. It's
10 much more of a valley, more amphetamines, and so
11 forth.
12 Cocaine use at 6 months, here are the
13 biggest -- excuse me. When we looked at stimulant
14 use 15 years earlier in Sacramento, the big
15 difference was that 95 percent of the people were
16 in the 1 to 4 days at 12 months. Here is where we
17 had in Sacramento 33, 33, 33 percent in the 1 to 4
18 days.
19 Here, this is where I guess we're seeing
20 that maybe that group is doing a lot better if
21 anyone can decide that 1 to 4 days is an adequate
22 outcome.

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1 FEMALE SPEAKER: You had about 46 percent
2 for whom that was their baseline monthly use?
3 DR. WEISNER: Yes. It was that 4, but there
4 was also -- I can go back to that. And this was
5 amphetamines. Yes.
6 FEMALE SPEAKER: Is this 1 to 4 days over
7 6 months, or is it 1 to 4 days in the past month?
8 So 1 to 4 days per month in a 1-month look-back at
9 6 months?
10 DR. WEISNER: This is asking them for an
11 average over the past year. I don't have that for
12 30 days with this group. And we also didn't urine
13 drug-test them at intake like we did the rest. So
14 this is averaged over the past year. This is
15 30 days before the follow-up, big grace period, as
16 Raye would call it, I guess.
17 So I think, just in summarizing what this
18 might be in terms of implications for new
19 medications again, the high prevalence of medical
20 and psychiatric conditions -- and believe me, the
21 clinicians, especially in primary care, want to
22 know how to handle that. There's a little

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1 indication that 1 to 4 days at the end of treatment
2 may have longer term benefits. And there are
3 really different issues if we're talking about
4 putting these services or these medications in
5 primary care and in specialty alcohol and drug
6 programs, which we can talk about if you'd like.
7 So again, this is a study of those entering
8 treatment rather than those dependent on only one
9 substance. Program goal is abstinence. There are
10 small samples. And here, we only examine stimulant
11 outcomes. I didn't look at other substance use or
12 other medical and social functioning, or healthcare
13 utilization, which I could do. I think I said hat
14 already. So I think that's it. Thank you.
15 (Applause.)
16 DR. WEISNER: Again, this was kind of not
17 last night, but doing it after the invitation, and
18 I know it's very preliminary.
19 DR. STRAIN: No. It's really interesting,
20 and I think I probably want to digest some of those
21 slides, the matrices, at some point. But my
22 question is, do you think that the cuts -- if you

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1 look at those tables, I think there were 3-by-3
2 tables, do you think the cuts at zero, 1 to 4, and
3 greater than 4 are the right cuts for this
4 disorder? I understand you based them on the
5 alcohol work. But maybe for this disorder, it
6 should be somewhere else. And I'm not sure where,
7 but it'd be interesting to model that.
8 DR. WEISNER: Yes. We could do that, and I
9 also can show you the frequency distributions if
10 anybody would like, if we're going to do more.
11 DR. CARROLL: This is Kathy. I think that's
12 about right. And we can probably have those tables
13 in a couple days now that we have our huge
14 data set, just to see. I think it would be
15 fascinating to pull them from a Bonds [ph]
16 data set, you know, the data sets that we've
17 collected so far, to see.
18 But on average, across all these trials,
19 they come in using between 1 and 16 days a month.
20 So if you broke it into those quadrants, I think
21 it's about right.
22 DR. WEISNER: This is an employed population

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1 or people who are spouses of, and often, a once a
2 week thing. It's often on the weekend.
3 DR. STRAIN: I'm sorry. If you could go
4 back to one of those, and it could be any one of
5 them, just as a model. So what this says is, in
6 the 30 days at month 6, if a person self-reported
7 zero days of use --
8 DR. WEISNER: And there was drug testing.
9 DR. STRAIN: -- and there was drug testing,
10 then at 12 months for the 30 days, 92 percent of
11 them reported no use. Right?
12 DR. WEISNER: Yes.
13 DR. STRAIN: So I guess my question, Kathy,
14 is, if you change that first category, for example,
15 from zero to 1 days, will you make any significant
16 difference on that 92 percent, or if you change the
17 second category from 1 to 4 to 1 to 3 or 1 to 2
18 days?
19 DR. CARROLL: Isn't it wonderful that that's
20 an empirical question that's answerable? I don't
21 know that right this minute, but I'll know it by
22 Friday.

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1 DR. STRAIN: What time on Friday?
2 DR. CARROLL: You already called her, didn't
3 you? Yes. We got it done.
4 MALE SPEAKER: People are working on it.
5 The best people are working on it now.
6 DR. WEISNER: I'll be eager to know, too.
7 Keith?
8 DR. ISENBERG: Yes. At the beginning, you
9 presented some information about the proportion of
10 the insured population with stimulant- and cocaine-
11 use disorders. Is that based on a single claim
12 with that diagnosis? Is that how those larger
13 populations were constructed?
14 DR. WEISNER: Yes. So first of all, we
15 don't have claims. We have encounter data.
16 DR. ISENBERG: Right.
17 DR. WEISNER: No. I have to remember
18 exactly, but we have done some record reviews. You
19 have to have two or three diagnoses at different
20 times. Yes.
21 DR. ISENBERG: So as opposed to a single
22 encounter diagnosis, you used two for those larger

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1 samples.

2 DR. WEISNER: Yes.

3 DR. ISENBERG: The reason for asking the

4 question has to do with how that larger population

5 maps to the treatment population. And that's a

6 very important question, I suspect, for your health

7 plan in addition to the research issues.

8 DR. WEISNER: Most diagnoses are made in

9 those 43 medical centers in the region rather than

10 primary care because of 42 CFR. I could do a whole

11 talk on 42 CFR --

12 DR. ISENBERG: Yes, no.

13 DR. WEISNER: -- and problems with

14 integration.

15 DR. ISENBERG: Regulations are a problem.

16 DR. WEISNER: Right.

17 DR. ISENBERG: But I'm still interested in

18 how the larger population maps to the smaller

19 treatment population because the first cut or the

20 first guess is, it's the additional conditions that

21 drive you into treatment, the additional medical

22 conditions. And then that becomes a driver to get

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1 attention from the medical community, is the reason

2 for trying to pose this.

3 DR. WEISNER: Again, I think that is the

4 case somewhat. On the other hand, as we were

5 talking about yesterday, 44 percent of the people

6 are there on employer mandate, depending over time

7 and which site, up to about 20 percent on a legal

8 mandate. You know, the lawyer says, "Get yourself

9 to treatment, and when we go, we maybe can get you

10 a better deal." So some of the people who drop out

11 of treatment are being successful that they've gone

12 to jail, whatever; or their family has said,

13 "Enough. To treatment, or you're out."

14 It just doesn't seem like they're getting

15 identified as much in primary care. I think they

16 are now with the hep C clinics more so. I think

17 that's why that Sacramento data or the 2014 data

18 look a little different.

19 MALE SPEAKER: I'm just so amazed, just

20 comparing this to the alcohol data. If the

21 zero days is abstinent, 1 to 4 would be low risk,

22 and then the 5 or more would be like the heavy. In

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1 the alcohol data, I think we saw a decent amount of

2 low-risk people go on to become heavy drinkers.

3 But here, it's not the case at all. The low-risk

4 people -- let's call them low risk, 1 to 4

5 days -- never really progress to be more days than

6 4. That's kind of interesting.

7 DR. WEISNER: Yes.

8 MALE SPEAKER: It would be interesting to

9 see two of these, if you're going to have time to

10 repeat, and see how the consequences go for these

11 groups later on.

12 DR. WEISNER: We should. When we compare

13 drug outcomes with alcohol outcomes, we have higher

14 levels of abstinence over time than we do for

15 alcohol. Once Kathy tells us how to do it or how

16 we should, we should then look and do some modeling

17 with this as well, but small sample.

18 FEMALE SPEAKER: I have a quick question

19 about the population. You've combined people who

20 met criteria at the time of DSM-IV. Right? You've

21 got DSM-IV dependence and DSM-IV abuse. Have you

22 tried to separate them out at all? Because I don't

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1 know whether all of those patients would

2 necessarily be pharmacologic treatment candidates.

3 DR. WEISNER: Well, for the stimulant

4 population, of the 28 percent, 26 were dependent.

5 It was more mixed with the cocaine population. It

6 was like half and half. The sample is so small, I

7 didn't do that analysis by that. I could if you'd

8 like.

9 Presentation - Eric Strain

10 DR. STRAIN: Thanks, Connie.

11 I'm going to take the prerogative -- because

12 Rhonda wasn't able to come, I wanted to make a

13 couple of points on this topic. So Elliot, if you

14 could hold just for a moment, I want to -- this is

15 the prerogative you get to make when you're

16 organizing the conference -- convey a few thoughts

17 about this topic, because I think it is one of

18 interest, that I've had of interest.

19 Wearing a different hat, Johns Hopkins

20 actually runs a managed-care organization that

21 covers over 250,000 Medicaid lives, an employee

22 plan, a TRICARE plan. So it's a growing part of

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1 the business of Hopkins. And I've had discussions
2 with the pharmacy management people there about
3 some of these sorts of issues. So I wanted to pass
4 along a couple of thoughts regarding this.
5 I want to caveat that this is an area I
6 think about, but it's not my usual focus. But an
7 expert is someone from out of town, and I'm from
8 out of town, so now I can pretend to be an expert
9 on this topic.
10 It seems to me, this is the realm of
11 cost-benefit analyses. In my read of addictions of
12 cost-benefit analyses, it's that there is some
13 controversy in this field regarding the measures,
14 for example. And it's especially difficult to
15 assess benefits as we think about pharmacotherapies
16 for stimulant-use disorders. So let me talk a
17 little bit about costs and then benefits as we
18 think about this area.
19 When you think about a new medication for an
20 indication, you could have a new pharmacologic
21 treatment, you could replace or have a cost
22 offset -- and I'm going to elaborate on each of

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1 these real quick -- or you can replace or
2 cost-offset a non-pharmacologic treatment.
3 So what do I mean by each of these? Well,
4 first, let's talk about a new pharmacologic
5 treatment. An example here would be something like
6 imipramine for depression, which was brought out in
7 1958, or buprenorphine for opiate addiction in 2003
8 could be in some ways viewed that way.
9 That is, it's a new medication, and the
10 costs have not been covered by a previous
11 medication, as it were. So it can be a medication
12 for the indication, but the new medication, the new
13 treatment is markedly different in how it's used,
14 for example, buprenorphine.
15 But the point is, this results in a
16 potential for new and substantial cost to a
17 healthcare system when you bring in something like
18 this. And I think buprenorphine is where this
19 really hit home for me because, for our Medicaid
20 managed-care organization, office-space
21 buprenorphine treatment was a 7-digit cost to their
22 pharmacy benefit once it got into full gear. And

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1 that was a cost that was new to them. It wasn't
2 something that they could say, "Well, we're saving
3 money" -- as I'll make the point in a
4 moment -- "from somewhere else due to that." And I
5 think that's the situation we have with this
6 stimulant-use disorder treatment medication.
7 So medication for stimulant-use disorder
8 will be a new medication. It's a new cost to a
9 healthcare system with respect to pharmacy cost.
10 Now, the second scenario is that you could
11 have a cost offset of an existing pharmacologic
12 treatment. So this, for example, is sertraline, or
13 paroxetine, or any of those things for depression.
14 I just picked sertraline as an example; Zoloft,
15 which came out in 1991.
16 So there could be incremental costs because
17 it's a new drug versus a generic, such as
18 fluoxetine. But the new cost is less likely than
19 if there was a completely new medication type. And
20 we're probably seeing this with buprenorphine now,
21 where you get a generic that comes on the market.
22 Now, the MCO, the Medicaid MCO, says, "We can cover

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1 that generic because we've already allocated
2 dollars for this line of medications. It's not
3 necessarily a new cost. If anything, it's a
4 savings to us in that respect."
5 Then the third is a cost offset of a
6 non-pharmacologic treatment. And an example here I
7 would argue is lithium, which came out in 1949,
8 versus institutionalization for bipolar disorder.
9 So we had patients who were being kept in
10 psychiatric hospitals for long periods of time for
11 bipolar disorder, for example. And lithium comes
12 along, and it's a new medication that may have cost
13 to a healthcare system, but it offsets some other
14 healthcare cost that is even more expensive, such
15 as inpatient treatment.
16 As I've been thinking about costs and how
17 they impact healthcare systems, what about benefits
18 then? And these are things that I think most all
19 of us have thought about, and I just wanted to make
20 sure that we're all keeping them in mind. Benefits
21 in addictions treatment can be hard to quantify.
22 And I'm well aware of the DATCP [ph] and all sorts

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1 of things like that.
2 There are healthcare-related ones and then
3 there are social benefits. The healthcare benefits
4 are certainly important, and, intuitively, we
5 clinicians think they occur. So whenever we get
6 into these discussions in clinical arenas, where I
7 work, the clinicians, myself included, are arguing,
8 "This is really helping patients and really making
9 an impact there."
10 The problem is that there's a lag between
11 the treatment and benefit that may make it hard to
12 demonstrate this on the healthcare side. And it
13 may be easier to shift the healthcare cost to
14 somewhere else if the healthcare benefit is not
15 quickly demonstrated. So rather than our MCO
16 treating somebody for IV drug abuse because it'll
17 save them on endocarditis costs that could occur
18 10 years from now, it's easier to say, "Hey, can we
19 get that patient to migrate over to a different
20 MCO?" We don't do that, but there is that sort of
21 logic there.
22 I think, in some respects, we're probably

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1 going to see this more with the Affordable Care Act
2 because there's more insurance out there, and I
3 think there's going to be more shifting of
4 high-risk patients to different healthcare plans to
5 try to get them off of your plan. I could give you
6 some anecdotes on ER dumps, for example, that we're
7 starting to see.
8 What about social benefits of new
9 medications? That's important as well, of course.
10 For addictions, there's a variety of impacts, work,
11 legal problems, family stabilization. These tend
12 to not have a direct payer benefit, so social good
13 is good. I'm not certainly arguing against that.
14 But it doesn't directly impact the payer's bottom
15 line.
16 I'm reminded here -- I wish I had taken a
17 picture of it -- when the CALDATA study was done,
18 which was back in the early '90s, CALDATA did this
19 whole cost-benefit analysis of addictions
20 treatment, and one of the conclusions was that a
21 dollar spent on methadone treatment, I think,
22 produced \$12 in savings. And there was a billboard

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1 in Baltimore that trumpeted that, that said, "A
2 dollar in addictions treatment will produce \$12 in
3 savings."
4 The problem is that those savings aren't
5 primarily healthcare savings. They were primarily
6 legal, employment, things like that. And quite
7 frankly, the MCO likes those things. They
8 certainly appreciate those sorts of things or the
9 payer, but they don't get a benefit out of those on
10 their bottom line.
11 So should a measure for stimulant-use
12 disorders show healthcare benefit or social
13 benefit, I think, is one of the things we need to
14 think about.
15 So final thought, having a measure that
16 shows healthcare benefit would seem to be
17 particularly persuasive to payers, a treatment that
18 decreases other healthcare costs in a relatively
19 quick manner. And demonstrating social benefits is
20 good, but will likely impact the payer primarily if
21 the payer is the state. So on the Medicaid or
22 Medicare side, for example, that's where it becomes

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1 particularly useful.
2 So I will thank you, and I appreciate the
3 chance to hop in here and try to cover what I was
4 hoping Rhonda might address.
5 Should we move to the discussant, or who all
6 has a question?
7 MALE SPEAKER: Question and comment. So at
8 Johns Hopkins Managed Care, how fungible are the
9 funds between different services? So is your
10 pharmacy budget fixed versus your medical budget?
11 DR. STRAIN: My understanding is there's
12 some fungibility there.
13 MALE SPEAKER: So when I think about
14 Medicaid across states, I would take issue with
15 your argument because, there, in most states, those
16 Medicaid budgets, let's say the pharmacy cost
17 budgets, are pretty rigid. And you're taking from
18 one pocket to another.
19 So for example, something like depot
20 naltrexone might not be available in every state,
21 even though it might be an effective treatment for
22 relapse prevention because the Medicaid budgets

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1 say, "We can't pay for it. We can only pay for
2 methadone."
3 So I'm not certain that the states have the
4 kind of aspirational view that you have, that
5 social good is the end. And until there's a little
6 bit more fungibility in those funds, I think we're
7 going to be in a hard place.
8 DR. STRAIN: You're more pessimistic than I
9 am, which is a little worrisome. What I would say
10 is that Maryland and Hopkins is especially a little
11 bit different because now, in Medicaid, the state
12 has decided to carve substance abuse out from the
13 rest of medical care, along with mental health
14 care, and administer it through a different ASO.
15 so we've lost fungibility on those funds, which has
16 been very distressing, actually.
17 Can I take one more?
18 FEMALE SPEAKER: I want to add one thing. I
19 think we have to look at costs a little more
20 broadly than we have in the past. We have a grant
21 where we looked at family members' costs. So
22 adults who were diagnosed with alcohol and drug

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1 disorders, their family members' costs were much
2 higher than other families for seven years before
3 that diagnosis. And they went back to "normal"
4 after the person had successful treatment.
5 That's a huge business case issue because
6 our patients don't get diagnosed right away. And
7 that made a huge difference in how we got the
8 health plan to use SPERT in identifying people
9 early, because something kind of magical happened
10 to the patient's family members.
11 Now, those are published papers. I really
12 wish that we could start thinking more broadly when
13 we make our business case.
14 DR. STRAIN: Thanks. Great point. I'm
15 going to -- because I have impinged on Elliot's
16 time. But I think these are points as well that we
17 can bring out in the discussion, so thanks.
18 Discussant – Elliot Ehrich
19 DR. EHRICH: Well, thank you. And I really
20 want to thank the organizers, Eric, and the other
21 organizers of this conference, coming together and
22 discussing this topic because developing a drug for

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1 the treatment of addiction is probably the most
2 challenging. I've been involved in the development
3 and registration of drugs for arthritis, for
4 asthma, and for diabetes. And this really is the
5 hardest.
6 I think it's the most difficult area to
7 develop and register a drug, and not just from the
8 perspective of endpoints, but how patients engage
9 with the healthcare system and also how people
10 think about medication treatments and their place
11 in the treatment of addictions.
12 I think it was Alan Leshner who was quoted
13 as saying, "Whenever we come out with a new
14 treatment for addiction, we circle the wagons,
15 point the guns at each other, and shoot." And I
16 think that's kind of the point. I think it's very
17 singular, the ambivalence that exists even within
18 the treatment community about which medication is
19 appropriate or even is it appropriate to use
20 medication treatments.
21 I thought the panel was really very
22 interesting, and there were a number of things that

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1 were said that I didn't quite expect, and actually,
2 things that weren't said or weren't really focused
3 on that I didn't expect.
4 But I think there was a number of important
5 themes that came up. Actually, we did talk about
6 costs towards the end, but really throughout most
7 of the presentations, the primary point that was
8 being put forward related to patient benefit; in
9 other words, really, what is it that we're trying
10 to achieve?
11 There's disagreement. Is it abstinence or
12 are other outcomes also acceptable? Are we in the
13 midst of changing what's considered to be
14 appropriate treatment? But I think that really
15 does get to the core. And I think as we think
16 about developing endpoints and focusing on what it
17 is that we want to come out of our trials, we
18 shouldn't lose sight of that fact, that it's
19 really, that is the core. And if we demonstrate
20 benefit, then we will succeed.
21 I think there are some great examples. We
22 talked about Sovaldi or some of the newer

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1 treatments for hepatitis C that are extraordinarily
2 expensive, and yet, there's little ambiguity that
3 there's important patient benefit. And I think we
4 as a society appear to be willing to pay for that.
5 I think there's something that's coming in
6 on the horizon, these PSKC9 inhibitors that seem to
7 do a better job than statins for cardiovascular
8 disease. They're biologics. They're infusions.
9 They're going to cost a lot of money. They could
10 potentially benefit a lot of people. And I think,
11 again, as a society, we're going to have to deal
12 with that. But I suspect that we're willing to
13 pay.
14 Again, I think this also comes back to the
15 area of addiction, where one of the places that we
16 suffer is a bias, that people don't necessarily
17 think of addiction as being the same thing as
18 cardiovascular disease, or diabetes, or cancer, in
19 that when we come up with new treatments, I think
20 there's still a lot of residual sentiment out there
21 that addictions are an issue of patient liability,
22 that they're a bad person, that they're doing the

Page 74

1 wrong thing, and to not necessarily treat it as a
2 medical disease.
3 So also, I think, as part of this process,
4 it's ongoing. But if we're going to make any
5 headway, we do need to really continue to make that
6 change as George Woody was alluding to about
7 changing the way that we think about these
8 disorders and overcoming that bias that, yes, these
9 are bona-fid medical disorders that we should be
10 treating with medical treatments.
11 There are also some other themes that are
12 just coming through again as we think about
13 endpoints and as we focused on a bit yesterday,
14 this whole concept of, yes, there is abstinence and
15 there are multiple stakeholders. But really, at
16 the end of the day, it is the patient who is the
17 primary stakeholder. It's the patient who has to
18 take the medication and not only gets the benefits,
19 but also has to endure whatever side effects are
20 associated. So we can't really lose sight about
21 that.
22 I think there was a number of interesting

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1 comments about how we should think about, are there
2 other types of proximal patient benefits about how
3 patients feel and function that we can focus on,
4 that may ultimately predict longer-term outcomes.
5 It may take a long period of time for deep-seated,
6 highly salient memories about the reactions to
7 substances, that may take a long time to change and
8 to really be observed in the context of a clinical
9 trial. So that's something really important.
10 One area I've seen particularly in the
11 arthritis area, some work done by Nick Bellamy on
12 the WOMAC, is literally taking -- the WOMAC is the
13 most commonly-used osteoarthritis questionnaire.
14 It has domains of pain, stiffness, and physical
15 functioning.
16 One thing that they do is they had
17 individual patients rate or use a spectrogram to
18 determine which of those domains were most
19 important to them, as a way of making the
20 instrument more responsible to the individual
21 patients. It's a little bit -- as Connie has been
22 talking about, the treatment or the importance of

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1 treatment can depend on where a patient is coming
2 from, if they're there for criminal justice reasons
3 or employment.
4 So that may also be something to think about
5 in terms of, if we are going to expand, or develop,
6 or trim the CSSA, are there ways that we can
7 customize it for individual patients and
8 potentially use that to enhance statistical power,
9 frankly, again, if you're addressing the areas that
10 means something for an individual patient. So
11 there may be some analyses or ways that we can do
12 it.
13 Just a couple of other comments. I thought
14 that it was very striking yesterday, the data that
15 George Woody showed about how setting can be really
16 important and ancillary treatments. In Iceland,
17 for example, they do a really good job, and
18 demonstrating medication effect can be challenging
19 in that kind of a situation.
20 I think it's just also a reminder that this
21 is MAT that we're talking about, medication-
22 assisted treatment. For example, the alcohol and

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1 the opioid medications, they're approved for use in
2 treating alcohol dependence or opioid dependence in
3 the context of psychosocial therapy. From that
4 perspective, they're combination medicines.
5 So I don't know exactly how we're going to
6 handle that. You can get into weird situations
7 where you create trials where the control group is
8 either contrived or masks the effect of a drug. So
9 it can be difficult and adds complexity, but it is
10 worthwhile also when you're thinking about the
11 overall import or impact of the treatment.
12 You saw, again, as George showed, going in
13 with IDC, there's these amazing changes from
14 pre-study to treatment, irrespective of treatment,
15 that are just engaging in the healthcare system,
16 getting regular visits, having whatever kind of
17 support that exists in terms of whatever
18 counseling, or support, or follow-up is given in
19 the context of trials that can make amazing
20 differences in the context of patients' use.
21 How do we really think about that if what
22 we're delivering with these treatment paradigms is

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1 a combination of psychosocial therapy plus
2 medication? I think we need to think about that
3 as, really, the clinical meaningfulness of what
4 we're delivering.
5 I think, finally, this whole issue about
6 beyond approval, and as we get into a drug that's
7 approved is being used in the clinical setting -- I
8 think, as Keith noted, once drugs are approved, how
9 they're actually used and where they're used is
10 quite different from the information that one has
11 in the context of approval.
12 I think that just also highlights the need
13 that that is the type of setting to really focus
14 more on, on not just what the drug does, but really
15 who is benefitting, because I think at the end of
16 the day, if you have something that works, and it
17 provides patient benefit, if you wanted to make it
18 affordable or to make sense from a cost
19 perspective, what we need to do, then, is really
20 determine who is it for whom is getting that
21 benefit. And I think if we do that, then we're in
22 the best situation of showing a positive cost

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1 benefit. So thanks.
2 (Applause.)
3 Q&A – Group Discussion
4 DR. MONTOYA: Time for discussion.
5 DR. BURKE: Hi. Laurie Burke. I think that
6 what's really important to come out of here, by the
7 time we finish in an hour or so, is that we need to
8 have a better idea of how we recommend people like
9 Elliot work on developing new drugs for this area
10 of treatment. And in order to do that, they really
11 have to understand what to measure as primary
12 endpoints in their clinical trials.
13 They're not going to do long-term clinical
14 trials to find out if these patients are going to
15 be abstinent 10 years down the road, 3 to 5 years
16 down the road, or even one year down the road.
17 They really need to understand how to identify
18 treatment benefit in a length of time that's
19 reasonable to do a clinical trial.
20 So I think that we can't forget about -- I
21 haven't heard any discussion here about how
22 patients feel and function may have an impact on

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1 that long-term abstinence; what makes a difference
2 in terms of how they feel and function in their
3 daily life that's going to determine whether they
4 keep taking the drug, even if they keep taking the
5 drug, whether there is enough benefit in their
6 daily life to make them abstain from whatever we're
7 trying to help them abstain from.
8 That is going to be determined not only by
9 how the treatment helps them with the withdrawal
10 symptoms, or the symptoms of craving, or whatever
11 it may be, but also how the treatment impacts them
12 in terms of the tolerability of side effects, which
13 also has to be, if you want to actually know
14 whether or not the treatment is tolerable in terms
15 of the patient signs and symptoms, you have to
16 measure that as a secondary endpoint also. It's
17 not something you can really conclude from the
18 spontaneous events that are measured during trial.
19 So I think that it would be really useful to
20 have some sort of a recommendation by this group,
21 experts in this field, about what drug sponsors
22 should be doing when they're just now thinking

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1 about taking a drug through the clinical trial
2 process.
3 That's a question.
4 DR. STRAIN: Raye, were you going to say
5 something?
6 DR. LITTEN: No. I had another question.
7 DR. STRAIN: Laurie, I hear what you're
8 saying, but I don't think we're there yet, is the
9 problem. I think that's the issue. It isn't that
10 we're saying --
11 DR. BURKE: Yes. I completely agree.
12 DR. STRAIN: -- well, should we use A, or
13 B, or C? We're not at a stage where we can say
14 we're trying to decide between this instrument, or
15 that instrument, or a third instrument.
16 DR. BURKE: Oh, no. I'm not recommending
17 thinking that you could come up with a
18 recommendation like that. But I'm just hearing a
19 lot of, it's got to be abstinence, managed care. I
20 understand why managed care wants abstinence,
21 because that's going to make all the difference for
22 them in their cost-benefit decision.

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1 But before you can get to a cost-benefit
2 decision, you have to actually have a risk-benefit
3 decision, and that has to be based on something
4 that is more proximal to the treatment. We're not
5 going to have these long-term abstinence data with
6 a new treatment. It's just not going to happen.
7 That's going to happen after it's on the market,
8 and you see what's going to happen.
9 What are we going to have that's going to be
10 convincing to our good friends over here on the
11 right side of the room that there's actually a
12 treatment benefit that's worth marketing?
13 DR. MONTOYA: Right. Yes. Raye?
14 DR. LITTEN: Well, I had a question about
15 the issue of comorbidity in this population. You
16 know, alcoholics who have a comorbidity, they seem
17 to seek treatment more, particularly a specialty
18 treatment. I thought it was interesting with
19 Connie's data. She said, well, people are coming
20 in because of the employer or other reasons, but
21 yet they're coming in with this comorbidity.
22 I guess one of the questions I would ask

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1 maybe Kathy's and some of the studies at Penn, when
2 you recruit people who have, say, a substance
3 stimulant abuse, do most of these people have a
4 comorbidity? Because that really gets complicated
5 when you're thinking about treatment and how do you
6 handle the comorbidity.
7 I know that we ended up, in alcohol, over
8 the past 15 years or so, ended up funding about 12
9 alcoholic depression studies. And we just wanted
10 to answer some very, very basic questions. If you
11 treat the psychiatric disorder, how will that
12 affect the drinking, or if it affects drinking, how
13 does it affect psychiatric?
14 It turned out it was never simple. It was
15 always complicated, which made you think because
16 alcohol is a heterogeneous disease and so is
17 depression, you probably have subtypes in there.
18 But I was just wondering how you deal with
19 this comorbidity because I think when you're
20 treating the substance or, say, the stimulant
21 abuse, you also have to have strategies for the
22 other medical and psychiatric.

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1 What we've found so far -- and I think you
2 were part of this study that Helen did -- is
3 actually found the combination of medications, one
4 for the depression, one for the alcohol, seems to
5 work the best.
6 So I was just wondering about that issue of
7 comorbidity, how you're going to handle that in
8 your population. And maybe that could mask some of
9 the effects from the medication. I don't know.
10 I'm not dealing with the comorbidity.
11 DR. CARROLL: Yes. It gets really
12 complicated, and one of the things is that you can
13 see how things work across different studies,
14 depending on their inclusion and exclusion
15 criteria. And that was a big point that happened
16 yesterday.
17 But one of the nice things about -- we now
18 have this nice little web-based computerized CBT
19 thing that's been now available in two trials, and
20 it's out there, and it's great. Those studies take
21 all-comers, which is great. So if you can walk, if
22 the outpatient place says you're good enough for

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1 them, we'll take you in our studies.
2 So we have really high rates of comorbidity
3 and, interestingly, CBT is good for what you have.
4 So we've split it by level of comorbidity. The
5 problem is that when you get into the drug studies,
6 you have to make sure that they're safe enough to
7 be taking the drugs, which means, pretty much, you
8 have to get rid of a lot of the comorbidity because
9 it gets rid of everybody who's taken
10 antidepressants.
11 It's the level of the benzos. We have a big
12 benzo problem to do it, too. So again, that's why
13 it's hard to do these studies, and I think that's
14 why data like Connie's, which really has the big
15 epi data and how comorbidity works in the broad
16 things -- but it is something that, again, we pay
17 attention to.
18 I think, again, that's why I'm becoming more
19 and more enamored over time of just if we can get a
20 handle on this good-enough business. They're not
21 using. They're sort of working. They're not
22 racking up giant hospital bills. They're not in

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1 the emergency room for psychiatric or medical
2 reasons all the time. So that's kind of where I'm
3 at on that.
4 DR. MONTOYA: Keith?
5 DR. ISENBERG: I appreciate the comments
6 about trying to define the value proposition for
7 any proposed treatment. I think that's critical.
8 There was a question about price pressure on
9 pharmacy benefits managers. You have to take a
10 step back. The pharmacy operates off of a budget.
11 Therefore, the concern when you work off of a
12 budget, especially by the states, is everybody
13 should have treatment. And as new drugs come on to
14 the market -- and indeed there is a pressure to
15 bring new treatments onto the market. The pressure
16 doesn't come from any particular drug. It comes
17 from all of them.
18 Finally, the other avenue that government
19 uses to manage cost is regulations and litigation.
20 And in my opinion, that's not where you want to be.
21 So defining the value, especially for -- and just
22 to call this out very specifically, define the

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1 value as it applies to states who fund Medicaid
2 programs is a critical issue, especially given some
3 of the other ways in which I believe the government
4 is more likely to try to manage benefits through
5 regulation and litigation.
6 DR. STRAIN: Amy?
7 DR. DUHIG: This is Amy Duhig. One of the
8 things that strikes me, I have not seen laid out,
9 even though this is an outcome measure discussion,
10 is a conceptual framework that kind of ties all
11 these pieces together of potential patient benefit,
12 and then what measures we actually have to address
13 them. And then for those of you who are interested
14 in registering a drug, what are the gaps in those
15 measures.
16 So it might be a takeaway from here. And
17 Kathy, maybe you can get your people on this.
18 (Laughter.)
19 DR. DUHIG: How do we lay all this out into
20 a framework that people can work with, whether it's
21 therapy or if it's drug treatment? And maybe this
22 already exists. I don't know.

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1 DR. CARROLL: No. I mean, people have taken
2 passes at it, but that's a great idea, I think. It
3 could be a very useful product of this meeting,
4 because, again, I think we've been doing this for
5 20 years but in some ways, we're at the beginning,
6 I think, of really understanding how to talk to the
7 various stakeholders, for lack of a better word.
8 MALE SPEAKER: I was just thinking here to
9 myself about something. When we're not finding
10 these non-drinking outcomes to be significant in a
11 short-term trial, why is that the case?
12 What Connie said is kind of resonating to
13 me, that maybe it's because people have such
14 different consequences, such different personal
15 goals that they would love to achieve. One person
16 is getting employment. Another is to have a better
17 relationship with their spouse.
18 So when you have a measure of consequences
19 that assesses all these things, it's not going to
20 move the dial because -- it just won't. So I'm
21 wondering if there's something about -- I know this
22 is kind of radical, but is there a relative outcome

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1 where it's basically about perceived benefit for a
2 particular individual? So the outcome
3 measure -- I'm just throwing this out
4 there -- would be, like, proportion of subjects
5 that achieve their own consequence/goal basically.
6 MALE SPEAKER: Personalized.
7 MALE SPEAKER: It's a personalized outcome.
8 Now, it has pros and cons, that it's not
9 standardized. It's like what's the clinical
10 benefit? It's kind of vague. If everyone has a
11 different goal, it's not standardized. But on the
12 other hand, if a good outcome is that which can be
13 moved, but also -- maybe that could be a good goal.
14 It's just open for discussion. Is there
15 some room for a goal, for an outcome like that?
16 FEMALE VOICE: There is some attempts at
17 that in terms of individualizing treatment with
18 goals. I know in schizophrenia there is.
19 MALE SPEAKER: Acceptable from different
20 stakeholders.
21 DR. SILVERMAN: This is Ken Silverman. I
22 think that's a terrific idea, but it seems unlikely

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1 as a good primary outcome measure, at least in the
2 near future. This focus or contrasting between
3 abstinence or the FDA feels and functions in daily
4 life, one reason why I think we're so focused on
5 abstinence is that the medications are focused on
6 promoting abstinence.
7 If there's any evidence for that, look at
8 the animal trials of where medications are tested
9 frequently first, and they try to decrease self-
10 administration of the drug. And it seems pretty
11 sensible. And in fact, what's likely to
12 happen -- and I think that you guys have said this
13 already -- is that if you could decrease
14 abstinence, it'll have different benefits for
15 different people.
16 That addresses the kind of assessment that
17 you're suggesting, which seems like a pretty good
18 idea, but is just an idea.
19 FEMALE SPEAKER: This goes back to my
20 previous comment. I'd like to propose that maybe
21 there is a different way to think about this. And
22 once again, I have to preface this with the fact

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1 that I'm not in your field. I'm not an expert in
2 stimulant abuse. But the treatment that would be
3 developed to me would be a treatment for stimulant
4 abuse.
5 So abstinence is the goal, but lack of
6 abstinence is really a lack of effect, which in
7 most other therapeutic areas is considered an
8 adverse outcome. It's not really the benefit, it's
9 the outcome that you measure benefit with.
10 So here, what is real benefit? And I think
11 that's part of this whole keeping -- we keep
12 talking about feels and functions. It's because,
13 really, the benefit to the patient is somehow they
14 can overcome their feelings of needing to abuse the
15 stimulants and be treated in the sense of their
16 condition of needing the abuseable substance is
17 eliminated.
18 Abstinence then is a failed treatment
19 outcome, but it's a failure to actually do the work
20 that the drug is indicated for. So this is why it
21 makes so much sense to try to figure out what it
22 is, how these patients feel, and you might have to

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1 just limit the clinical trials to a subset of
2 patients that have a defined set of symptoms at
3 baseline, and then figure out whether this drug can
4 affect those symptoms that seem to be related to
5 their abuse.
6 DR. MONTOYA: Connie?
7 DR. WEISNER: Also, just following up,
8 thinking a little bit more about what Dan just
9 said, would it be helpful, I mean, in terms of what
10 Celia said yesterday about surrogate outcomes and
11 other kinds, if we looked -- I think NIAAA did this
12 kind of thing with their alcohol.
13 If we looked at some of our longer-term
14 data sets and some of your studies, different kinds
15 of studies, and looked at whether abstinence or
16 low-risk use, however you want to define that,
17 modeling that has later. And those other data sets
18 have better social functioning outcomes that are
19 measured by the ASI in some of the studies, that
20 are measured by non-using emergency rooms, and so
21 forth, does that help?
22 Can those kinds of things be paired with the

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1 short-term outcomes studies? Can a different kind
2 of study make the leap that, if you're using this
3 much at 12 weeks, this is your other outcomes, or
4 patient, how you feel, and everything, and how
5 you're functioning is looking a year later?
6 I don't know, I mean, whether that ever
7 happens using different --
8 MALE SPEAKER: Long-term studies are going
9 to be really beneficial to measure how patients
10 feel. And long-term studies, though, when you use
11 urinalysis, very burdensome. You're not going to
12 keep people around for very long.
13 If you can get rid of urinalysis, then
14 you've got an advantage to go to long-term studies.
15 The way you get rid of urinalyses is that you pare
16 down who gets into your clinical trial by using
17 Connie's idea of why are you here.
18 If you could find the pure patient who
19 really wants to get rid of drug use because they're
20 sick and tired of it, you would have an enriched
21 population to study, who would be willing to be
22 truthful about whether they used or not. And

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1 therefore, self-report becomes the endpoint of
2 choice that's not burdensome, easy to handle.
3 Aren't we looking then at the patient who
4 the payers want to pay for treatment for? And to
5 me, it just all comes together. If you can use
6 self-report and trust it, if you pare down the
7 patient population to what you'd call something
8 enriched, then you could do long-term studies and
9 look at real outcomes over a long time.
10 DR. MONTOYA: Yes. I think very interesting
11 discussion, but we should take a break because now
12 we are running into the break time.
13 DR. STRAIN: So let's take a 10-minute
14 break, and then I think Dr. Preston may be
15 speaking.
16 Thanks for a great session.
17 (Whereupon, a recess was taken.)
18 DR. STRAIN: I am going to convene this
19 session. And it's my pleasure to introduce Kenzie
20 Preston, who will be talking about practicalities
21 of conducting biologic assessments for drug use.
22 Dr. Preston?

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1 Presentation – Kenzie Preston
2 DR. PRESTON: Thanks for inviting me. And
3 I've come down to the realm of brass tacks rather
4 than the more hypothetical today. So there's a lot
5 of question about why we use biological measures.
6 They're costly. They're inconvenient. And some
7 really, really question whether it's necessary.
8 And when we look at the alcohol research, we
9 actually say, well, maybe you don't need it.
10 On the other hand, there's good evidence
11 that people underreport it. And I don't think it's
12 a question if people underreport. They do
13 underreport. It's just a matter of degree and how
14 important maybe that is. And of course, having an
15 objective biological measure adds credibility to
16 your results.
17 The ideal drug testing program for a
18 clinical trial would have a test that has good
19 efficacy, sensitivity, and specificity, and has a
20 low cost, and is quick and easy. And the specimen
21 should be easily and safely collected, have a low
22 risk of contamination from external sources, and be

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1 easily stored and, if necessary, transported if you
2 need to keep specimens for any reason.
3 But probably the most important thing is the
4 correspondence between the window of detection that
5 matches the specimen collection schedule. So if
6 you have a test that tests positive only for
7 24 hours, and you're testing 24 hours, you're going
8 to catch every use.
9 But if you're testing only once a week,
10 you're going to probably miss some uses, which is
11 problematic, but it's not as much of a problem as
12 if say your test has a window of detection of a
13 week, and you're testing every day, because then
14 you're getting multiple positives for single uses.
15 So one of the challenges is to match up the window
16 of detection of your test with your data collection
17 schedule and still be practical for participants
18 and the researchers.
19 So I think the good news is that this is a
20 huge business, the drug testing, and it's used for
21 a wide variety of uses, so this has generated a lot
22 of technology development in the industry. But I

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1 think one of the issues is that the goals for these
2 really very frequent uses are not necessarily the
3 same as our monitoring of drug use in clinical
4 trials, so their solutions to problems don't
5 necessarily work out so well for us.
6 The other thing I want to point out is that
7 in the real world, drug testing is usually done in
8 a two-step process, so there's a screening test
9 usually, like an amino acid, that's very sensitive,
10 but maybe not so specific. It has usually only a
11 qualitative test, positive versus negative, and
12 tends to be quite cheap, which is good. Then if
13 there are positives, then those are sent out for
14 the more specific, expensive, quantitative testing
15 like with GCMS.
16 So virtually, all these applications, they
17 do a screening, and for some of them, because of
18 legal ramifications, they definitely do
19 confirmation. I think for clinical and drug
20 treatment, they may or may not do it depending on
21 the exact circumstance of the testing. But
22 generally for our clinical trials, we haven't been

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1 doing the confirmation testing. We've been relying
2 on screening tests.
3 So as I mentioned, there's a lot of research
4 going on in drug testing, and I just did a SCOPE
5 search on drug testing and addiction and saw that
6 the numbers of papers published each year is going
7 up.
8 What this has led to is improvements in,
9 say, on-site testing for urine drug screens, but
10 also development of a lot of alternative matrices
11 beyond urine such as hair, sweat, oral fluid,
12 breath now. There's breath tests for cocaine and
13 marijuana. And the newest thing I'm told is the
14 dried blood spot.
15 We've been talking about these alternative
16 matrices for a really long time. And so I thought
17 if I'm going to give a talk about this, maybe I
18 should see how they are being used. Maybe they're
19 replacing urine testing in the field.
20 So I did the SCOPA search, and I looked at
21 methamphetamine dependence and cocaine dependence,
22 and filtered it for clinical trials. And of

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1 course, there are many trials or published papers
2 with urine. I found a couple for hair and a couple
3 papers for sweat, not just the development, say,
4 test, tests, but actual use in the clinical trial,
5 but none for oral fluid or breath. And I actually
6 didn't look for dried blood spots.
7 So then I thought, well, maybe those studies
8 haven't been published yet, so I went to
9 ClinicalTrials.gov and did a search on
10 methamphetamine dependence and cocaine dependence.
11 And I did a word search in the outcome measure
12 category, and there were absolutely none for any of
13 these matrices, so ongoing trials. That's not to
14 say they're not including them in the trials, but
15 they're not identifying them as, say, their primary
16 outcome measures.
17 So I think the bottom line is they really
18 have not caught on and been adopted into clinical
19 trials.
20 I'm going to do a brief survey of the
21 different matrices and cover these different
22 categories, and I'll start reading with urine. For

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1 urine, the major analyte is the metabolite, and for
2 cocaine, that's benzoylecgonine mostly, the
3 detection time. And this goes across a lot of
4 different drugs. It kind of seems to be drug
5 independent, a detection time of 2 to 4 days.
6 Think about whether we can differentiate
7 recent use and whether it might be sensitive to
8 changes in rates of drug use. And for urine,
9 that's pretty much yes for detecting recency of
10 use. It shows up in the urine pretty quickly. But
11 like I said earlier, if you're testing more
12 frequently than the drug is eliminated, you can get
13 carryover, which could make your test insensitive
14 to changes in frequency of drug use.
15 The collection convenience, I would say, for
16 urine is not really convenient at all. You have to
17 have special facilities, and if you're doing
18 observed testing, you need same-sex observers.
19 Contamination is not generally a problem with
20 urine. There is now on-site testing. And as far
21 as the other issues, it's been used a lot. It's
22 almost the only one that's used, so it has well

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1 established concentrations cut-offs, and it's
2 established as an outcome measure in clinical
3 trials.
4 Another advantage for urine testing
5 specifically is that the labs across the country
6 tend to use the same or very similar assays. So
7 you can look across trials, and they have used the
8 same assay. Now, to Kathy's point, what you do
9 with those data are not necessarily the same, but
10 you're at least working with the same assay, pretty
11 much.
12 So this was a study where we were interested
13 in the effect of concentration cut-off on the
14 window of detection, so we brought people into our
15 residential unit and collected all of their urine
16 specimens. This is the concentration cut-off
17 against how many hours it took to actually reach
18 that concentration.
19 That dotted line is 300 nanogram per mL,
20 which is the standard cut-off. And that's about 42
21 hours, which is actually a little shorter than the
22 2 to 4 days. But these people hadn't necessarily

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1 used right before they came in.
2 But anyway, you can lengthen the window by
3 lowering your cut-off, so down at 100, you're out
4 here at 60 hours or so, or you could shorten your
5 window of detection simply by raising your cut-off,
6 and that down here at 500 nanograms per mL, we're
7 looking at just over a day and a half or so.
8 We talked a little bit about concentrations
9 yesterday, so I thought I would present some of
10 those data. So this is the results of a clinical
11 trial. It was a contingency management where
12 people were randomized to get an incentive for
13 being cocaine negative or they were randomized to a
14 control group that got the same value of
15 incentives, but independent of their urine results.
16 What we found is, there was a significant
17 increase in longest duration of sustained
18 abstinence with kind of a bimodal response in our
19 contingent group, with about half people -- we
20 called them responders and half not responders.
21 And so we were collaborating with Ed Cone at the
22 time, and he did the urine benzoylecgonine

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1 concentrations for our study.
2 This is the baseline period before they were
3 randomized, and post-randomization is at this
4 dotted line. And you can see that our responders
5 just kept on using, whereas our responders -- and
6 maybe this is that grace period where it took them
7 a while to actually decrease down to not testing
8 positive. This is the limit of detection here for
9 that particular test.
10 I'll just go back. In fact, it turns out
11 that the non-responders were actually using more
12 drug before they even were randomized. This is a
13 non-responder looking at the benzoylecgonine
14 concentration across time. And these were urines
15 collected Monday, Wednesday, Friday. And this is a
16 log scale, so it goes all the way from about 10 all
17 the way up to about a million.
18 The person is not using continuously,
19 obviously, because we're getting lots of ups and
20 downs here, even a period of abstinence. So if we
21 apply the 300 nanogram per mL cut-off for this
22 participant, we got 11 occasions when that person

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1 tested negative. But there are also some times
2 when it looks like, yes, if we just waited a little
3 longer to collect that specimen, they might have
4 actually been negative, especially if you're using
5 high doses. It might take actually a longer window
6 of detection.
7 One solution might be to just raise that
8 cut-off, and if we raise it up to 3,000 nanograms
9 per mL, we increased our number of negatives from
10 11 to 23. But we weren't totally satisfied with
11 that idea, so we actually went back, thinking about
12 the pharmacokinetics of benzoylecgonine, its
13 half-life. Maybe we could develop a better way of
14 identifying carryover positives versus times when
15 people actually use, so I'm not going to go into
16 the details of this. But basically, we compared
17 the concentration from the current urine to the
18 just previously-collected urine. And when we did
19 that, in fact, we identified 12 occasions of
20 carryover that are in the green and left us with 28
21 occasions of new use.
22 I think this may not be the real answer, but

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1 if you have all of those concentrations from other
2 trials, it might be that using some
3 machine-learning algorithm, you could develop a
4 better way of differentiating new use from old use.
5 And that's actually the concentration cut-off if we
6 go back to 3,000 nanograms per mL, which you see
7 greens on both sides of that line. So I don't
8 think that just raising the concentration cut-off
9 might be the solution.

10 Just going back to this idea of self-report,
11 this was the percent positive for the
12 non-responders and the responders at baseline and
13 intervention. When we add in the bars for
14 self-report, we see that it's about 50 percent.
15 But when we put in our new-use criteria, we see
16 that it kind of splits the difference. And what
17 that suggests to me is that there is some
18 underreporting, but some of our problem is actually
19 overtesting. So we need to be keeping that in mind
20 as we do clinical trials.

21 So I'm going to move on to hair testing.
22 Just as a point of reference, hair grows at about

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1 1 centimeter per month. The major analyte in hair
2 is parent compound, but you also find metabolite.
3 The detection line, the time is 1 week to months.
4 And that of course depends on how long the hair is
5 there. Some people have advocated segmenting hair
6 to actually be able to break it down. It's not
7 quite as clean as it seems like it ought to be.

8 As far as detection of recent use, in fact,
9 you can't detect a recent use with hair because the
10 drug gets incorporated in the hair, in the
11 follicles below the scalp. So it takes about a
12 week for the hair to grow out so you could actually
13 capture the hair.

14 As far as a convenient collection, it's kind
15 of convenient. But I would say that my staff and
16 my participants really didn't like it. And
17 obviously, it's going to be easier for some
18 patients than for others.

19 The other big issue with hair testing is
20 that you can get environmental contamination of
21 hair, and that's been demonstrated both from having
22 people who are positive handle hair as well as just

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1 washing the hair with drugs, and then it's not
2 possible to wash out again.

3 There is no on-site testing. It's a pretty
4 elaborate matrix to work with, although I
5 understand there's a company that's working on
6 doing better methods for hair testing. And as far
7 as other issues, the concentration that you see in
8 hair actually is affected by hair color and
9 treatments. So the darker the hair, the more drug
10 that you'll find, and bleaching helps you have less
11 drug in your hair.

12 On the plus side, it's the only matrix where
13 you can actually go back, so you lost a specimen.
14 A week later, you go get another specimen, chances
15 are the results are going to be the same.

16 So this was a study that was done at the ARC
17 by Ed Cone and his group, and they brought cocaine
18 users in. They had them wash out the drug from
19 their system, and then they administered two doses
20 of cocaine, a low dose and a high dose. And one of
21 the things you can see is the concentration of
22 cocaine is a lot higher than the cocaine

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1 metabolite, but you also saw a dose-related
2 concentration. So there is some potential value in
3 hair testing going forward.

4 There is a couple of groups that have been
5 doing hair testing in clinical trials. And this
6 group looked at the relationship between reports of
7 use in the past three months against the actual
8 concentration of cocaine in the hair. And they got
9 significant correlation, although that was somewhat
10 decreased if you only looked at the hair tests that
11 tested positive. But overall, they got a good
12 concordance, with 86 percent concordance, and a
13 specificity of more than 90 percent, and
14 sensitivity of 65 percent.

15 They also included amphetamine in their
16 trial, and they got a correspondence of 86 percent
17 for amphetamine, with a specificity of 90 percent.
18 But the sensitivity was actually pretty low, so
19 there were fewer people who tested positive with
20 their hair than reported amphetamine use.

21 So they actually also did a clinical trial
22 with this, using hair testing, and it was a

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1 comparison of computerized versus inpatient brief
2 intervention. And they collected hair, and
3 self-report at baseline, and at 3 months follow-up.
4 And overall, they didn't find a significant
5 difference between their treatments. And they
6 looked at a combination of self-report and hair
7 testing when they included all the drugs. But when
8 they looked at drugs independently, they did see a
9 significant difference in their marijuana use and
10 their cocaine use that was detectable by including
11 hair in the test. So I think that's also
12 promising.

13 Another trial that was done was at Yale.
14 And this was a trial, testing office-based
15 methadone treatment against methadone delivered in
16 the standard drug treatment program. And they did
17 hair testing at baseline, 3- and 6-month
18 follow-ups, and they also measured self-report and
19 urine toxicology.

20 So I guess from the trial study
21 purpose -- in fact, they found no differences in
22 outcomes between those two groups. And that was

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1 true for all of their outcome measures; although
2 the hair testing did identify two additional people
3 who had otherwise not reported or tested positive
4 for illicit drugs, and that was true in both
5 groups.

6 They also found that urine drug screens, a
7 positive hair test predicted drug use during the
8 trial. So if we're thinking about things that
9 might be indicators of how well people are doing,
10 that might be one, even if you're not collecting
11 data on every single use.

12 Next one is sweat. Sweat is collected on
13 these patches that are like little pieces of
14 blotter paper that are attached to the body with a
15 semi-permeable membrane. And the major analyte in
16 sweat is also the parent compound greater than the
17 metabolite. Detection time is entirely dependent
18 on how long people wear that patch.

19 The nice thing is, you might be able to have
20 it on for a longer period of time and detect any
21 drug use. So that also determines your ability to
22 detect recent use or sensitivity to change in rate.

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1 The collection is sort of convenient. You
2 don't need same-sex application. But you have to
3 be so careful when you apply those patches because
4 it's very possible to get external contamination on
5 them. And there's no on-site testing, so these
6 things need to be sent out to an outside lab.

7 There's also a problem with people being
8 allergic to the adhesive. Patches can fall off.
9 It hasn't been used as an outcome measure in a
10 trial. Well, it was tried; I'll show you.

11 Currently, there's only one company that's actually
12 doing it.

13 This was study, an inpatient study -- no,
14 this was our outpatient study, one of our
15 contingency management trials. These are data from
16 two different people. On the left is a person who
17 was a responder. On the right is a person who was
18 a non-responder. This is sweat cocaine
19 concentrations, and at the bottom are their urine,
20 cocaine, and benzoylecgonine concentrations. And
21 you can see that, in fact, the decrease in drug use
22 here is reflected in a decrease in cocaine in the

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1 patch in this person, and no change in drug use,
2 basically, is reflected in the patch of the
3 non-responder. And we looked at the sensitivity.
4 We got a 97 percent sensitivity and a 60.5 percent
5 specificity.

6 So the same group that did the hair testing
7 has tried to use the patch in a trial. And this
8 was a buprenorphine trial, and they tested it, used
9 the sweat patches in 63 participants. And they
10 applied over 500 patches, and they got just over
11 half of them back in unadulterated states, though
12 they had been properly worn. People either took
13 them off, or they fell off, or they were partly
14 off.

15 I think their conclusion was that it was not
16 really a practical way of drug testing, although
17 they got good agreement between their urine and
18 their patch results for the patches that they did
19 collect with them, 92 percent concurrence for
20 cocaine and somewhat less for opiates.

21 The last one I'm going to talk about is oral
22 fluid. There's been a huge improvement in

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1 technology in this field. This is the old way that
2 we used to do it. We put a cotton roll in the
3 mouth, and sucked up some oral fluid, and stuck it
4 in a tube, and froze it. But now, they have these
5 devices that actually you put the end of the device
6 in the mouth. It absorbs some of the oral fluid,
7 and then acts like a cassette, and can be put into
8 the detecting instrument. So it's really quite
9 convenient.

10 The major analyte is parent over metabolite.
11 The detection time is 1 to 2 days, and that depends
12 on the cut-off you choose as well as the analyte
13 that you choose. I'll show you some data. It's
14 very good for detecting recent use and could be
15 very sensitive for looking at rate of change of
16 use.

17 The collection is quite convenient now with
18 those devices. Contamination can be a problem if
19 the drug is taken orally, smoked, or snorted. You
20 can get a temporarily high concentration that's not
21 really reflective of the dose that was taken.

22 It is an on-site test that you can do, but

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1 it hasn't really been used as an outcome measure,
2 and the concentration of drug in the oral fluid is
3 affected by flow rate and pH.

4 So this is a study that was done by Marilyn
5 Huestis, and this is cocaine concentrations and
6 benzoylecgonine concentrations with two different
7 doses of cocaine, 75 and 150 milligrams
8 administered. And what they found is that cocaine
9 was detectable virtually immediately, but was
10 present only about 12 hours. The benzoylecgonine
11 on the other hand took a while to show up, but it
12 lasted somewhat longer. So this looks like kind of
13 an intriguing test.

14 That's the data I was going to present. I
15 was thinking about what we might do to improve
16 these things. One thing we might do is optimize
17 our concentration cut-offs that would affect our
18 detection windows because the purpose -- most of
19 the tests are designed to catch everybody, but we
20 don't necessarily want that. We might think about
21 combining different biological matrices to optimize
22 our windows of drug detection.

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1 I think we should be investigating methods
2 to improve adherence to the specimen collection, at
3 least for trials. And I think we also ought to be
4 thinking about methods to improve our remote
5 collection of specimens because there's lots of
6 sensor development going on, and maybe that would
7 be a good approach.

8 So I'd be happy to answer any questions.
9 (Applause.)

10 DR. STRAIN: Question?

11 MALE SPEAKER: Kenzie, with the new-use
12 rules, the improvement in the concordance, has it
13 been replicated by any other studies?

14 DR. PRESTON: I don't think so.

15 MALE SPEAKER: That's something that we have
16 the data. We could also --

17 DR. PRESTON: Yes. It would be interesting.
18 We only had limited funding for doing the testing,
19 so we actually don't do it routinely anymore.

20 MALE SPEAKER: Right.

21 DR. PRESTON: It was a very brief period of
22 time.

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1 DR. STRAIN: Other questions for Kenzie?
2 It's a great systematic review of the topic area.
3 I appreciate it.

4 Actually, let me just quickly ask, the oral
5 fluid mechanism, I actually haven't seen. Is it
6 that the strips go in, and then you put the strips
7 in the little device, or is it that the plastic
8 device has the strips, and you hold the plastic
9 device while the person puts the strip in their
10 mouth?

11 DR. PRESTON: The strip is attached to the
12 device while it's in the person's mouth.

13 DR. STRAIN: Got it.

14 DR. PRESTON: Now, I don't know the details
15 of do you use the same device with different
16 strips. I've actually seen it demonstrated, but I
17 don't recall how it was done.

18 DR. CARROLL: This is Kathy. Any idea on
19 how much it costs?

20 DR. PRESTON: It was quite a lot. It was,
21 like \$30 a test, I think.

22 MALE SPEAKER: Is it immunoassay based?

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1 Might you have false positives? Because at least
2 with urine, you could ship a sample for
3 confirmatory, but if it's immunoassay based, you
4 have false positives, and you wouldn't have
5 anything to use for confirmatory testing.
6 DR. PRESTON: I don't remember the exact
7 basis of the testing that's done, but as far as I
8 know, you actually still have the thing that you
9 collected the specimen on to begin with. So
10 potentially, those would be available for retesting
11 in a different way.
12 MALE SPEAKER: Question about
13 benzoyllecgonine cut-off. I am hearing that Xcenda
14 and the industry have 150 as a cut-off, and you
15 measured about 300. So we are looking for the
16 endpoint as abstinence, never cocaine. Then it
17 depends. We are doing a different endpoint, a
18 value for the negative urine? So what is your
19 thought on that?
20 DR. PRESTON: Well, I think that's a very
21 good point. I know they've changed the
22 concentration cut-off for some other drugs. These

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1 groups that are primarily interested in drug
2 driving and workplace use are the ones that are
3 sitting at the table determining what these values
4 ought to be.
5 I think it depends on the purpose. If
6 you're doing very infrequent testing, and you want
7 to know if they used any drug, then you might want
8 to have the most sensitive test that you could
9 possibly get.
10 I think for the purpose like I showed you
11 with our participant, where they're kind of going
12 along, if we have too low of a detection to report
13 a positive, then you might be detecting use when
14 use didn't actually occur. So I'm not sure I
15 answered your question.
16 MALE SPEAKER: My point is, is all in the
17 industry, academic, we use the same standard for
18 the cocaine?
19 DR. PRESTON: Well, SAMHSA is the one who
20 determines the concentration for the U.S. There's
21 a different group that determines it for Europe.
22 But I think if we, as a community, chose that we

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1 wanted to select a different cut-off, we might be
2 able to arrange to have the tests be set to be
3 sensitive to a different cut-off concentration that
4 we felt was optimal for what we wanted to do.
5 FEMALE SPEAKER: The SAMHSA cut-off is not
6 for research purposes. Their cut-off is
7 established for different purposes.
8 DR. PRESTON: Right, exactly.
9 FEMALE SPEAKER: So that's one thing you
10 have to bear in mind.
11 DR. PRESTON: Right. But the commercial
12 tests, then, are all geared to that cut-off.
13 FEMALE SPEAKER: Right.
14 DR. PRESTON: And that's what's generally
15 available to us.
16 FEMALE SPEAKER: Right.
17 DR. STRAIN: Thank you.
18 Celia, you were going to come up to discuss
19 this, please? Thanks.
20 Discussant – Celia Winchell
21 DR. WINCHELL: I'm going to sit down to do
22 this because I've taken a lot of notes, and I need

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1 to organize them. I'm only supposed to be
2 discussing Dr. Preston's talk, but I am going to
3 broaden my comments a little because I want to
4 integrate a little bit of other things that I've
5 heard.
6 It sounds as if, much as we would love to
7 ultimately demonstrate that a medication could
8 improve the way a patient feels or functions, a lot
9 of people really do care about whether or not the
10 patient is using cocaine.
11 So it seems as if the strategy of trying to
12 establish some measures of cocaine use as valid
13 surrogates for stable change that translates to
14 clinical benefit is not a bad route to take.
15 As we accept that we're focusing on trying
16 to characterize the nature of patients' cocaine
17 use, first, I want to understand whether it is even
18 possible to measure reductions in drug use as
19 defined as less use per occasion or have we given
20 up on that entirely because, much as people find it
21 attractive -- and someone always mentions it
22 whenever we talk about these things -- it just

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1 can't be done.
2 So if we have consensus that that's just
3 something that can't be done no matter how much you
4 might think that's important, or valuable, or
5 important to some patient, put that aside. It
6 can't be done. If there is some consensus on that
7 point, that might be one thing that we can emerge
8 from this process.
9 DR. STRAIN: I'm sorry, but repeat that
10 point. I want to be sure I got it clear.
11 DR. WINCHELL: The reductions -- a change in
12 someone's drug use pattern is defined as less use
13 per occasion. Can you say -- this always -- "If I
14 have some patients, that if they injected 6 times a
15 day instead of 8 times a day, I would consider that
16 a victory." There's always somebody who will bring
17 out that straw man. But if that cannot be
18 measured, then maybe we have to put that aside.
19 DR. STRAIN: So let me interrupt you, if I
20 can, just to say -- because this is great. This in
21 part is the discussion that I think we need to have
22 in the last half-hour, but we can morph into that

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1 discussion because I think those are great points.
2 If that's the case, then I'm going to ask
3 Brian to go to the post-it board on steroids,
4 because one of the goals I would like to see out of
5 this is that we do have some agreement about some
6 of the take-home points that we've got based on the
7 last day and a half.
8 So I want to continue this discussion, but I
9 want to pull Brian up there because he's going to
10 be pulling together some materials here into some
11 sort of paper. And if we got agreement on things,
12 then it would be good for him to make sure that
13 he's got those locked in, as well as all of us.
14 So let's go back to your point if we could.
15 Is that all right with everybody?
16 DR. PRESTON: I mean, the point's been made.
17 I feel like I haven't heard anyone talk about that
18 being feasible. And we can only choose endpoints
19 that can be operationalized. So no matter how much
20 we might like a particular idea, if it cannot be
21 measured, if it is grossly sensitive to missing
22 data, which we know we're going to have, if it's

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1 ridiculously expensive, if it requires us to follow
2 our patients around with some kind of test kit and
3 test them every 20 minutes, it just can't be done.
4 So we need to let go of some sentimental
5 attachments to certain ideas when we confront what
6 is real and what is not real.
7 So that's one question. I didn't hear
8 anybody talk about whether it is possible to do,
9 but it doesn't sound like it is.
10 FEMALE SPEAKER: I don't think, based on the
11 existing biological tests, that that is possible
12 beyond self-report.
13 MALE SPEAKER: Right. And I think
14 self-report, that's what we're focused on; could
15 you get the number of grams of cocaine use per day,
16 if that's what we're focused on, exact quantity of
17 use. Some of the issues we haven't talked about is
18 we don't know what street purity is. Some people
19 smoke it. Some people inject it. So a certain
20 amount injected is not the same as a certain amount
21 snorted or smoked.
22 So I don't know whether we want to say it's

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1 impossible to quantify, but it's so complicated,
2 given multiple routes of administration, unknown
3 street purity. It's certainly not as easy as
4 alcohol, where you know what a beer is or a glass
5 of wine.
6 MALE SPEAKER: In many of the clinical
7 trials that would we did at the ARC many years ago,
8 we used to collect amount and cost of the drug.
9 And it was so unreliable, that it was not worth it
10 to continue.
11 DR. WINCHELL: So we may actually have a
12 list of things that are frequently suggested or
13 bandied about as potential things to measure that
14 we can all agree are barking up the wrong tree.
15 DR. STRAIN: So let me --
16 DR. WINCHELL: But if I don't finish my
17 thoughts, which are spread out over six pages, I
18 will be here all day.
19 DR. STRAIN: That's all right. We've got
20 until noon.
21 DR. WINCHELL: Oh, okay.
22 DR. STRAIN: Because I'm giving you -- we're

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1 going to do -- we've got 45 minutes.
2 DR. WINCHELL: Oh, okay.
3 DR. STRAIN: But I want to just be clear
4 because are we saying that a self-report measure of
5 number of days of use out of the last --
6 DR. WINCHELL: No. See, that's the next
7 thing on my page here.
8 (Laughter.)
9 DR. WINCHELL: I also hear that although the
10 world may need to be convinced that using less
11 cocaine -- or using cocaine less frequently without
12 attaining complete abstinence translates to
13 clinical benefit, it could be possible to do that,
14 and that additional explorations could be done.
15 But we nevertheless need to understand the
16 limitations of how we detect frequently of use and
17 what is realistic. And we have heard that if we
18 test too frequently, we need a mathematical
19 algorithm to actually translate that to actual
20 frequency of use. If we test too infrequently, we
21 might not know the truth about frequency of use,
22 but we maybe create some type of a bogus pipeline

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1 effect that increases the veracity of self-report.
2 I find myself wondering whether, actually,
3 greatly lowering the cut-off and greatly reducing
4 the frequency of visits could be a -- if we're
5 willing to characterize patterns of drug use not in
6 terms of days but in terms of weeks -- we get
7 somebody in once a week with a low cut-off, and we
8 say, well, that's a clean week.
9 If that's good enough for us, maybe we can
10 reduce the cost and the burden of biological
11 verification, but we need some kind of a balance
12 between the fine-grain characterization of what
13 people are doing and the realistic constraints of
14 how fine-grain we can actually get it and know that
15 we've got the truth.
16 I could stop there for people to respond to
17 that or I could try to get out all my other
18 thoughts. But I will let Dr. Strain decide which
19 of those things I am going to do.
20 DR. STRAIN: Any thought? Did you want to
21 say something, Kathy? Press on.
22 DR. WINCHELL: Okay. It also sounds like

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1 there are very promising sources of information
2 available to validate the idea that 30 days of
3 abstinence at the 6-month time point looks pretty
4 table. Those shift tables look really good. Of
5 course, is that going to translate into other
6 populations?
7 So one of the first things, I think, would
8 be great to do would be to explore those cut points
9 and additional cut points, to the extent that we
10 can characterize them, in other data sets, clinical
11 trial data sets, epidemiologic data sets, anything
12 else we can get our hands on.
13 It looks like the Yale data may be
14 converging on a similar point, but I'd really like
15 to see a much higher correlation to call something
16 a surrogate. Like, it's positively correlated, but
17 to really substitute A for B, just a positive R
18 isn't enough. It has to be super high. So I was
19 wondering about looking at the pattern at 6 months.
20 How does the six-month follow-up predict the
21 12-month follow-up and predict the good outcome,
22 and to pursue some of those studies.

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1 Now, I know nobody wants to do a 6-month
2 trial. But one reason that we may not be able to
3 see a difference on measures of impact of changing
4 drug use is that it just does take a while for
5 things to come into place. And your study may need
6 to be long enough to move the needle.
7 An obesity trial is 12 months long, or
8 24 months sometimes. That's how long it takes
9 people to lose that much weight. So if we want a
10 study to look at how people are looking at
11 6 months, it doesn't necessarily mean we have to
12 bring them in 3 days a week for 6 months. They're
13 not going to stand for that.
14 So some of our thinking has to go around
15 what can we conveniently, economically, and
16 credibly capture, and measure, and characterize for
17 that amount of time. And if we think that the
18 definition of good outcome that the Yale group has
19 used has some face validity, pursuing whether that
20 type of information is available in other data sets
21 gives us an opportunity both to validate 30 days of
22 abstinence during month 6 against a distal measure

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1 of how patients feel and function and other
2 patterns that we may have been able to
3 characterize.
4 But it sounds like some effort to develop
5 things like remote testing. We now have the
6 technology to watch a person on their cell phone
7 blowing into an alcohol sensor. Can we do
8 something like that with cocaine, with
9 methamphetamine, or improve the long window of
10 detection? If what we're interested in is
11 abstinence, then measures that have long windows of
12 detection, like sweat patches, are very beneficial.
13 If we're not interested in complete
14 abstinence, then we don't want measures with long
15 windows of detection. So some of where our efforts
16 and enthusiasms go may turn on that decision point.
17 I think I've got them all. I'm sure there's
18 more, but those are my thoughts. Thank you.
19 Q&A – Group Discussion
20 DR. STRAIN: Thank you.
21 So let's take a step back, actually, because
22 there's an opportunity to have a little bit of

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1 discussion about biologic assays and to sort of
2 think that through -- so Brian, if you want to, you
3 can take a break from that; well, it's up to
4 you -- and then we'll go into a more general
5 discussion.
6 So thoughts on Kenzie's talk or Celia's talk
7 with respect to biologic assays? Yes, Raye?
8 DR. LITTEN: I have a question for Kenzie
9 or, actually, it's more to NIDA, to Dave, or Phil.
10 We're developing our alcohol sensors, and we have
11 some out there. What's really nice about it is
12 that it can measure alcohol objectively in real
13 time. And I don't know if that's possible to
14 measure, say, a cocaine sensor, a metabolite, or
15 some of these other using a sensor that actually
16 tells you when it was taken and approximately how
17 much was in the bloodstream.
18 Is that something feasible that you all have
19 looked at? Because that would certainly solve the
20 problem of quantitative -- I mean, that would solve
21 a lot of problems. You could tell how much they
22 were taking it and when.

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1 MALE SPEAKER: Yes, as long as -- yes.
2 DR. LITTEN: It would solve a lot of your
3 problems if that's possible.
4 DR. McCANN: Well, I mean, the factor that
5 you have to add in there is cooperation from the
6 subject to use whatever, wear the patch or whatever
7 device you're talking about. I think we support
8 through SBRI a lot of very innovative work, but
9 when we have such trouble getting people to take a
10 pill once a day, developing technologies to monitor
11 that may require even more compliance than taking
12 the pills becomes a challenge.
13 I don't think we're driven to do that
14 because we do have urine testing where we can
15 follow BE. In the alcohol field, you're relying so
16 much on self-report that I think you're pushing
17 that technology and you want to be able to measure
18 that.
19 DR. LITTEN: Well, I will just say this.
20 These are things -- once you put them on, it's
21 really hard to take off. And if you do take it
22 off, you can tell because there's a temperature

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1 probe on there.
2 DR. McCANN: This is like a monitoring
3 alcohol bracelet? If you were under house arrest,
4 it would be clipped to your ankle, and it would be
5 on there for good.
6 DR. LITTEN: Well, even house arrest. Right
7 now, we have to prove it, but it's around the ankle
8 right now.
9 DR. McCANN: We're constantly trying to get
10 the right patients for our studies, but some
11 individuals and maybe some IRBs might consider that
12 coercive, that sort of an ankle bracelet, if you
13 will.
14 I'm just saying I think it's a great idea.
15 We have oxygen sensors, and maybe that could be
16 detected. But I just worry about just the function
17 of putting that on. If you have a drug approved
18 and it works in the real world, they're not going
19 to be wearing a sensor. It's an interesting idea.
20 DR. LITTEN: Well, I think the technology
21 would probably be the most challenging to come up
22 with something like that. I was just wondering if

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1 you had thought of that or if it's even feasible.
2 That's all.
3 DR. McCANN: I tend to think more simple
4 things. The benzoylecgonine is pretty good. When
5 you look at day-by-day subject's self-reported use
6 versus the BE, a lot of them tell the truth, and
7 there's a group that underreports. Clearly, there
8 is some underreporting.
9 I've had the idea -- we haven't implemented
10 on anything -- of trying to use contingency
11 management to reward accurate self-report, not
12 contingency management to pay for clean urines, but
13 to say, as long as there's no conflict between our
14 urine test results and what you're telling us,
15 you'll go home with \$10. I think that that could
16 substantially improve our self-report, if you just
17 say, "Look. We just want to know accurately what
18 you're doing," and we pay them a little bit.
19 It's complicated, but please think about
20 that because that could be a fairly inexpensive and
21 low-tech way to improve the accuracy of the urine
22 test.

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1 DR. PRESTON: So we're doing real-time --
2 MALE SPEAKER: I'm sorry.
3 DR. PRESTON: -- self-report, and we do pay
4 for correspondence between reporting on electronic
5 diary and the urine results. So it is possible to
6 do that.
7 FEMALE SPEAKER: You should write that down.
8 DR. STRAIN: I'm sorry. Actually, I
9 couldn't hear. So repeat it, Kenzie or Dave.
10 DR. McCANN: The general point was to use
11 contingency management to reward accurate
12 self-report and correspondence with the urine. And
13 Kenzie is saying that she's done some of that with
14 the electronic diary. So I think there's probably
15 something good to mention in the paper, encourage
16 people to think about more.
17 DR. STRAIN: Sharon, did you have a comment?
18 DR. HERTZ: Yes. I think that, at this
19 stage, it seems like there is a worry about
20 situations that is a little premature. You guys
21 have a huge challenge here in contrast to some of
22 the other drug groups because you have no known

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1 effective drug therapies. So you don't know
2 whether your measures can pick them up or not. And
3 you don't have measures that you know necessarily
4 will detect an effective drug therapy.
5 So I would say that the kind of work that we
6 heard this morning -- what was her name from
7 Keiser -- yes, Connie, is great. But basically, it
8 seems like an all-hands-on-deck, throw-everything-
9 at-every-study and see what turns up because
10 eventually, something is going to show the adequate
11 sensitivity and specificity so that when a therapy
12 that's effective comes along you'll -- I mean, it's
13 going to take some data drudging to comb it up, to
14 sort this all out, but we can handle things like
15 ankle bracelets with informed consent and the
16 ability to have it taken off tomorrow if you
17 withdraw consent.
18 So I wouldn't throw anything out the window
19 yet. But I think the key is to try and be as
20 systematic as possible. Even things that are
21 expensive now, granted that you need the money to
22 do the study, but if it becomes useful in the

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1 future, the price will become competitive, and
2 you'll have a competitive market, and it'll come
3 down.
4 I don't know if there's familiarity with
5 this, but I want to just introduce a concept that
6 speaks to a little bit of what Laurie said about
7 challenges with the duration of following patients
8 and understanding the impact of outcome measures
9 for long-term improvement in survival.
10 You may be familiar with some of the
11 accelerated programs that we have, fast track, and
12 priority, and that sort of thing. But there's a
13 different concept of accelerated approval under
14 something called subpart H, which is in 21 CFR.
15 It's 314.500. And this is subpart H, accelerated
16 approval of new drugs for serious or
17 life-threatening illness.
18 I am going to read it, just a little
19 paragraph.
20 "FDA may grant marketing approval for a new
21 drug product on the basis of adequate and
22 well-controlled clinical trials, establishing that

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1 the drug product has an effect on a surrogate that
2 is reasonably likely, based on epidemiologic" -- I
3 can't read my writing, something -- "and
4 pathophysiologic or other evidence to predict
5 clinical benefit, or on the basis of an effect on a
6 clinical endpoint other than survival or
7 irreversible morbidity."
8 This is subject to the requirement that the
9 applicant study the drug further to verify and
10 describe the clinical benefit. So postmarketing
11 studies are required.
12 But if you have an endpoint now that looks
13 very promising and it seems to be a reasonable
14 surrogate, it doesn't have to be proven ahead of
15 therapeutic development of a clinical trial and
16 drug development.
17 FEMALE SPEAKER: I think what we've been
18 debating a lot is what reasonably likely means.
19 DR. HERTZ: And that's okay.
20 FEMALE SPEAKER: That's where the
21 differences in opinion lie.
22 DR. HERTZ: That's okay. I mean, that still

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1 is the big initial hurdle. But once something,
2 some conglomeration of endpoints, whatever it is,
3 looks good, the opportunity to use this subpart H
4 might be helpful rather than waiting for that
5 10-year, long-term survival outcome or whatever.
6 It is extremely important that if this is
7 embarked upon, that the understanding of the
8 requirement for postmarketing follow-up is there,
9 there's the concept of approaching that with due
10 diligence.
11 I will say that, although rare, failure to
12 either do the study or get the right result from
13 the study can result in market withdrawal through
14 the appropriate legal proceedings. So even if
15 you/we can get to the point of that, our
16 opportunities to get this on the market, get
17 something on the market, and then follow up.
18 So if that helps at all take some of the
19 burden of understanding the surrogate now, perhaps
20 that helps move things along.
21 DR. STRAIN: No. That's great. Yes, Phil?
22 DR. SKOLNICK: I think, Sharon, that's a

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1 really important point because part of the
2 issue -- I think part of the reason why we don't
3 have any effective meds approved is because we had
4 difficulty getting pharma interested in cocaine as
5 a therapeutic endpoint for multiple reasons. But
6 with that information at hand, with perhaps some of
7 the things we've discussed today, that may be able
8 to incent potential partners that will be able to
9 develop the drugs. I think this is a really
10 important point.
11 DR. STRAIN: Thank you.
12 Connie, before you go, let me just say, I
13 think we're now going to morph into the more
14 general discussion of conclusions and where we may
15 have some agreement on some points, so I want to
16 open it up for a wider discussion. And I have a
17 couple of points I'd like to throw out, maybe after
18 Connie, to see if there is agreement on that.
19 Yes, Connie. Go ahead.
20 DR. WEISNER: This is just anecdotal, but I
21 can just tell you that many companies are coming to
22 Kaiser asking to try out some sensors for drug

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1 testing that are really small, look like little
2 Fitbits and things like that, and things you could
3 do with an app on your cell phone.
4 I'm just thinking that while we're drudging
5 these other data sets, I have no idea how valid
6 these are going to be or where they are in the
7 process, but I think that there's a lot of action
8 going on with that.
9 DR. STRAIN: Thanks.
10 Dave, those companies aren't on your radar
11 screen? I don't know. Maybe that's a discussion
12 to have with Connie about who they are, whether
13 they're named after a fruit.
14 DR. McCANN: Yes. We do support -- and not
15 necessarily just from our division, but the other
16 divisions of NIDA that would be supporting some
17 technology development in terms of assays also, so
18 we have the long-term approach to improving
19 technologies.
20 DR. STRAIN: So let me see if there are some
21 things that we can agree upon. Maybe I'll start
22 with low-hanging fruit. So it seems to me, looking

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1 back on the last day and a half -- and I want to
2 thank everybody for your engagement in this
3 process. It seems to me, first of all, that we can
4 use alcohol as an experience, as a model sort of
5 for at least how to think about approaching this.
6 Maybe that seems overly simplistic, but I think
7 it's useful to get that out there, that we're not
8 going just off into uncharted territory. There's
9 been this experience that's helpful and can inform
10 this.

11 Certainly, we need to keep in mind this trio
12 of points about how the patients feel, function, or
13 survive from an FDA perspective as critical
14 aspects, as we look at measures.

15 We may want to consider if there are
16 ways -- and I want to think on this, but if there
17 are particular aspects of the motivations of the
18 patient to enter treatment that might need to be
19 accounted for some way, that may be a ripe area for
20 consideration. And Connie, I'm trying to reflect
21 the points that you raised yesterday and today in
22 that respect.

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1 Then it also seems to me that we've talked a
2 lot about abstinence. And I think it's been sort
3 of underlying this, but I'm not sure it's been
4 specifically stated. But I think that we've talked
5 about abstinence as a goal and also abstinence as a
6 measure during treatment. And as a goal, it may be
7 that there is a step between pre-treatment and
8 abstinence, where there's a decrease in use as a
9 step towards abstinence. And I think we're okay
10 with that.

11 MALE SPEAKER: Or another way to put that is
12 intermittent abstinence --

13 DR. STRAIN: That's nice.

14 MALE SPEAKER: -- instead of decreased use,
15 which doesn't sound as impressive.

16 DR. STRAIN: Yes.

17 MALE SPEAKER: Having intermittent
18 abstinence is going periods of time without drug
19 use sounds a lot better. It's the same thing.

20 DR. STRAIN: Yes.

21 FEMALE SPEAKER: And it may all be what you
22 label it.

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1 DR. STRAIN: Well, words are powerful,
2 although I find myself thinking about intermittent
3 abstinence in my daughter and wondering whether
4 intermittent abstinence is -- I think I want
5 abstinence.

6 (Laughter.)

7 FEMALE SPEAKER: The point about
8 intermittent -- since we've began this thing in
9 2011 or '12, it's been hard to get anybody to give
10 me a useful definition of what reduced use would
11 be. I like Connie's, the 1 to 4, that there's
12 variation of it. But the field, as we look for it,
13 would say that there is something to this notion of
14 intermittent abstinence, periods of abstinence, the
15 contingency management data. Some of the
16 medication data has it, CBT. The data does point
17 us that way.

18 MALE SPEAKER: So if you're aiming for the
19 end of a trial having sustained abstinence for 3 or
20 4 weeks at the end of a 12-week trial, not
21 everybody is going to achieve that, but you're
22 going to get periods of quitting and periods of

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1 relapse throughout. And hopefully, the frequency
2 of abstinence will become longer.

3 I think, if we start thinking about it in
4 those terms, or reduced use in terms of periods of
5 abstinence that are growing, it would be a good
6 thing.

7 DR. STRAIN: I like that, yes.

8 That sort of morphs into a point about how
9 we quantify -- when we think about self-reports,
10 how do we quantify self-reports. And I want to
11 pick up on Celia's point that we don't have a
12 standard drink for stimulants, and we're not going
13 to find a standard drink for stimulants in the
14 analog to that. But that doesn't mean that there
15 aren't self-report metrics of use that can be
16 helpful. And it's probably -- people so far seem
17 to be agreeing with me. It's probably the case
18 that those self-reports are days of use out of some
19 period.

20 Kathy just winced when I said that.

21 MALE SPEAKER: In most of our existing
22 database, that's what we have.

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1 MALE SPEAKER: Right, had a series of
2 continuous measures that were associated with good
3 outcome. Some self-reports were in there, a
4 percent negative or a percent positive in urine
5 samples. Using those might be helpful.
6 DR. STRAIN: I want to come back to urine
7 samples, but I guess what I'm trying to figure out
8 is do we think -- do we want to get into number of
9 uses per week, or should we say number of days of
10 use is the metric in this area? And maybe we don't
11 have a consensus or agreement on that at this
12 point.
13 My kneejerk is to say, especially after
14 Celia's comments, well, maybe we should look at
15 number of days of use out of 30 or whatever.
16 (No response.)
17 DR. STRAIN: Okay. So you all agree with
18 me. Okay.
19 MALE SPEAKER: One of the things that I
20 learned from the alcohol literature is, it's most
21 useful to let the data be your guide for these. So
22 I don't know. Percent days of abstinence has been

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1 around for a long time and has failed to impress or
2 convince anyone, this notion of frequency. We
3 don't know yet which cut point matters. We don't
4 know if going from 30 to 15 or 15 to 1 and how
5 long, we don't know yet. Those are all useful
6 empirical questions.
7 DR. STRAIN: Let me put it this way,
8 though -- and maybe we're in the same -- maybe
9 we're running in parallel here. We can't say we're
10 going to look at changes from heavy drug use days
11 to fewer heavy drug use days because we have a hard
12 time quantifying what is a heavy drug use day,
13 unlike alcohol.
14 So given that, all we can do is say, is it a
15 drug use day or not. And I think that's the unit
16 of measurement that at least we need to explore and
17 model, is what I'm arguing.
18 MALE SPEAKER: I misunderstood. I thought
19 we're suggesting that we move away from any sort of
20 arguments about quantity and just make the quantity
21 versus frequency stay with frequency.
22 DR. STRAIN: Yes, as opposed to -- so for

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1 example, in the opiate area, we have often reported
2 number of times of use per day or number of times
3 of use per week, especially for heroin, because
4 it's pretty common that it's 3 to 5 times a day,
5 7 days a week. But I think there's a lot more
6 variability here.
7 So let's go back. Ken brought up urine
8 results, and I want to bring up urine results
9 because I found myself today thinking about this.
10 And I wondered where we were with this.
11 Yesterday, I was thinking about urine
12 results as an in-treatment measure. Today, I found
13 myself thinking, could urine results be a longer
14 term outcome measure? And if so, do they represent
15 improvements? Is urine results a surrogate measure
16 for improvements in health and social function?
17 My gut reaction is to say yes. But do we
18 know that for stimulants? Yes, Kenzie?
19 DR. PRESTON: Since a positive urine on the
20 first day of treatment is a good predictor of
21 continued use during treatment, it seems to me that
22 a positive urine in a follow-up phase probably also

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1 predicts continued drug use. I think I'm agreeing
2 with you is that in fact it is an indicator that we
3 shouldn't be ignoring, even though the period that
4 it's looking at is relatively brief.
5 DR. STRAIN: So I guess maybe this is an
6 FDA -- and I really don't want to put FDA on the
7 spot or something, or anybody actually who has
8 experience on this point. But would you generally
9 see a negative urine result as indicating good
10 health or good social function?
11 FEMALE SPEAKER: So here's what I can
12 answer. We have always been willing to accept that
13 demonstration that people have completely
14 discontinued their drug use for a good chunk of
15 time, a chunk of time long enough to predict that
16 they're going to stay that way, that that is a
17 valid surrogate for clinical benefit, quitting
18 smoking, stopping drinking.
19 We have not ever required any additional
20 data to validate that abstinence from drug use is a
21 valid surrogate for clinical benefit. Where we
22 have felt the need for some data to validate

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1 surrogate endpoints is when they are not abstinence
2 endpoints. We've been willing to accept that if
3 you stop using, you will benefit.
4 DR. STRAIN: That's helpful. That's great.
5 Yes, David?
6 DR. McCANN: I was just thinking about the
7 issue of percent clean urines, percent dirty urines
8 versus number of days use. If you think about
9 real-world applicability, how many people are going
10 to be able to go into a doc and say I've got a
11 cocaine problem? And then where does the
12 discussion go? They don't go into what percentage
13 of your urines are dirty or clean. It's how many
14 days you have used.
15 So in terms of practical application, it
16 seems like focusing on number of days use with
17 urine testing to try and confirm that might be
18 better than talking -- say, in a clinical trial
19 result, such a percentage reduction in urines, I
20 don't know how a physician is really going to
21 relate that to their patients.
22 I guess, if you think about the labeling

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1 that would be in there, what would guide a
2 physician. That's where I'm going with that.
3 DR. STRAIN: I like that. Thanks.
4 FEMALE SPEAKER: I don't remember who said
5 this first, but I am fond of quoting it, that
6 cocaine [ph] is not the disorder we're trying to
7 treat. So I think that Dave is right, that even as
8 you say, Eric, words are important, to talk about
9 it in terms of patterns of use instead of patterns
10 of drug test results, of course we need to
11 understand better how much we know about people's
12 pattern of use and how well our biological measures
13 capture them. But I think that would help people
14 understand the impact a little better.
15 MALE SPEAKER: There is a parallel. The
16 alcohol literature is useful, but the smoking
17 literature is also useful. It's CO, confirmed
18 abstinence, at a certain point. My understanding
19 is they're moving away from that a little bit
20 because it's a little insensitive, but people get
21 it. Doctors get it. It's a short time point, but
22 it's useful.

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1 DR. STRAIN: But if you could say -- would
2 it be valuable to be able to say, if you used this
3 treatment at the end of 3 months, if your patient
4 is reporting that they've stopped use or they've
5 decreased use -- if they've stopped use, then
6 there's this likelihood that they'll continue to
7 abstain over the next 12 months. If they've
8 decreased their use to less than 4 days a month in
9 the final or something, or one day a week, or
10 something -- what's that?
11 MALE SPEAKER: Or not more than 4 because
12 that would be once a week.
13 DR. STRAIN: Yes. Then there's a greater
14 than 80 percent likelihood that they'll be
15 abstaining or something. I think that's -- I'm
16 looking at David. Isn't that that you're
17 suggesting?
18 DR. McCANN: I think I've said everything I
19 have to say. It's just in terms of the words that
20 we use, if we can relate it to everyday life and
21 what you've discussed with your physician, I think
22 number of days used, number of times you've used in

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1 the past month, that would be more beneficial than
2 talking about percent of clean urines, although
3 that still may be something good to look at in
4 terms of statistics and meaningful difference for a
5 medication.
6 DR. STRAIN: Well, the analogy might
7 be -- not to belabor this, but when I see a patient
8 who's depressed, I talk to them about, what is the
9 base rate of depression in the population? And I
10 strip it down to very simple sort of stories. And
11 then I say, if you're on an antidepressant at the
12 end of 12 weeks for a garden-variety depression,
13 this is what the chances are that you'll be
14 improved if you take this medicine regularly.
15 So it's those sort of very simple messages I
16 think that, from a clinical standpoint, we're
17 trying to convey.
18 Our time is ticking down, and I want to open
19 up as well to see if there are other points or
20 agreements that we might be coming to based upon
21 this, agreements not necessarily that are
22 conclusions, but agreements also about what we need

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1 to investigate further.

2 MALE SPEAKER: Well, I think the point that

3 Sharon made earlier about being able to prove some

4 of the benefits postmarketing for something -- I'm

5 looking for her exact words here. When you had a

6 surrogate that looks reasonably likely for the

7 benefit, I think that that would be important to

8 put in the paper and to discuss maybe in a little

9 bit more detail how that might play out.

10 So a company might get a phase 2 study where

11 they see in the data something that they think is

12 reasonably likely to be a benefit. They could then

13 have a discussion with the FDA and there could be

14 some discussion about whether there's agreement

15 about whether they think that's reasonably likely

16 to have a benefit.

17 I think it would be good to get that out in

18 the literature, to say how that might play out.

19 FEMALE SPEAKER: I think they would be

20 really helpful for people who have data to begin to

21 explore some things that are reasonably likely, so

22 that a company could come to us, saying, based on

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1 these analyses, we think this endpoint is

2 reasonably likely.

3 That would be much better than having

4 somebody say, here's what we found. Don't you

5 think this is reasonably likely? Because we would

6 need something to go on, to reach agreement, even

7 on that reasonably-likely point.

8 DR. McCANN: The only reason I'm saying that

9 is because we don't have an effective medication

10 yet. I'm always hopeful that the next trial we do,

11 wow, we're going to have an effect, and now, we've

12 got something new, which we would bring to you.

13 FEMALE SPEAKER: But just remember, phase 2,

14 reasonably likely, the discussion would be so

15 that's a good surrogate to take into phase 3.

16 Right? Because this is all predicated on adequate

17 and well-controlled trials? So the conversation

18 wouldn't be, it's reasonably likely on phase 2, so

19 we're going to just go for an NDA. It would be, so

20 this would be the right outcome to take forward as

21 a surrogate, and here's a long-term plan for

22 phase 3, and then postmarketing.

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1 DR. McCANN: And that's exactly what I was

2 thinking. Some companies want to jump in. In the

3 very first trial they do, they want it to be a

4 pivotal trial of the first two. And in a way, you

5 could encourage -- you could get people away from

6 that type of thinking, to say, do a study, see what

7 signal you get, and then come talk to us.

8 MALE SPEAKER: Just one thing that I hope we

9 add to the overall proceedings, the discussion

10 yesterday about the endothelial factor and its

11 potential relationship to cardiac morbidity. I

12 recognize it's super, super early, early days,

13 limited number of patients, but it is a way of

14 connecting decrease in use with probably the

15 primary adverse medical manifestation.

16 There are drugs approved for lowering blood

17 pressure by 5 millimeters of mercury. And I don't

18 know, if you could show that by taking this

19 medication, decreasing use of cocaine, and showing

20 a decrease in diastolic blood pressure by X amount,

21 maybe would also be another way of translating

22 benefit; so just something to consider as

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1 alternative or supportive evidence.

2 MALE SPEAKER: The first manuscript is in

3 press. I think you know that, Eric. Yes? It's in

4 your journal. So it might be useful -- If I send

5 Dr. Lai an e-mail, he might send you a manuscript.

6 You may want to incorporate that into the menu

7 because it's still early, but it's pretty

8 compelling.

9 MALE SPEAKER: There was discussion

10 yesterday about whether to have equivalent of a

11 drink measure, a consequence measure for drugs.

12 It's not necessarily so sensitive in alcohol

13 trials, but maybe it will be more sensitive in drug

14 trials.

15 FEMALE SPEAKER: Can I make a comment on

16 that? Kind of going back to the context of

17 evaluating somebody's improvement in the context of

18 how they enter treatment, I know that several of

19 the industry-sponsored opiate trials, including

20 probuphine, I believe, uses a global assessment of

21 functioning. It's just a single-item measure.

22 I was thinking something like that might be

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1 useful, where an individual is just instructed to
2 assess themselves based on their own employment,
3 and legal, and family problems at treatment intake,
4 and then they can reassess themselves at the end.
5 And it would be easy to administer just a
6 single-item continuous measure, but it would kind
7 of eliminate this problem that we have with the
8 ASI, where some people are entering in with no
9 employment problems. And so we can't expect
10 improvements in employment problems over time and
11 so on.
12 MALE SPEAKER: I think we routinely get to
13 CGI in all our trials. It hasn't been shown to be
14 especially sensitive, but then, we haven't found an
15 effective medicine yet either.
16 DR. STRAIN: And let me point out that we
17 have no effective medicines, but, I mean, we could
18 theoretically at least -- we have contingency
19 management interventions that could be effective.
20 And they could be used as models for trying to
21 manipulate use, quite frankly, so that we could see
22 if measures have value.

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1 MALE SPEAKER: Yes, if they're sensitive, at
2 least, yes. If you have a decrease in cocaine use,
3 you should see a movement in consequences,
4 hopefully, if consequences measured is sensitive.
5 DR. STRAIN: So the big hand is almost on
6 the 12, I think. Any last thoughts people have?
7 Yes, David? Sure.
8 DR. McCANN: I want to clarify for the
9 board -- I mentioned this on the side to Eric. The
10 data that Amy presented, they aren't complete yet.
11 But if she has no plans to publish those data,
12 putting certain aspects of that into this paper
13 might be good.
14 I was impressed. Clearly, clinicians, they
15 like the idea of abstinence, but there was a very
16 high percentage that liked the idea -- I'm sorry,
17 not clinicians, the payers. They liked the idea of
18 decreased use.
19 I don't know how that's going to turn out
20 when she has all of her data, but it might be
21 useful to have that data there. If it doesn't get
22 there, it probably won't get anywhere. So it would

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1 be good to include if she's willing.
2 DR. STRAIN: Yes, we should try to get that
3 out in some way, yes.
4 MALE SPEAKER: Someone else has suggested
5 trying to do that survey on all the stakeholders
6 and compare. I don't know if that can be
7 commissionable, but that would be really
8 interesting.
9 DR. STRAIN: Dave, did you have a comment?
10 MALE SPEAKER: Yes, include employers.
11 DR. STRAIN: What's that?
12 MALE SPEAKER: Include employers, please.
13 DR. STRAIN: Oh, employers. I thought you
14 said, include lawyers, and I thought that was --
15 (Laughter.)
16 DR. STRAIN: Employers, yes. Thank you.
17 Yes, George?
18 DR. WOODY: Would it be useful to separate
19 what would maybe improve the patient but wouldn't
20 be acceptable to the employer? Like impaired
21 healthcare professionals, you really want them to
22 be abstinent, or airplane pilots.

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1 So there are certain social situations where
2 you could say, well, the patient is better, but
3 it's not good enough for whatever that person is
4 doing. Maybe there are two different dimensions
5 there. I don't know how they interact with
6 decisions.
7 Adjournment
8 DR. STRAIN: It resonates with Connie's
9 points from yesterday as well about the motivations
10 as well and the particulars of the population.
11 So let me thank all of you for yesterday and
12 today. I think it's been a really fruitful
13 conversation and dialogue. I feel very
14 intellectually engaged. I wish I could single out
15 each of you to thank you by name, but we'd probably
16 be here for about another half-hour.
17 I think the value of something like this is
18 that almost everybody in the room was both a
19 participant in the audience, but also a presenter,
20 so it makes it for a small but very fruitful
21 dialogue, I think, and I appreciate that.
22 This is a process that likely doesn't end

1 here, and I suspect that, depending upon Bob
2 Dworkin, and ACTTION, and how they feel, this might
3 continue in other forums or in other ways. So you
4 may well hear of another meeting at some point.
5 We'll have to see.

6 But in the meantime, I want to thank all of
7 you for your attention, for your enthusiasm, and
8 for the great conversation. Thanks.

9 (Applause.)

10 (Whereupon, the meeting was adjourned.)

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ACTTION
Measures of Outcome for Stimulant Trials (MOST)

March 26, 2015

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