ACTTION

Measures of Outcome for Stimulant Trials (MOST)

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A Matter of Record

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ACTTION

MEASURES OF OUTCOME FOR STIMULANT TRIALS (MOST)

Thursday, March 26, 2015

Hilton Rockville Hotel and Executive Meeting Center
Rockville, Maryland

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

DR. STRAIN: So we're going to go ahead and get started. Let's see, just a couple of housekeeping things, I think, most pretty much the same stuff as before. If you haven't signed in, please make sure you sign in and silencing your cell phones, things of that sort.

Just to remind you that, if you need a taxi, there is not a taxi stand at this hotel with standing taxis, so do let Valorie or one of the staff know if you're going to need a taxi to the airport at the end of the day. There will be boxed lunches available at the end of the meeting if you want to grab one to take with you on the way out.

Without further ado -- maybe it is further ado -- I'm going to invite Ivan Montoya up to moderate this next session. Thanks.

Moderator – Ivan Montoya

DR. MONTOYA: Good morning. So the first session of the morning is identifying an endpoint that would be persuasive for reimbursement. I understand that the first speaker --

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DR. STRAIN: Rhonda Beale is not able to be here this morning, so She won't be delivering the first of this session's papers.

DR. MONTOYA: So the first speaker is Keith Isenberg?

Presentation – Keith Isenberg

DR. ISENBERG: Good morning. I appreciate the opportunity to be here. My name is Keith Isenberg. I'm a medical director for Anthem Health Plans. That gives me a particular perspective. As you can see, I change things a little bit. I'm going to try to talk about health plans in as general a fashion as possible. In particular, I am going to try to talk about some of what goes into formulary decisions. And I'd be happy to answer questions to try to address your concerns as best I can.

So what do health plans do? Well, we sell insurance. And that seems like a straightforward sort of proposition. But this slide should reveal that it is not a straightforward proposition, and the thing I want you to take away from this is that

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the characteristics of the people to whom we sell the product has an influence on what the benefits are.

So as you all know, because you have jobs, most insurance is sold through employers. It's probably marketed to you as a benefit. It's something that comes -- it's a perk, something that you get because you're employed. That distinguishes the U.S. healthcare system in a substantial way from other healthcare systems.

There's a history to that. I won't go into that. But I think the other important point to make about that is that may be changing as a result of the Affordable Care Act. And I will try to come back to that. Nevertheless, the bulk of insurance sold in the United States is still sold through employers. Employers come in sizes, small and large.

On average, small employers will tend to be more concerned about cost. If you think about what you've read about the Affordable Care Act, you're aware of that. A small employer is very concerned

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about the mandates and their effect on their viability. Large employers tend to be more concerned about persuading you that you're getting a benefit, that this is something that's a good deal, that you want to continue to work here because the insurance is good, and it's going to be good for you when things go south.

Now, these are tendencies because the countertendencies are for large employers to try to shift some of the cost back to you. You probably have noticed that.

In addition, some small employers really are interested in perks. So how does that work? Well, think about professional firms, architects, lawyers, and whatnot. They may be interested in really having gold-plated insurance with the caveat that, again, the Affordable Care Act comes in there with some surcharges, excise taxes on those type of plans. Complicated.

States. We manage Medicaid plans. The states tend to have very specific ideas about benefits. They contract with us with those ideas

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in mind. They can be very specific, and from a formulary perspective, tend to be more aggressive about stipulating rules about how the benefit is to be managed.

If you doubt that, you should be attentive to the developing story about hepatitis C treatment because, I assure you, as a rule of thumb, the states have been more particular about how those treatments are to be administered. Sometimes our contracts often spell out exactly what we're supposed to do in these matters.

The federal government is a contract. We have contracting relations with the federal government. Those contracting relationships include Medicare, which as you know is a plan for the elderly and for this group, the disabled, lots of disabled folks.

However, in addition to Medicare, the federal government has employees. I believe we have some of them here in the audience today. I assure you that the population insured by the federal employees' plan is different than the

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Medicare plan, and I will also assure you that the benefits have some very important differences. And the population health matters are obviously different.

Finally, the federal government has military personnel in their dependence. This is a different population yet again. It'll tend to be younger than the two populations and will have different health issues.

We also sell policies to individuals, and that was changed by the Affordable Care Act. I am not going to dwell on some of the politics that have transpired. My job is just to tell you that the Affordable Care Act changed the individual health plan market substantially. And it has also familiarized you folks to some extent with the idea of purchasing insurance on exchanges.

In addition, there is a movement for employers to do the same thing. So you in the future may be purchasing your insurance off of some exchange vehicle in that annual, however that plays out for the particular employer, process. In other

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words, you'll get online, look at the benefits, be confused, pick something, and move on.

I'd be the first to tell you that part of the challenge with managing insurance benefits is the complexity. So start with this idea that these populations are different, and they have different healthcare needs. And then that has implications for formulary development.

Next concept is, healthcare management is predicated on the concept of medical necessity. I will generally keep my talk to public sources and this is a very public and well-known source about what the definition of medical necessity is. Our definition, the Anthem definition, is not proprietary. It's a little different. It also depends to some extent on the health plans.

So back to those states and the federal employees, those health plans have definitions that are different than we use in other places for our commercial insurance. All of the other definitions of medical necessity that I am aware of spend a lot of time on this concept of accepted standard of

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medicine.

That is a little vague there. Try to sharpen that. But in general, what that means is, we tried to examine a variety of sources to determine just what the practice of medicine involves.

So what does that mean for pharmacy management? Well, first of all, FDA approval, which supports the concept that a drug is safe and effective is necessary. In addition, we mine the prescribing information for the characteristics of that approval.

We want to support the prescription of medications as is believed to be the best way, and the place you start with that is the prescribing information. I have listed a variety of elements from the prescribing information that are looked at to try to figure out how are you supposed to prescribe a drug.

We also examine the peer-reviewed literature, a couple of reasons for that. One is, published information about trials sometimes

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contains information that elucidates or explains a little bit more about how the drug is supposed to be used.

Finally, that last one, authoritative body guidance. What does that mean? That sounds vague, doesn't it? Well, I have already alluded to the role of states in the defining of benefits. They're authoritative. And we manage things by contract, regardless. We're obligated to do that. However, there are other authoritative bodies that we look at.

I suspect everyone in the room is aware of the Substance Abuse and Mental Health Service Administration's guidance on treatment. They have published a variety of extensive information about what you're supposed to do, which is not always congruent with the prescribing information. But be that as it may, we're supposed to look at that. Finally, professional societies offer advice about how to manage medications, and we look at that.

So we take all this information and try to make decisions about how medications are to be made

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available for use.
Nevertheless, whatever work you good folks do in terms of trials, and devising tools, and all the rest of that, it's going to be different when it gets out in the community, guaranteed.
So the concept that we're paying attention to how drugs are used after they're on the market is very important. It is relevant to safety, and there are continuing efforts to try to use claims data to become more knowledgeable about the adverse effect of drugs and devices.
This is a complex and contentious area. Some of you may be aware of the medical device issues going on about identifying particular medical devices by type. If you're not, you might want to look into that. That's kind of interesting.
So what happens to drugs after they're on the market should have some implications for how they're used. And the Food and Drug Administration of course is involved in that. But we also try to pay attention to how the drugs are used.

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When we put in place formulary interventions like prior authorizations, quantity limits, step therapy, all the rest of that good stuff, we try to look and see how that plays out over the passage of time to determine whether or not the management that we're trying to put in place is reasonable, always subject to some debate as to exactly what that means.
So in the end, what I do, or what I'm interested in, or what health plans we're interested in is defining what the standard of care is; what should people be receiving. The conversations of yesterday were very interesting to me, that you folks are trying to determine where we're going. I'm trying to figure out where we're at and trying to make that as consistent and as effective as possible.
I am a believer in what I would say is a Medicare or CMS principle, which is that people, regardless of where they are, should have access to treatment that is as fairly available as we can make it.

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There will be, inevitably, inequities. I've forgotten which conversation I was in yesterday where people talked about -- where there's a discussion about how different the American landscape is because of its diversity, as opposed to some of the other countries in the world, where there's a bit more homogeneity. So it's going to be more complex here in the United States.
From the perspective of a pharmacy, the question of a formulary is, what is the place of a drug and treatment? You folks are informing me that, for stimulus-use disorders, not so much a drug. But then the alternative becomes the therapies that are available, contingency management and cognitive behavioral therapy.
If you think trying to support prudent and sensible use of medications is a challenge -- and it is -- how therapy is administered in the larger community, I would offer the opinion that it's a greater challenge.
Then I just have some general comments to reflect on what I've heard over the past couple of

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days, and these are related to the standard of care.
The standard of care now is abstinence. I understand that there are reasons to move beyond that. But I would encourage you to be mindful of the fact that the patients, their families, and significant others, employers, states, and the criminal justice system are going to cling to abstinence.
So if there are treatments devised that are based on other parameters -- and abstinence was not looking all that bad yesterday. I understood from the data that was available, maybe the patients who have stimulus-use disorders are not so interested in that. But nevertheless, that may still be the most relevant measure.
Regardless, the good news is, the concept that abstinence is a goal is widely accepted. You all are familiar with who is arguably the most famous stimulant user. That would be -- Raye's heard me give part of this talk before, so I'm probably boring. The most famous stimulant user is

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

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

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

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

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

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

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

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

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disorder treatment in particular improve. I believe that's what I share with you folks. And I believe that the challenge that you're confronting is, okay, how we use data to guess where we need to go next.

The asks are to be mindful of what the standard of care is now because, as challenging as it is to determine what we should be measuring and what are the disease concepts we should be addressing -- and those are challenging -- moving the field and getting out of this 20-year interval is widely accepted as something that ought to happen.

If my memory serves, I believe the President of the United States has expressed an opinion of that sort. And for anybody that's interested, there's an article in the Wall Street Journal from this morning, and probably other papers as well, so you don't have to choose that one -- that's the one I picked up at the front desk -- that says we should be paying for quality. So there's a lot of interest in mechanisms to shorten this time

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interval.

Having said that, it's going to be tough. The other burden, I think, for the substance-use disorder treatment is the regulations. I just used methadone as an example, as something that's been around a long time and is still just burdened with regulatory and other approaches that leave it outside of the practice of medicine in many ways, and I don't think that's right.

I mean, I've used the drug. I know enough about the drug to tell you that it shouldn't be outside the practice of medicine. If I were a primary care doctor or other specialist, I would want to know about this.

How do you make that happen? I'm just saying, that's the nature of the -- if you think about it from that perspective, that's the nature of the problem.

DR. MONTOYA: I'm also concerned about the time.

DR. ISENBERG: Sorry. Thank you very much.

DR. MONTOYA: Sorry about that, but we need

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to move on. Thank you so much, excellent presentation. Very interesting.

So the next speaker is Amy Duhig. Amy?

DR. DUHIG: It's a hard one. I'm sorry. I used to be Smith. Now I'm not.

DR. MONTOYA: That would be much easier.

Presentation – Amy Duhig

DR. DUHIG: Well, I want to take a minute to thank you for the invitation. And actually, when I got this invitation a couple months ago, I thought, "My gosh, is my boss going to let me do this? I don't get paid for this. It's not billable hours." But I sent along the e-mail and he graciously said, "Go for it." And so thank you for the invite.

Then I thought, "Boy, now what am I going to say? I don't really know too much about stimulant addiction. I know alcohol. Thanks, Raye Litten, for getting me into this." One of the things that we do -- I work for a company called Xcenda. And we work for a broader company called AmerisourceBergen, which is a pharmacy distributor.

So Xcenda is a scientific and commercial

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consulting company. And with that comes the opportunity to actually reach out to payers, to providers, to understand kind of the unmet need and what their thoughts are. So I thought, "Well, maybe I can get my boss to pay these guys to fill out this survey," and he said yes.

So I actually do have data for you guys. And it's not a huge end. We do have this survey called PayerPulse, that once a month, we send out forms usually from pharma companies and questions that they want real quick feedback on, on specific items.

So we have about 150 people in our managed-care network, that we call it at Xcenda. And this thing fielded on Friday. And I just got data yesterday and, last night, I'm working on Excel sheets, and graphs, and stuff. And I ended up with a response of 34. But the nice thing is that it's pretty heterogeneous in terms of the messages that I got back, so I think it might be useful. And then they had some open fields that they could then also provide some information.

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So we have this double-blinded online survey that was conducted in five days. And again, it was sent through our PayerPulse survey. When I added up the number of covered lives by these payers, on the low end it's about 70 million. We do have a range, though. They had little buckets that they could pick, how many lives are in their plan.

So I would estimate probably, not conservatively, about 100 million. So we had a pretty good split between pharmacy directors and medical directors. And actually, the national versus regional plans was split down the middle. So that was also pretty nice.

Now, because of the small ends but mostly because of the time that I had, I didn't go down and dig and cut data by pharmacy and medical directors or national and regional plans. And also, we're still fielding this, so I should get some more data in that I'm happy to compile and then update you guys if anything changes.

So the majority of advisers or payers that responded were from managed-care organizations.

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And you can see NCO with integrated health delivery systems and PBMs. So just looking at pharmacy benefits only, or the PBMs, were equal.

So who were these folks and what kind of business did they actually run? The majority had commercial Medicare and managed Medicaid. And then the others just kind of trickle down. So what did I find? Well, do you want to know what I asked?

The questions are actually on the bottom of the slides. So the first question I asked was just to get a broad idea of what they thought about the unmet need for stimulus addiction treatment. And I defined it as -- I said cocaine and I had some other examples. And when I went back and I looked at their open-ended responses, a lot of them went straight to stimulant abuse in terms of Ritalin and other things like that.

So, yes. So there were a few mentions of cocaine, but for the most part, I think maybe because they deal with medications all the time, they were thinking, "Oh, my gosh. This stimulant abuse is ridiculous."

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So to put this kind of in context, payers will usually tell us -- we run advisory boards and we run these types of surveys and telephone interviews for companies. And the likelihood of them saying that something is a high unmet need, it just doesn't happen, especially in fields where there's a lot of generics and a really established disease state.

So frankly, their response kind of surprised me, even though this is something that there aren't any available treatments for, but they usually would just kind of be lukewarm. So this is positive, I think, for the field in terms of what they view is needed.

So here's some quotes. And I think it just gives you a feel of the kind of things that they're thinking about. These folks are difficult to engage. There's a large gap between need and solution. There is inadequate support, inadequate guidelines for diagnosis and treatment. And this is not everyone. I selected some of the sexy quotes, but there are some other ones like, "I

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don't know much about this," or things like that.

So then I asked how important is it for new pharmacotherapies to come out. And you see pretty similar -- some of the comments, though, were, "A pharmacotherapy is not going to solve this problem alone. We need behavioral therapies." And I immediately thought that Kathy would be happy to hear that. So some of them that were a little more sophisticated said, "A pill isn't going to fix this."

So then I asked about what do you know about it just in genera. So stepping back from stimulant use, what do they know addiction in clinical -- I'm sorry, in addiction treatment? I thought, "Well, they might know something about alcohol and they might be familiar with opioid treatments."

So there were some folks on the tails, but this isn't bad. At least you have some people who have done a little bit of work in this space and have some sort of familiarity.

So then I asked the endpoint question, what would you value? So from no value at all to

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extremely valuable, how important are these concepts in terms of the value to your formulary decision-making process? So when they look at the data, what are the different endpoints that they would think are important?

Well, of course, you see the resource use up there, but abstinence was number one. But if you look at reduction in use right above it, that's not too bad. And I thought, well, usually, they hate quality of life. That's the worst thing for them. And if they're not an employer-based plan, they're usually not concerned about work productivity. But I thought they were pretty generous in this space. And again, it is 34 folks, but that's probably more folks than we've talked to, period about this.

So then I asked about credibility of endpoints. The lower rating -- the least credible sources are patient-reported sources of information. And that's usually around the efficacy endpoint, not so much about -- I think yesterday we were talking about feel and function. I mean, those things obviously need to come from

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patient in most cases.

But in terms of improvement reported by another person, that was kind of just on par with patient-reported outcomes, but, really, they believe that they wanted those biological measures. And I said non-biological testing. I gave them examples of neuropsych assessment. And they believe in things that are standardized, that are measurable, and that they can kind of hang their hat on.

So here are some quotes about the endpoints. I like the idea of -- I'm truly -- I guess I'm patient-centric first, then caregiver, then observer. The best way would be to use a collection of these measures as a means of cross-validation. And it really goes back to what we were talking about yesterday in terms of cross-validation of measures.

So again, there were some that said, "I don't trust anything that comes from a patient." So it was all over the place, but I thought these were kind of more enlightened responses. And

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that's all I have.

So again, I am happy to go back and look at this a little more systematically, especially if I get more information.

(Applause.)

DR. ISENBERG: Keith Isenberg. Your survey was of pharmacy managers and health plan managers?

DR. DUHIG: Pharmacy directors, yes. We have MDs and PharmDs and so forth. Yes.

DR. ISENBERG: Sure. The reason for focus on prescribed drugs is the concern about diversion. That would be why you would worry about prescribed drugs as opposed to cocaine. And as you probably are aware, there have been some recent events in Florida that would make you kind of sensitive to those kind of concerns.

DR. DUHIG: Yes. If I had, I think, more time and more questions -- I only have a certain amount of questions that I could ask. It's definitely worth diving in a little bit more to that.

DR. MONTOYA: Okay. Thank you so much.

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Do you have a question?

DR. STRAIN: Yes. Could you go back to probably around your fourth slide back? I just wanted to kind of digest this. It was a great talk, by the way, really, yes. And it's interesting. So what they're saying is they would rate abstinence as the most valuable of all in these.

DR. DUHIG: Yes. And you can see I clumped them by -- I split them by 1 to 3 is not valuable. So this is kind of crude. I think it's a low-hanging fruit, but it doesn't mean that other things aren't acceptable as supportive evidence or as a primary. And I think it gets back to what you were saying about what is standard of care.

I don't know if payers really know what the SoC is, not saying people that don't specialize, but someone who doesn't pay much to this, pay much attention to addiction, they're really not going to know what the standard of care is in making decisions without digging in and really finding out.

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

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

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

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

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to be changing a little bit. And then treatment entry and the implications for outcome.

So I talked a little bit about this yesterday in the question/answer period. I'm not going to go into it very much. But in all of our studies that you're going to see today, we have asked all the addiction severity questions. And at the end of each domain -- alcohol, employment, legal, family, mental health, drug, medical problems -- we say how important to you now is treatment for these problems, one by one?

As I said yesterday, the reason that people came to treatment, that's what they say extremely important for. So you can have somebody say, "It's extremely important for me to get my job back," or, "To not have this trial I've got for interpersonal violence coming up go well. But it's not at all important for me to stop using." I mean, that truly happens.

So a lot of our questions that we do in our studies about readiness for change and everything, that just focus on that, are kind of missing the

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boat. And again, we do have more people whose their own personal treatment goal is not abstinence, but that is still what they're being held to.

Also, as I mentioned yesterday -- I think I'm realizing how much I talked in the question-and-answer period now -- the reasons for people coming to treatment are very diverse. And we really see that the non-alcohol and drug outcomes are really related to those reasons.

So I am going to present a little bit of data from another kind of health plan. This is Kaiser Permanente. It's an integrated health plan where alcohol, drug, psychiatric services are run in a staff model. Everyone is employed by the same healthcare system. Northern California has about 3.7 million members. And we have data with the other Kaisers and also 14 other health plans that are harmonized. If there's time at the end, I want to talk about that a little bit in terms of opportunities for research.

This raises some slight differences in terms

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of formulary issues and everything from what Keith has talked about and Amy, but not big enough to go into that. I think, on the whole, we're facing the very same issues that they talked about. I would say also that many of the federally qualified health centers in our counties and states are moving towards this model and finding ways to integrate their alcohol, and drug, and mental health programs.

So what do patients with stimulant disorder diagnoses look like in this health plan? There were, in 2014, 7400 people on the whole. Sixty percent were men, pretty good age distribution up until age 65, and about 57 percent white.

What about for cocaine disorders? Here, it's a little different. The gender difference is pretty much the same. I think the major difference is where there was a larger percentage of white stimulant disorder diagnoses.

Here, there's much more of a difference. In fact, I think I have that number wrong. The African-American population is larger. I'm very

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sorry. I made a mistake there.

MALE SPEAKER: Is this the subpopulation of the [inaudible – off mic]?

DR. WEISNER: No. Because of, really, some patient differences, we have coded stimulant amphetamine disorders separate from cocaine, so it's a separate population. And if I forget to say later, there's about an 8 percent overlap in our treatment samples.

Now, I guess the point I want to make that I think bears on medications, something we've talked about with alcohol findings as well, is that these patients are complex patients. They have a lot of health problems and a lot of mental health problems. Here, I'm just looking at the mental health diagnoses are among the membership of people who are stimulant dependent.

As you can see, it's high. And it probably isn't a surprise to you, but it's always an issue when our clinicians want to give medications. And in case I forget to say this later, one of the things I don't think Raye mentioned yesterday in

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the data that we looked at is that the low-risk drinking outcomes were robust when we controlled for medical and mental health diagnoses and other drug diagnoses, but I don't know that would happen here. And for those who met dependence-disorder diagnoses, again, for cocaine, we have, again, a high rate of other mental health disorders.

So I'm going to present just a little bit of data on what the patients look like in their outcomes in several treatment studies. Now, these are all randomized studies, but they're pragmatic trials, and so they were studying models of care.

The first two studies are the ones that we used for the work with Raye and Dan. One was randomizing patients to getting their healthcare right in the clinic, the substance abuse clinic. The other one was two different levels of treatment. And then the third study is a new one just finished, actually, I should say, 213, that was a medical home study. So patients were randomized to a patient activation intervention while they were in treatment. So they kind of span

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locations and time.

This is what treatment looks like in this health plan. Detoxification is mainly ambulatory. It's all mostly group based, abstinence based. The main part of treatment, the intense part of treatment, is the first two or three weeks, where it's like a day treatment, which is recommended for most people, and then lesser treatment the next three weeks, and then aftercare up to a year, although very few people avail themselves of that.

There is regular drug testing of all patients and increasingly use of medications in the specialty treatment programs, the ones below being used, although disulfiram isn't used very much anymore.

So here is what the stimulant-dependent patients look like. And what we asked patients when we did the dependence interview was have -- amphetamine or speed, crank, meth, ice. This is the years of regular stimulant use, that those who were dependent or abuse, who met that criteria, showed. So very few of them only had

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been using for less than a year.

By the way, I think I'll show this later, but this is about 28 percent of the sample: 26 were dependent; 2 percent were meeting abuse criteria. In terms of looking at cocaine dependence, here we had, again, only 12 percent who had used it for less than a year.

What about their medical and psychiatric conditions? Fifty percent of them had either medical or psychiatric; 34 percent a medical condition and 31 percent a psychiatric condition. And for the cocaine-dependent patients, very similar, about half had one or the other, and 38 percent medical and 24 percent psychiatric.

So here now, I'm trying to take a first little preliminary look at outcomes. So this is measuring 30 days before the 6-month and 30 days before the 12-month follow-ups. So those who were stimulant dependent at intake, those who used no stimulants at 6 months, 95 percent of them were not using stimulants at 12 months; 3 percent were using them 1 to 4 days, those who were using.

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So I did this -- just looked at the frequencies and tried to mimic what we did with the alcohol a little bit in terms of saying zero days, 1 to 4 days, or 5 or more days. So again, of those using stimulants 1 to 4 days at 6 months, 77 percent of them were not using at 12 months and 18 percent. We did urine tests with these studies, by the way. And as you can see, those who were using 5 or more days in the last 30 days did not do so well.

So what about for cocaine? Here, those who did not use any cocaine at 6 months, 95 percent of them were not using at 12 months. And of those using 1 to 4 days at 6 months, there's a pretty even spread. Only 66 percent could meet that kind of no-harm, whatever, if you wanted to call it that, and again, those people who were using 5 or more days.

One thing I have to say, these are pragmatic trials. They are in the course of treatment, real-life programs. So sometimes these patients have gone back to treatment, all of that. I can

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look at if this is interesting, the samples are large enough.

This is a recent study in San Francisco, so it's a smaller sample size. Here is a breakdown of the medical conditions that we found in this sample. Again, two-thirds had a psychiatric condition. About 52 percent had a medical condition, and they're listed there.

Here's where we see hep C coming into the picture. This is a big issue in the health plan, especially for alcohol. They are coming to us and saying, "All of these people are drinkers. These are the sins of the '60s and they're still drinkers. We need to do some intervention in the hep C clinics," because, as you know, those treatments are very costly. When we looked at medical conditions for the cocaine-dependent patients, we found even really higher rates of medical and psychiatric conditions.

In this sample, I accidentally asked for the wrong ones here, so I don't have years of regular use here. But it's how often were they using

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amphetamines in the year before treatment entry, and 45 percent were using them 4 or more times a week, 17 percent, 2 or 3 times a week. And over the past year, those using cocaine in the year before treatment, 28 percent, 4 or more times a week, 27 percent.

So we don't have a sample like 90 percent of people are using it every day or anything, but they do have severity characteristics with medical and mental health issues.

In terms of the prescription stimulants, our providers haven't found that to be as big of a deal. They're also really on top -- they say -- now of addressing ADHD in adults much more than they have in the past in the treatment programs, so I don't know how much this is. But this is before treatment.

So when we look at this sample now and we look at stimulant use in the 30 days before the 12-month interview based on 30 days before the 6-month interview, there are some similarities and some differences. I think the biggest

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difference -- I won't walk you through again, but I think the biggest difference is that when we looked at the old Sacramento study, we found that 1 to 4 days group was 33 percent, 33 percent, 33 percent.

So it looks like -- I hope that in the last 15 years, the treatment has improved a lot and that could be why. But it's also a different population in San Francisco than it is in Sacramento. It's much more of a valley, more amphetamines, and so forth.

Cocaine use at 6 months, here are the biggest -- excuse me. When we looked at stimulant use 15 years earlier in Sacramento, the big difference was that 95 percent of the people were in the 1 to 4 days at 12 months. Here is where we had in Sacramento 33, 33, 33 percent in the 1 to 4 days.

Here, this is where I guess we're seeing that maybe that group is doing a lot better if anyone can decide that 1 to 4 days is an adequate outcome.

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FEMALE SPEAKER: You had about 46 percent for whom that was their baseline monthly use?

DR. WEISNER: Yes. It was that 4, but there was also -- I can go back to that. And this was amphetamines. Yes.

FEMALE SPEAKER: Is this 1 to 4 days over 6 months, or is it 1 to 4 days in the past month? So 1 to 4 days per month in a 1-month look-back at 6 months?

DR. WEISNER: This is asking them for an average over the past year. I don't have that for 30 days with this group. And we also didn't urine drug-test them at intake like we did the rest. So this is averaged over the past year. This is 30 days before the follow-up, big grace period, as Raye would call it, I guess.

So I think, just in summarizing what this might be in terms of implications for new medications again, the high prevalence of medical and psychiatric conditions -- and believe me, the clinicians, especially in primary care, want to know how to handle that. There's a little

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indication that 1 to 4 days at the end of treatment may have longer term benefits. And there are really different issues if we're talking about putting these services or these medications in primary care and in specialty alcohol and drug programs, which we can talk about if you'd like.

So again, this is a study of those entering treatment rather than those dependent on only one substance. Program goal is abstinence. There are small samples. And here, we only examine stimulant outcomes. I didn't look at other substance use or other medical and social functioning, or healthcare utilization, which I could do. I think I said hat already. So I think that's it. Thank you.

(Applause.)

DR. WEISNER: Again, this was kind of not last night, but doing it after the invitation, and I know it's very preliminary.

DR. STRAIN: No. It's really interesting, and I think I probably want to digest some of those slides, the matrices, at some point. But my question is, do you think that the cuts -- if you

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look at those tables, I think there were 3-by-3 tables, do you think the cuts at zero, 1 to 4, and greater than 4 are the right cuts for this disorder? I understand you based them on the alcohol work. But maybe for this disorder, it should be somewhere else. And I'm not sure where, but it'd be interesting to model that.

DR. WEISNER: Yes. We could do that, and I also can show you the frequency distributions if anybody would like, if we're going to do more.

DR. CARROLL: This is Kathy. I think that's about right. And we can probably have those tables in a couple days now that we have our huge data set, just to see. I think it would be fascinating to pull them from a Bonds [ph] data set, you know, the data sets that we've collected so far, to see.

But on average, across all these trials, they come in using between 1 and 16 days a month. So if you broke it into those quadrants, I think it's about right.

DR. WEISNER: This is an employed population

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or people who are spouses of, and often, a once a week thing. It's often on the weekend.

DR. STRAIN: I'm sorry. If you could go back to one of those, and it could be any one of them, just as a model. So what this says is, in the 30 days at month 6, if a person self-reported zero days of use --

DR. WEISNER: And there was drug testing.

DR. STRAIN: -- and there was drug testing, then at 12 months for the 30 days, 92 percent of them reported no use. Right?

DR. WEISNER: Yes.

DR. STRAIN: So I guess my question, Kathy, is, if you change that first category, for example, from zero to 1 days, will you make any significant difference on that 92 percent, or if you change the second category from 1 to 4 to 1 to 3 or 1 to 2 days?

DR. CARROLL: Isn't it wonderful that that's an empirical question that's answerable? I don't know that right this minute, but I'll know it by Friday.

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DR. STRAIN: What time on Friday?

DR. CARROLL: You already called her, didn't you? Yes. We got it done.

MALE SPEAKER: People are working on it. The best people are working on it now.

DR. WEISNER: I'll be eager to know, too. Keith?

DR. ISENBERG: Yes. At the beginning, you presented some information about the proportion of the insured population with stimulant- and cocaine-use disorders. Is that based on a single claim with that diagnosis? Is that how those larger populations were constructed?

DR. WEISNER: Yes. So first of all, we don't have claims. We have encounter data.

DR. ISENBERG: Right.

DR. WEISNER: No. I have to remember exactly, but we have done some record reviews. You have to have two or three diagnoses at different times. Yes.

DR. ISENBERG: So as opposed to a single encounter diagnosis, you used two for those larger

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samples.
DR. WEISNER: Yes.
DR. ISENBERG: The reason for asking the question has to do with how that larger population maps to the treatment population. And that's a very important question, I suspect, for your health plan in addition to the research issues.
DR. WEISNER: Most diagnoses are made in those 43 medical centers in the region rather than primary care because of 42 CFR. I could do a whole talk on 42 CFR --
DR. ISENBERG: Yes, no.
DR. WEISNER: -- and problems with integration.
DR. ISENBERG: Regulations are a problem.
DR. WEISNER: Right.
DR. ISENBERG: But I'm still interested in how the larger population maps to the smaller treatment population because the first cut or the first guess is, it's the additional conditions that drive you into treatment, the additional medical conditions. And then that becomes a driver to get

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attention from the medical community, is the reason for trying to pose this.
DR. WEISNER: Again, I think that is the case somewhat. On the other hand, as we were talking about yesterday, 44 percent of the people are there on employer mandate, depending over time and which site, up to about 20 percent on a legal mandate. You know, the lawyer says, "Get yourself to treatment, and when we go, we maybe can get you a better deal." So some of the people who drop out of treatment are being successful that they've gone to jail, whatever; or their family has said, "Enough. To treatment, or you're out."
It just doesn't seem like they're getting identified as much in primary care. I think they are now with the hep C clinics more so. I think that's why that Sacramento data or the 2014 data look a little different.
MALE SPEAKER: I'm just so amazed, just comparing this to the alcohol data. If the zero days is abstinent, 1 to 4 would be low risk, and then the 5 or more would be like the heavy. In

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the alcohol data, I think we saw a decent amount of low-risk people go on to become heavy drinkers. But here, it's not the case at all. The low-risk people -- let's call them low risk, 1 to 4 days -- never really progress to be more days than 4. That's kind of interesting.
DR. WEISNER: Yes.
MALE SPEAKER: It would be interesting to see two of these, if you're going to have time to repeat, and see how the consequences go for these groups later on.
DR. WEISNER: We should. When we compare drug outcomes with alcohol outcomes, we have higher levels of abstinence over time than we do for alcohol. Once Kathy tells us how to do it or how we should, we should then look and do some modeling with this as well, but small sample.
FEMALE SPEAKER: I have a quick question about the population. You've combined people who met criteria at the time of DSM-IV. Right? You've got DSM-IV dependence and DSM-IV abuse. Have you tried to separate them out at all? Because I don't

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know whether all of those patients would necessarily be pharmacologic treatment candidates.
DR. WEISNER: Well, for the stimulant population, of the 28 percent, 26 were dependent. It was more mixed with the cocaine population. It was like half and half. The sample is so small, I didn't do that analysis by that. I could if you'd like.
Presentation - Eric Strain
DR. STRAIN: Thanks, Connie.
I'm going to take the prerogative -- because Rhonda wasn't able to come, I wanted to make a couple of points on this topic. So Elliot, if you could hold just for a moment, I want to -- this is the prerogative you get to make when you're organizing the conference -- convey a few thoughts about this topic, because I think it is one of interest, that I've had of interest.
Wearing a different hat, Johns Hopkins actually runs a managed-care organization that covers over 250,000 Medicaid lives, an employee plan, a TRICARE plan. So it's a growing part of

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the business of Hopkins. And I've had discussions with the pharmacy management people there about some of these sorts of issues. So I wanted to pass along a couple of thoughts regarding this.

I want to caveat that this is an area I think about, but it's not my usual focus. But an expert is someone from out of town, and I'm from out of town, so now I can pretend to be an expert on this topic.

It seems to me, this is the realm of cost-benefit analyses. In my read of addictions of cost-benefit analyses, it's that there is some controversy in this field regarding the measures, for example. And it's especially difficult to assess benefits as we think about pharmacotherapies for stimulant-use disorders. So let me talk a little bit about costs and then benefits as we think about this area.

When you think about a new medication for an indication, you could have a new pharmacologic treatment, you could replace or have a cost offset -- and I'm going to elaborate on each of

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these real quick -- or you can replace or cost-offset a non-pharmacologic treatment.

So what do I mean by each of these? Well, first, let's talk about a new pharmacologic treatment. An example here would be something like imipramine for depression, which was brought out in 1958, or buprenorphine for opiate addiction in 2003 could be in some ways viewed that way.

That is, it's a new medication, and the costs have not been covered by a previous medication, as it were. So it can be a medication for the indication, but the new medication, the new treatment is markedly different in how it's used, for example, buprenorphine.

But the point is, this results in a potential for new and substantial cost to a healthcare system when you bring in something like this. And I think buprenorphine is where this really hit home for me because, for our Medicaid managed-care organization, office-space buprenorphine treatment was a 7-digit cost to their pharmacy benefit once it got into full gear. And

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that was a cost that was new to them. It wasn't something that they could say, "Well, we're saving money" -- as I'll make the point in a moment -- "from somewhere else due to that." And I think that's the situation we have with this stimulant-use disorder treatment medication.

So medication for stimulant-use disorder will be a new medication. It's a new cost to a healthcare system with respect to pharmacy cost.

Now, the second scenario is that you could have a cost offset of an existing pharmacologic treatment. So this, for example, is sertraline, or paroxetine, or any of those things for depression. I just picked sertraline as an example; Zoloft, which came out in 1991.

So there could be incremental costs because it's a new drug versus a generic, such as fluoxetine. But the new cost is less likely than if there was a completely new medication type. And we're probably seeing this with buprenorphine now, where you get a generic that comes on the market. Now, the MCO, the Medicaid MCO, says, "We can cover

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that generic because we've already allocated dollars for this line of medications. It's not necessarily a new cost. If anything, it's a savings to us in that respect."

Then the third is a cost offset of a non-pharmacologic treatment. And an example here I would argue is lithium, which came out in 1949, versus institutionalization for bipolar disorder. So we had patients who were being kept in psychiatric hospitals for long periods of time for bipolar disorder, for example. And lithium comes along, and it's a new medication that may have cost to a healthcare system, but it offsets some other healthcare cost that is even more expensive, such as inpatient treatment.

As I've been thinking about costs and how they impact healthcare systems, what about benefits then? And these are things that I think most all of us have thought about, and I just wanted to make sure that we're all keeping them in mind. Benefits in addictions treatment can be hard to quantify. And I'm well aware of the DATCP [ph] and all sorts

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

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

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

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

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say, "We can't pay for it. We can only pay for methadone."

So I'm not certain that the states have the kind of aspirational view that you have, that social good is the end. And until there's a little bit more fungibility in those funds, I think we're going to be in a hard place.

DR. STRAIN: You're more pessimistic than I am, which is a little worrisome. What I would say is that Maryland and Hopkins is especially a little bit different because now, in Medicaid, the state has decided to carve substance abuse out from the rest of medical care, along with mental health care, and administer it through a different ASO. so we've lost fungibility on those funds, which has been very distressing, actually.

Can I take one more?

FEMALE SPEAKER: I want to add one thing. I think we have to look at costs a little more broadly than we have in the past. We have a grant where we looked at family members' costs. So adults who were diagnosed with alcohol and drug

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disorders, their family members' costs were much higher than other families for seven years before that diagnosis. And they went back to "normal" after the person had successful treatment.

That's a huge business case issue because our patients don't get diagnosed right away. And that made a huge difference in how we got the health plan to use SPERT in identifying people early, because something kind of magical happened to the patient's family members.

Now, those are published papers. I really wish that we could start thinking more broadly when we make our business case.

DR. STRAIN: Thanks. Great point. I'm going to -- because I have impinged on Elliot's time. But I think these are points as well that we can bring out in the discussion, so thanks.

Discussant – Elliot Ehrich

DR. EHRICH: Well, thank you. And I really want to thank the organizers, Eric, and the other organizers of this conference, coming together and discussing this topic because developing a drug for

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the treatment of addiction is probably the most challenging. I've been involved in the development and registration of drugs for arthritis, for asthma, and for diabetes. And this really is the hardest.

I think it's the most difficult area to develop and register a drug, and not just from the perspective of endpoints, but how patients engage with the healthcare system and also how people think about medication treatments and their place in the treatment of addictions.

I think it was Alan Leshner who was quoted as saying, "Whenever we come out with a new treatment for addiction, we circle the wagons, point the guns at each other, and shoot." And I think that's kind of the point. I think it's very singular, the ambivalence that exists even within the treatment community about which medication is appropriate or even is it appropriate to use medication treatments.

I thought the panel was really very interesting, and there were a number of things that

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were said that I didn't quite expect, and actually, things that weren't said or weren't really focused on that I didn't expect.

But I think there was a number of important themes that came up. Actually, we did talk about costs towards the end, but really throughout most of the presentations, the primary point that was being put forward related to patient benefit; in other words, really, what is it that we're trying to achieve?

There's disagreement. Is it abstinence or are other outcomes also acceptable? Are we in the midst of changing what's considered to be appropriate treatment? But I think that really does get to the core. And I think as we think about developing endpoints and focusing on what it is that we want to come out of our trials, we shouldn't lose sight of that fact, that it's really, that is the core. And if we demonstrate benefit, then we will succeed.

I think there are some great examples. We talked about Sovaldi or some of the newer

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treatments for hepatitis C that are extraordinarily expensive, and yet, there's little ambiguity that there's important patient benefit. And I think we as a society appear to be willing to pay for that.

I think there's something that's coming in on the horizon, these PSKC9 inhibitors that seem to do a better job than statins for cardiovascular disease. They're biologics. They're infusions. They're going to cost a lot of money. They could potentially benefit a lot of people. And I think, again, as a society, we're going to have to deal with that. But I suspect that we're willing to pay.

Again, I think this also comes back to the area of addiction, where one of the places that we suffer is a bias, that people don't necessarily think of addiction as being the same thing as cardiovascular disease, or diabetes, or cancer, in that when we come up with new treatments, I think there's still a lot of residual sentiment out there that addictions are an issue of patient liability, that they're a bad person, that they're doing the

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wrong thing, and to not necessarily treat it as a medical disease.

So also, I think, as part of this process, it's ongoing. But if we're going to make any headway, we do need to really continue to make that change as George Woody was alluding to about changing the way that we think about these disorders and overcoming that bias that, yes, these are bona-fid medical disorders that we should be treating with medical treatments.

There are also some other themes that are just coming through again as we think about endpoints and as we focused on a bit yesterday, this whole concept of, yes, there is abstinence and there are multiple stakeholders. But really, at the end of the day, it is the patient who is the primary stakeholder. It's the patient who has to take the medication and not only gets the benefits, but also has to endure whatever side effects are associated. So we can't really lose sight about that.

I think there was a number of interesting

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comments about how we should think about, are there other types of proximal patient benefits about how patients feel and function that we can focus on, that may ultimately predict longer-term outcomes. It may take a long period of time for deep-seated, highly salient memories about the reactions to substances, that may take a long time to change and to really be observed in the context of a clinical trial. So that's something really important.

One area I've seen particularly in the arthritis area, some work done by Nick Bellamy on the WOMAC, is literally taking -- the WOMAC is the most commonly-used osteoarthritis questionnaire. It has domains of pain, stiffness, and physical functioning.

One thing that they do is they had individual patients rate or use a spectrogram to determine which of those domains were most important to them, as a way of making the instrument more responsible to the individual patients. It's a little bit -- as Connie has been talking about, the treatment or the importance of

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treatment can depend on where a patient is coming from, if they're there for criminal justice reasons or employment.

So that may also be something to think about in terms of, if we are going to expand, or develop, or trim the CSSA, are there ways that we can customize it for individual patients and potentially use that to enhance statistical power, frankly, again, if you're addressing the areas that means something for an individual patient. So there may be some analyses or ways that we can do it.

Just a couple of other comments. I thought that it was very striking yesterday, the data that George Woody showed about how setting can be really important and ancillary treatments. In Iceland, for example, they do a really good job, and demonstrating medication effect can be challenging in that kind of a situation.

I think it's just also a reminder that this is MAT that we're talking about, medication-assisted treatment. For example, the alcohol and

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the opioid medications, they're approved for use in treating alcohol dependence or opioid dependence in the context of psychosocial therapy. From that perspective, they're combination medicines.

So I don't know exactly how we're going to handle that. You can get into weird situations where you create trials where the control group is either contrived or masks the effect of a drug. So it can be difficult and adds complexity, but it is worthwhile also when you're thinking about the overall import or impact of the treatment.

You saw, again, as George showed, going in with IDC, there's these amazing changes from pre-study to treatment, irrespective of treatment, that are just engaging in the healthcare system, getting regular visits, having whatever kind of support that exists in terms of whatever counseling, or support, or follow-up is given in the context of trials that can make amazing differences in the context of patients' use.

How do we really think about that if what we're delivering with these treatment paradigms is

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a combination of psychosocial therapy plus medication? I think we need to think about that as, really, the clinical meaningfulness of what we're delivering.

I think, finally, this whole issue about beyond approval, and as we get into a drug that's approved is being used in the clinical setting -- I think, as Keith noted, once drugs are approved, how they're actually used and where they're used is quite different from the information that one has in the context of approval.

I think that just also highlights the need that that is the type of setting to really focus more on, on not just what the drug does, but really who is benefitting, because I think at the end of the day, if you have something that works, and it provides patient benefit, if you wanted to make it affordable or to make sense from a cost perspective, what we need to do, then, is really determine who is it for whom is getting that benefit. And I think if we do that, then we're in the best situation of showing a positive cost

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benefit. So thanks.

(Applause.)

Q&A – Group Discussion

DR. MONTOYA: Time for discussion.

DR. BURKE: Hi. Laurie Burke. I think that what's really important to come out of here, by the time we finish in an hour or so, is that we need to have a better idea of how we recommend people like Elliot work on developing new drugs for this area of treatment. And in order to do that, they really have to understand what to measure as primary endpoints in their clinical trials.

They're not going to do long-term clinical trials to find out if these patients are going to be abstinent 10 years down the road, 3 to 5 years down the road, or even one year down the road. They really need to understand how to identify treatment benefit in a length of time that's reasonable to do a clinical trial.

So I think that we can't forget about -- I haven't heard any discussion here about how patients feel and function may have an impact on

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that long-term abstinence; what makes a difference in terms of how they feel and function in their daily life that's going to determine whether they keep taking the drug, even if they keep taking the drug, whether there is enough benefit in their daily life to make them abstain from whatever we're trying to help them abstain from.

That is going to be determined not only by how the treatment helps them with the withdrawal symptoms, or the symptoms of craving, or whatever it may be, but also how the treatment impacts them in terms of the tolerability of side effects, which also has to be, if you want to actually know whether or not the treatment is tolerable in terms of the patient signs and symptoms, you have to measure that as a secondary endpoint also. It's not something you can really conclude from the spontaneous events that are measured during trial.

So I think that it would be really useful to have some sort of a recommendation by this group, experts in this field, about what drug sponsors should be doing when they're just now thinking

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

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

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

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

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

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

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

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

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where it's basically about perceived benefit for a particular individual? So the outcome measure -- I'm just throwing this out there -- would be, like, proportion of subjects that achieve their own consequence/goal basically.

MALE SPEAKER: Personalized.

MALE SPEAKER: It's a personalized outcome. Now, it has pros and cons, that it's not standardized. It's like what's the clinical benefit? It's kind of vague. If everyone has a different goal, it's not standardized. But on the other hand, if a good outcome is that which can be moved, but also -- maybe that could be a good goal.

It's just open for discussion. Is there some room for a goal, for an outcome like that?

FEMALE VOICE: There is some attempts at that in terms of individualizing treatment with goals. I know in schizophrenia there is.

MALE SPEAKER: Acceptable from different stakeholders.

DR. SILVERMAN: This is Ken Silverman. I think that's a terrific idea, but it seems unlikely

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as a good primary outcome measure, at least in the near future. This focus or contrasting between abstinence or the FDA feels and functions in daily life, one reason why I think we're so focused on abstinence is that the medications are focused on promoting abstinence.

If there's any evidence for that, look at the animal trials of where medications are tested frequently first, and they try to decrease self-administration of the drug. And it seems pretty sensible. And in fact, what's likely to happen -- and I think that you guys have said this already -- is that if you could decrease abstinence, it'll have different benefits for different people.

That addresses the kind of assessment that you're suggesting, which seems like a pretty good idea, but is just an idea.

FEMALE SPEAKER: This goes back to my previous comment. I'd like to propose that maybe there is a different way to think about this. And once again, I have to preface this with the fact

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that I'm not in your field. I'm not an expert in stimulant abuse. But the treatment that would be developed to me would be a treatment for stimulant abuse.

So abstinence is the goal, but lack of abstinence is really a lack of effect, which in most other therapeutic areas is considered an adverse outcome. It's not really the benefit, it's the outcome that you measure benefit with.

So here, what is real benefit? And I think that's part of this whole keeping -- we keep talking about feels and functions. It's because, really, the benefit to the patient is somehow they can overcome their feelings of needing to abuse the stimulants and be treated in the sense of their condition of needing the abuseable substance is eliminated.

Abstinence then is a failed treatment outcome, but it's a failure to actually do the work that the drug is indicated for. So this is why it makes so much sense to try to figure out what it is, how these patients feel, and you might have to

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just limit the clinical trials to a subset of patients that have a defined set of symptoms at baseline, and then figure out whether this drug can affect those symptoms that seem to be related to their abuse.

DR. MONTOYA: Connie?

DR. WEISNER: Also, just following up, thinking a little bit more about what Dan just said, would it be helpful, I mean, in terms of what Celia said yesterday about surrogate outcomes and other kinds, if we looked -- I think NIAAA did this kind of thing with their alcohol.

If we looked at some of our longer-term data sets and some of your studies, different kinds of studies, and looked at whether abstinence or low-risk use, however you want to define that, modeling that has later. And those other data sets have better social functioning outcomes that are measured by the ASI in some of the studies, that are measured by non-using emergency rooms, and so forth, does that help?

Can those kinds of things be paired with the

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short-term outcomes studies? Can a different kind of study make the leap that, if you're using this much at 12 weeks, this is your other outcomes, or patient, how you feel, and everything, and how you're functioning is looking a year later?

I don't know, I mean, whether that ever happens using different --

MALE SPEAKER: Long-term studies are going to be really beneficial to measure how patients feel. And long-term studies, though, when you use urinalysis, very burdensome. You're not going to keep people around for very long.

If you can get rid of urinalysis, then you've got an advantage to go to long-term studies. The way you get rid of urinalyses is that you pare down who gets into your clinical trial by using Connie's idea of why are you here.

If you could find the pure patient who really wants to get rid of drug use because they're sick and tired of it, you would have an enriched population to study, who would be willing to be truthful about whether they used or not. And

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therefore, self-report becomes the endpoint of choice that's not burdensome, easy to handle.

Aren't we looking then at the patient who the payers want to pay for treatment for? And to me, it just all comes together. If you can use self-report and trust it, if you pare down the patient population to what you'd call something enriched, then you could do long-term studies and look at real outcomes over a long time.

DR. MONTOYA: Yes. I think very interesting discussion, but we should take a break because now we are running into the break time.

DR. STRAIN: So let's take a 10-minute break, and then I think Dr. Preston may be speaking.

Thanks for a great session.

(Whereupon, a recess was taken.)

DR. STRAIN: I am going to convene this session. And it's my pleasure to introduce Kenzie Preston, who will be talking about practicalities of conducting biologic assessments for drug use. Dr. Preston?

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Presentation – Kenzie Preston

DR. PRESTON: Thanks for inviting me. And I've come down to the realm of brass tacks rather than the more hypothetical today. So there's a lot of question about why we use biological measures. They're costly. They're inconvenient. And some really, really question whether it's necessary. And when we look at the alcohol research, we actually say, well, maybe you don't need it.

On the other hand, there's good evidence that people underreport it. And I don't think it's a question if people underreport. They do underreport. It's just a matter of degree and how important maybe that is. And of course, having an objective biological measure adds credibility to your results.

The ideal drug testing program for a clinical trial would have a test that has good efficacy, sensitivity, and specificity, and has a low cost, and is quick and easy. And the specimen should be easily and safely collected, have a low risk of contamination from external sources, and be

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easily stored and, if necessary, transported if you need to keep specimens for any reason.

But probably the most important thing is the correspondence between the window of detection that matches the specimen collection schedule. So if you have a test that tests positive only for 24 hours, and you're testing 24 hours, you're going to catch every use.

But if you're testing only once a week, you're going to probably miss some uses, which is problematic, but it's not as much of a problem as if say your test has a window of detection of a week, and you're testing every day, because then you're getting multiple positives for single uses. So one of the challenges is to match up the window of detection of your test with your data collection schedule and still be practical for participants and the researchers.

So I think the good news is that this is a huge business, the drug testing, and it's used for a wide variety of uses, so this has generated a lot of technology development in the industry. But I

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think one of the issues is that the goals for these really very frequent uses are not necessarily the same as our monitoring of drug use in clinical trials, so their solutions to problems don't necessarily work out so well for us.

The other thing I want to point out is that in the real world, drug testing is usually done in a two-step process, so there's a screening test usually, like an amino acid, that's very sensitive, but maybe not so specific. It has usually only a qualitative test, positive versus negative, and tends to be quite cheap, which is good. Then if there are positives, then those are sent out for the more specific, expensive, quantitative testing like with GCMS.

So virtually, all these applications, they do a screening, and for some of them, because of legal ramifications, they definitely do confirmation. I think for clinical and drug treatment, they may or may not do it depending on the exact circumstance of the testing. But generally for our clinical trials, we haven't been

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doing the confirmation testing. We've been relying on screening tests.

So as I mentioned, there's a lot of research going on in drug testing, and I just did a SCOPE search on drug testing and addiction and saw that the numbers of papers published each year is going up.

What this has led to is improvements in, say, on-site testing for urine drug screens, but also development of a lot of alternative matrices beyond urine such as hair, sweat, oral fluid, breath now. There's breath tests for cocaine and marijuana. And the newest thing I'm told is the dried blood spot.

We've been talking about these alternative matrices for a really long time. And so I thought if I'm going to give a talk about this, maybe I should see how they are being used. Maybe they're replacing urine testing in the field.

So I did the SCOPA search, and I looked at methamphetamine dependence and cocaine dependence, and filtered it for clinical trials. And of

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course, there are many trials or published papers with urine. I found a couple for hair and a couple papers for sweat, not just the development, say, test, tests, but actual use in the clinical trial, but none for oral fluid or breath. And I actually didn't look for dried blood spots.

So then I thought, well, maybe those studies haven't been published yet, so I went to ClinicalTrials.gov and did a search on methamphetamine dependence and cocaine dependence. And I did a word search in the outcome measure category, and there were absolutely none for any of these matrices, so ongoing trials. That's not to say they're not including them in the trials, but they're not identifying them as, say, their primary outcome measures.

So I think the bottom line is they really have not caught on and been adopted into clinical trials.

I'm going to do a brief survey of the different matrices and cover these different categories, and I'll start reading with urine. For

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urine, the major analyte is the metabolite, and for cocaine, that's benzoylecgonine mostly, the detection time. And this goes across a lot of different drugs. It kind of seems to be drug independent, a detection time of 2 to 4 days.

Think about whether we can differentiate recent use and whether it might be sensitive to changes in rates of drug use. And for urine, that's pretty much yes for detecting recency of use. It shows up in the urine pretty quickly. But like I said earlier, if you're testing more frequently than the drug is eliminated, you can get carryover, which could make your test insensitive to changes in frequency of drug use.

The collection convenience, I would say, for urine is not really convenient at all. You have to have special facilities, and if you're doing observed testing, you need same-sex observers. Contamination is not generally a problem with urine. There is now on-site testing. And as far as the other issues, it's been used a lot. It's almost the only one that's used, so it has well

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established concentrations cut-offs, and it's established as an outcome measure in clinical trials.

Another advantage for urine testing specifically is that the labs across the country tend to use the same or very similar assays. So you can look across trials, and they have used the same assay. Now, to Kathy's point, what you do with those data are not necessarily the same, but you're at least working with the same assay, pretty much.

So this was a study where we were interested in the effect of concentration cut-off on the window of detection, so we brought people into our residential unit and collected all of their urine specimens. This is the concentration cut-off against how many hours it took to actually reach that concentration.

That dotted line is 300 nanogram per mL, which is the standard cut-off. And that's about 42 hours, which is actually a little shorter than the 2 to 4 days. But these people hadn't necessarily

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used right before they came in.

But anyway, you can lengthen the window by lowering your cut-off, so down at 100, you're out here at 60 hours or so, or you could shorten your window of detection simply by raising your cut-off, and that down here at 500 nanograms per mL, we're looking at just over a day and a half or so.

We talked a little bit about concentrations yesterday, so I thought I would present some of those data. So this is the results of a clinical trial. It was a contingency management where people were randomized to get an incentive for being cocaine negative or they were randomized to a control group that got the same value of incentives, but independent of their urine results.

What we found is, there was a significant increase in longest duration of sustained abstinence with kind of a bimodal response in our contingent group, with about half people -- we called them responders and half not responders. And so we were collaborating with Ed Cone at the time, and he did the urine benzoylecgonine

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concentrations for our study.

This is the baseline period before they were randomized, and post-randomization is at this dotted line. And you can see that our responders just kept on using, whereas our responders -- and maybe this is that grace period where it took them a while to actually decrease down to not testing positive. This is the limit of detection here for that particular test.

I'll just go back. In fact, it turns out that the non-responders were actually using more drug before they even were randomized. This is a non-responder looking at the benzoylecgonine concentration across time. And these were urines collected Monday, Wednesday, Friday. And this is a log scale, so it goes all the way from about 10 all the way up to about a million.

The person is not using continuously, obviously, because we're getting lots of ups and downs here, even a period of abstinence. So if we apply the 300 nanogram per mL cut-off for this participant, we got 11 occasions when that person

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tested negative. But there are also some times when it looks like, yes, if we just waited a little longer to collect that specimen, they might have actually been negative, especially if you're using high doses. It might take actually a longer window of detection.

One solution might be to just raise that cut-off, and if we raise it up to 3,000 nanograms per mL, we increased our number of negatives from 11 to 23. But we weren't totally satisfied with that idea, so we actually went back, thinking about the pharmacokinetics of benzoylecgonine, its half-life. Maybe we could develop a better way of identifying carryover positives versus times when people actually use, so I'm not going to go into the details of this. But basically, we compared the concentration from the current urine to the just previously-collected urine. And when we did that, in fact, we identified 12 occasions of carryover that are in the green and left us with 28 occasions of new use.

I think this may not be the real answer, but

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

There's also a problem with people being allergic to the adhesive. Patches can fall off. It hasn't been used as an outcome measure in a trial. Well, it was tried; I'll show you. Currently, there's only one company that's actually doing it.

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

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

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

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

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

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

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

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

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

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

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

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

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

So I'd be happy to answer any questions.

(Applause.)

DR. STRAIN: Question?

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

DR. PRESTON: I don't think so.

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

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

MALE SPEAKER: Right.

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

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

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

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

DR. STRAIN: Got it.

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

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

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

MALE SPEAKER: Is it immunoassay based?

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Might you have false positives? Because at least with urine, you could ship a sample for confirmatory, but if it's immunoassay based, you have false positives, and you wouldn't have anything to use for confirmatory testing.

DR. PRESTON: I don't remember the exact basis of the testing that's done, but as far as I know, you actually still have the thing that you collected the specimen on to begin with. So potentially, those would be available for retesting in a different way.

MALE SPEAKER: Question about benzoylecgonine cut-off. I am hearing that Xcenda and the industry have 150 as a cut-off, and you measured about 300. So we are looking for the endpoint as abstinence, never cocaine. Then it depends. We are doing a different endpoint, a value for the negative urine? So what is your thought on that?

DR. PRESTON: Well, I think that's a very good point. I know they've changed the concentration cut-off for some other drugs. These

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groups that are primarily interested in drug driving and workplace use are the ones that are sitting at the table determining what these values ought to be.

I think it depends on the purpose. If you're doing very infrequent testing, and you want to know if they used any drug, then you might want to have the most sensitive test that you could possibly get.

I think for the purpose like I showed you with our participant, where they're kind of going along, if we have too low of a detection to report a positive, then you might be detecting use when use didn't actually occur. So I'm not sure I answered your question.

MALE SPEAKER: My point is, is all in the industry, academic, we use the same standard for the cocaine?

DR. PRESTON: Well, SAMHSA is the one who determines the concentration for the U.S. There's a different group that determines it for Europe. But I think if we, as a community, chose that we

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wanted to select a different cut-off, we might be able to arrange to have the tests be set to be sensitive to a different cut-off concentration that we felt was optimal for what we wanted to do.

FEMALE SPEAKER: The SAMHSA cut-off is not for research purposes. Their cut-off is established for different purposes.

DR. PRESTON: Right, exactly.

FEMALE SPEAKER: So that's one thing you have to bear in mind.

DR. PRESTON: Right. But the commercial tests, then, are all geared to that cut-off.

FEMALE SPEAKER: Right.

DR. PRESTON: And that's what's generally available to us.

FEMALE SPEAKER: Right.

DR. STRAIN: Thank you.

Celia, you were going to come up to discuss this, please? Thanks.

Discussant – Celia Winchell

DR. WINCHELL: I'm going to sit down to do this because I've taken a lot of notes, and I need

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to organize them. I'm only supposed to be discussing Dr. Preston's talk, but I am going to broaden my comments a little because I want to integrate a little bit of other things that I've heard.

It sounds as if, much as we would love to ultimately demonstrate that a medication could improve the way a patient feels or functions, a lot of people really do care about whether or not the patient is using cocaine.

So it seems as if the strategy of trying to establish some measures of cocaine use as valid surrogates for stable change that translates to clinical benefit is not a bad route to take.

As we accept that we're focusing on trying to characterize the nature of patients' cocaine use, first, I want to understand whether it is even possible to measure reductions in drug use as defined as less use per occasion or have we given up on that entirely because, much as people find it attractive -- and someone always mentions it whenever we talk about these things -- it just

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

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

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

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

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

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

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

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

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of how patients feel and function and other patterns that we may have been able to characterize.

But it sounds like some effort to develop things like remote testing. We now have the technology to watch a person on their cell phone blowing into an alcohol sensor. Can we do something like that with cocaine, with methamphetamine, or improve the long window of detection? If what we're interested in is abstinence, then measures that have long windows of detection, like sweat patches, are very beneficial.

If we're not interested in complete abstinence, then we don't want measures with long windows of detection. So some of where our efforts and enthusiasms go may turn on that decision point.

I think I've got them all. I'm sure there's more, but those are my thoughts. Thank you.

Q&A – Group Discussion

DR. STRAIN: Thank you.

So let's take a step back, actually, because there's an opportunity to have a little bit of

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discussion about biologic assays and to sort of think that through -- so Brian, if you want to, you can take a break from that; well, it's up to you -- and then we'll go into a more general discussion.

So thoughts on Kenzie's talk or Celia's talk with respect to biologic assays? Yes, Raye?

DR. LITTEN: I have a question for Kenzie or, actually, it's more to NIDA, to Dave, or Phil. We're developing our alcohol sensors, and we have some out there. What's really nice about it is that it can measure alcohol objectively in real time. And I don't know if that's possible to measure, say, a cocaine sensor, a metabolite, or some of these other using a sensor that actually tells you when it was taken and approximately how much was in the bloodstream.

Is that something feasible that you all have looked at? Because that would certainly solve the problem of quantitative -- I mean, that would solve a lot of problems. You could tell how much they were taking it and when.

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MALE SPEAKER: Yes, as long as -- yes.

DR. LITTEN: It would solve a lot of your problems if that's possible.

DR. McCANN: Well, I mean, the factor that you have to add in there is cooperation from the subject to use whatever, wear the patch or whatever device you're talking about. I think we support through SBRI a lot of very innovative work, but when we have such trouble getting people to take a pill once a day, developing technologies to monitor that may require even more compliance than taking the pills becomes a challenge.

I don't think we're driven to do that because we do have urine testing where we can follow BE. In the alcohol field, you're relying so much on self-report that I think you're pushing that technology and you want to be able to measure that.

DR. LITTEN: Well, I will just say this. These are things -- once you put them on, it's really hard to take off. And if you do take it off, you can tell because there's a temperature

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probe on there.

DR. McCANN: This is like a monitoring alcohol bracelet? If you were under house arrest, it would be clipped to your ankle, and it would be on there for good.

DR. LITTEN: Well, even house arrest. Right now, we have to prove it, but it's around the ankle right now.

DR. McCANN: We're constantly trying to get the right patients for our studies, but some individuals and maybe some IRBs might consider that coercive, that sort of an ankle bracelet, if you will.

I'm just saying I think it's a great idea. We have oxygen sensors, and maybe that could be detected. But I just worry about just the function of putting that on. If you have a drug approved and it works in the real world, they're not going to be wearing a sensor. It's an interesting idea.

DR. LITTEN: Well, I think the technology would probably be the most challenging to come up with something like that. I was just wondering if

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you had thought of that or if it's even feasible. That's all.

DR. McCANN: I tend to think more simple things. The benzoylecgonine is pretty good. When you look at day-by-day subject's self-reported use versus the BE, a lot of them tell the truth, and there's a group that underreports. Clearly, there is some underreporting.

I've had the idea -- we haven't implemented on anything -- of trying to use contingency management to reward accurate self-report, not contingency management to pay for clean urines, but to say, as long as there's no conflict between our urine test results and what you're telling us, you'll go home with $10. I think that that could substantially improve our self-report, if you just say, "Look. We just want to know accurately what you're doing," and we pay them a little bit.

It's complicated, but please think about that because that could be a fairly inexpensive and low-tech way to improve the accuracy of the urine test.

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DR. PRESTON: So we're doing real-time --

MALE SPEAKER: I'm sorry.

DR. PRESTON: -- self-report, and we do pay for correspondence between reporting on electronic diary and the urine results. So it is possible to do that.

FEMALE SPEAKER: You should write that down.

DR. STRAIN: I'm sorry. Actually, I couldn't hear. So repeat it, Kenzie or Dave.

DR. McCANN: The general point was to use contingency management to reward accurate self-report and correspondence with the urine. And Kenzie is saying that she's done some of that with the electronic diary. So I think there's probably something good to mention in the paper, encourage people to think about more.

DR. STRAIN: Sharon, did you have a comment?

DR. HERTZ: Yes. I think that, at this stage, it seems like there is a worry about situations that is a little premature. You guys have a huge challenge here in contrast to some of the other drug groups because you have no known

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effective drug therapies. So you don't know whether your measures can pick them up or not. And you don't have measures that you know necessarily will detect an effective drug therapy.

So I would say that the kind of work that we heard this morning -- what was her name from Keiser -- yes, Connie, is great. But basically, it seems like an all-hands-on-deck, throw-everything-at-every-study and see what turns up because eventually, something is going to show the adequate sensitivity and specificity so that when a therapy that's effective comes along you'll -- I mean, it's going to take some data drudging to comb it up, to sort this all out, but we can handle things like ankle bracelets with informed consent and the ability to have it taken off tomorrow if you withdraw consent.

So I wouldn't throw anything out the window yet. But I think the key is to try and be as systematic as possible. Even things that are expensive now, granted that you need the money to do the study, but if it becomes useful in the

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future, the price will become competitive, and you'll have a competitive market, and it'll come down.

I don't know if there's familiarity with this, but I want to just introduce a concept that speaks to a little bit of what Laurie said about challenges with the duration of following patients and understanding the impact of outcome measures for long-term improvement in survival.

You may be familiar with some of the accelerated programs that we have, fast track, and priority, and that sort of thing. But there's a different concept of accelerated approval under something called subpart H, which is in 21 CFR. It's 314.500. And this is subpart H, accelerated approval of new drugs for serious or life-threatening illness.

I am going to read it, just a little paragraph.

"FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials, establishing that

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the drug product has an effect on a surrogate that is reasonably likely, based on epidemiologic" -- I can't read my writing, something -- "and pathophysiologic or other evidence to predict clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity."

This is subject to the requirement that the applicant study the drug further to verify and describe the clinical benefit. So postmarketing studies are required.

But if you have an endpoint now that looks very promising and it seems to be a reasonable surrogate, it doesn't have to be proven ahead of therapeutic development of a clinical trial and drug development.

FEMALE SPEAKER: I think what we've been debating a lot is what reasonably likely means.

DR. HERTZ: And that's okay.

FEMALE SPEAKER: That's where the differences in opinion lie.

DR. HERTZ: That's okay. I mean, that still

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is the big initial hurdle. But once something, some conglomeration of endpoints, whatever it is, looks good, the opportunity to use this subpart H might be helpful rather than waiting for that 10-year, long-term survival outcome or whatever.

It is extremely important that if this is embarked upon, that the understanding of the requirement for postmarketing follow-up is there, there's the concept of approaching that with due diligence.

I will say that, although rare, failure to either do the study or get the right result from the study can result in market withdrawal through the appropriate legal proceedings. So even if you/we can get to the point of that, our opportunities to get this on the market, get something on the market, and then follow up.

So if that helps at all take some of the burden of understanding the surrogate now, perhaps that helps move things along.

DR. STRAIN: No. That's great. Yes, Phil?

DR. SKOLNICK: I think, Sharon, that's a

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really important point because part of the issue -- I think part of the reason why we don't have any effective meds approved is because we had difficulty getting pharma interested in cocaine as a therapeutic endpoint for multiple reasons. But with that information at hand, with perhaps some of the things we've discussed today, that may be able to incent potential partners that will be able to develop the drugs. I think this is a really important point.

DR. STRAIN: Thank you.

Connie, before you go, let me just say, I think we're now going to morph into the more general discussion of conclusions and where we may have some agreement on some points, so I want to open it up for a wider discussion. And I have a couple of points I'd like to throw out, maybe after Connie, to see if there is agreement on that.

Yes, Connie. Go ahead.

DR. WEISNER: This is just anecdotal, but I can just tell you that many companies are coming to Kaiser asking to try out some sensors for drug

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testing that are really small, look like little Fitbits and things like that, and things you could do with an app on your cell phone.

I'm just thinking that while we're drudging these other data sets, I have no idea how valid these are going to be or where they are in the process, but I think that there's a lot of action going on with that.

DR. STRAIN: Thanks.

Dave, those companies aren't on your radar screen? I don't know. Maybe that's a discussion to have with Connie about who they are, whether they're named after a fruit.

DR. McCANN: Yes. We do support -- and not necessarily just from our division, but the other divisions of NIDA that would be supporting some technology development in terms of assays also, so we have the long-term approach to improving technologies.

DR. STRAIN: So let me see if there are some things that we can agree upon. Maybe I'll start with low-hanging fruit. So it seems to me, looking

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

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

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

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

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

DR. STRAIN: That's nice.

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

DR. STRAIN: Yes.

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

DR. STRAIN: Yes.

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

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

(Laughter.)

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

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

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

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

DR. STRAIN: I like that, yes.

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

Kathy just winced when I said that.

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

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MALE SPEAKER: Right, had a series of continuous measures that were associated with good outcome. Some self-reports were in there, a percent negative or a percent positive in urine samples. Using those might be helpful.

DR. STRAIN: I want to come back to urine samples, but I guess what I'm trying to figure out is do we think -- do we want to get into number of uses per week, or should we say number of days of use is the metric in this area? And maybe we don't have a consensus or agreement on that at this point.

My kneejerk is to say, especially after Celia's comments, well, maybe we should look at number of days of use out of 30 or whatever.

(No response.)

DR. STRAIN: Okay. So you all agree with me. Okay.

MALE SPEAKER: One of the things that I learned from the alcohol literature is, it's most useful to let the data be your guide for these. So I don't know. Percent days of abstinence has been

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around for a long time and has failed to impress or convince anyone, this notion of frequency. We don't know yet which cut point matters. We don't know if going from 30 to 15 or 15 to 1 and how long, we don't know yet. Those are all useful empirical questions.

DR. STRAIN: Let me put it this way, though -- and maybe we're in the same -- maybe we're running in parallel here. We can't say we're going to look at changes from heavy drug use days to fewer heavy drug use days because we have a hard time quantifying what is a heavy drug use day, unlike alcohol.

So given that, all we can do is say, is it a drug use day or not. And I think that's the unit of measurement that at least we need to explore and model, is what I'm arguing.

MALE SPEAKER: I misunderstood. I thought we're suggesting that we move away from any sort of arguments about quantity and just make the quantity versus frequency stay with frequency.

DR. STRAIN: Yes, as opposed to -- so for

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example, in the opiate area, we have often reported number of times of use per day or number of times of use per week, especially for heroin, because it's pretty common that it's 3 to 5 times a day, 7 days a week. But I think there's a lot more variability here.

So let's go back. Ken brought up urine results, and I want to bring up urine results because I found myself today thinking about this. And I wondered where we were with this.

Yesterday, I was thinking about urine results as an in-treatment measure. Today, I found myself thinking, could urine results be a longer term outcome measure? And if so, do they represent improvements? Is urine results a surrogate measure for improvements in health and social function?

My gut reaction is to say yes. But do we know that for stimulants? Yes, Kenzie?

DR. PRESTON: Since a positive urine on the first day of treatment is a good predictor of continued use during treatment, it seems to me that a positive urine in a follow-up phase probably also

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predicts continued drug use. I think I'm agreeing with you is that in fact it is an indicator that we shouldn't be ignoring, even though the period that it's looking at is relatively brief.

DR. STRAIN: So I guess maybe this is an FDA -- and I really don't want to put FDA on the spot or something, or anybody actually who has experience on this point. But would you generally see a negative urine result as indicating good health or good social function?

FEMALE SPEAKER: So here's what I can answer. We have always been willing to accept that demonstration that people have completely discontinued their drug use for a good chunk of time, a chunk of time long enough to predict that they're going to stay that way, that that is a valid surrogate for clinical benefit, quitting smoking, stopping drinking.

We have not ever required any additional data to validate that abstinence from drug use is a valid surrogate for clinical benefit. Where we have felt the need for some data to validate

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surrogate endpoints is when they are not abstinence endpoints. We've been willing to accept that if you stop using, you will benefit.

DR. STRAIN: That's helpful. That's great. Yes, David?

DR. McCANN: I was just thinking about the issue of percent clean urines, percent dirty urines versus number of days use. If you think about real-world applicability, how many people are going to be able to go into a doc and say I've got a cocaine problem? And then where does the discussion go? They don't go into what percentage of your urines are dirty or clean. It's how many days you have used.

So in terms of practical application, it seems like focusing on number of days use with urine testing to try and confirm that might be better than talking -- say, in a clinical trial result, such a percentage reduction in urines, I don't know how a physician is really going to relate that to their patients.

I guess, if you think about the labeling

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that would be in there, what would guide a physician. That's where I'm going with that.

DR. STRAIN: I like that. Thanks.

FEMALE SPEAKER: I don't remember who said this first, but I am fond of quoting it, that cocainuria [ph] is not the disorder we're trying to treat. So I think that Dave is right, that even as you say, Eric, words are important, to talk about it in terms of patterns of use instead of patterns of drug test results, of course we need to understand better how much we know about people's pattern of use and how well our biological measures capture them. But I think that would help people understand the impact a little better.

MALE SPEAKER: There is a parallel. The alcohol literature is useful, but the smoking literature is also useful. It's CO, confirmed abstinence, at a certain point. My understanding is they're moving away from that a little bit because it's a little insensitive, but people get it. Doctors get it. It's a short time point, but it's useful.

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DR. STRAIN: But if you could say -- would it be valuable to be able to say, if you used this treatment at the end of 3 months, if your patient is reporting that they've stopped use or they've decreased use -- if they've stopped use, then there's this likelihood that they'll continue to abstain over the next 12 months. If they've decreased their use to less than 4 days a month in the final or something, or one day a week, or something -- what's that?

MALE SPEAKER: Or not more than 4 because that would be once a week.

DR. STRAIN: Yes. Then there's a greater than 80 percent likelihood that they'll be abstaining or something. I think that's -- I'm looking at David. Isn't that that you're suggesting?

DR. McCANN: I think I've said everything I have to say. It's just in terms of the words that we use, if we can relate it to everyday life and what you've discussed with your physician, I think number of days used, number of times you've used in

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the past month, that would be more beneficial than talking about percent of clean urines, although that still may be something good to look at in terms of statistics and meaningful difference for a medication.

DR. STRAIN: Well, the analogy might be -- not to belabor this, but when I see a patient who's depressed, I talk to them about, what is the base rate of depression in the population? And I strip it down to very simple sort of stories. And then I say, if you're on an antidepressant at the end of 12 weeks for a garden-variety depression, this is what the chances are that you'll be improved if you take this medicine regularly.

So it's those sort of very simple messages I think that, from a clinical standpoint, we're trying to convey.

Our time is ticking down, and I want to open up as well to see if there are other points or agreements that we might be coming to based upon this, agreements not necessarily that are conclusions, but agreements also about what we need

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to investigate further.
MALE SPEAKER: Well, I think the point that Sharon made earlier about being able to prove some of the benefits postmarketing for something -- I'm looking for her exact words here. When you had a surrogate that looks reasonably likely for the benefit, I think that that would be important to put in the paper and to discuss maybe in a little bit more detail how that might play out.
So a company might get a phase 2 study where they see in the data something that they think is reasonably likely to be a benefit. They could then have a discussion with the FDA and there could be some discussion about whether there's agreement about whether they think that's reasonably likely to have a benefit.
I think it would be good to get that out in the literature, to say how that might play out.
FEMALE SPEAKER: I think they would be really helpful for people who have data to begin to explore some things that are reasonably likely, so that a company could come to us, saying, based on

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these analyses, we think this endpoint is reasonably likely.
That would be much better than having somebody say, here's what we found. Don't you think this is reasonably likely? Because we would need something to go on, to reach agreement, even on that reasonably-likely point.
DR. McCANN: The only reason I'm saying that is because we don't have an effective medication yet. I'm always hopeful that the next trial we do, wow, we're going to have an effect, and now, we've got something new, which we would bring to you.
FEMALE SPEAKER: But just remember, phase 2, reasonably likely, the discussion would be so that's a good surrogate to take into phase 3. Right? Because this is all predicated on adequate and well-controlled trials? So the conversation wouldn't be, it's reasonably likely on phase 2, so we're going to just go for an NDA. It would be, so this would be the right outcome to take forward as a surrogate, and here's a long-term plan for phase 3, and then postmarketing.

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DR. McCANN: And that's exactly what I was thinking. Some companies want to jump in. In the very first trial they do, they want it to be a pivotal trial of the first two. And in a way, you could encourage -- you could get people away from that type of thinking, to say, do a study, see what signal you get, and then come talk to us.
MALE SPEAKER: Just one thing that I hope we add to the overall proceedings, the discussion yesterday about the endothelial factor and its potential relationship to cardiac morbidity. I recognize it's super, super early, early days, limited number of patients, but it is a way of connecting decrease in use with probably the primary adverse medical manifestation.
There are drugs approved for lowering blood pressure by 5 millimeters of mercury. And I don't know, if you could show that by taking this medication, decreasing use of cocaine, and showing a decrease in diastolic blood pressure by X amount, maybe would also be another way of translating benefit; so just something to consider as

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alternative or supportive evidence.
MALE SPEAKER: The first manuscript is in press. I think you know that, Eric. Yes? It's in your journal. So it might be useful -- If I send Dr. Lai an e-mail, he might send you a manuscript. You may want to incorporate that into the menu because it's still early, but it's pretty compelling.
MALE SPEAKER: There was discussion yesterday about whether to have equivalent of a drink measure, a consequence measure for drugs. It's not necessarily so sensitive in alcohol trials, but maybe it will be more sensitive in drug trials.
FEMALE SPEAKER: Can I make a comment on that? Kind of going back to the context of evaluating somebody's improvement in the context of how they enter treatment, I know that several of the industry-sponsored opiate trials, including probuphine, I believe, uses a global assessment of functioning. It's just a single-item measure.
I was thinking something like that might be

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useful, where an individual is just instructed to assess themselves based on their own employment, and legal, and family problems at treatment intake, and then they can reassess themselves at the end. And it would be easy to administer just a single-item continuous measure, but it would kind of eliminate this problem that we have with the ASI, where some people are entering in with no employment problems. And so we can't expect improvements in employment problems over time and so on.

MALE SPEAKER: I think we routinely get to CGI in all our trials. It hasn't been shown to be especially sensitive, but then, we haven't found an effective medicine yet either.

DR. STRAIN: And let me point out that we have no effective medicines, but, I mean, we could theoretically at least -- we have contingency management interventions that could be effective. And they could be used as models for trying to manipulate use, quite frankly, so that we could see if measures have value.

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MALE SPEAKER: Yes, if they're sensitive, at least, yes. If you have a decrease in cocaine use, you should see a movement in consequences, hopefully, if consequences measured is sensitive.

DR. STRAIN: So the big hand is almost on the 12, I think. Any last thoughts people have? Yes, David? Sure.

DR. McCANN: I want to clarify for the board -- I mentioned this on the side to Eric. The data that Amy presented, they aren't complete yet. But if she has no plans to publish those data, putting certain aspects of that into this paper might be good.

I was impressed. Clearly, clinicians, they like the idea of abstinence, but there was a very high percentage that liked the idea -- I'm sorry, not clinicians, the payers. They liked the idea of decreased use.

I don't know how that's going to turn out when she has all of her data, but it might be useful to have that data there. If it doesn't get there, it probably won't get anywhere. So it would

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be good to include if she's willing.

DR. STRAIN: Yes, we should try to get that out in some way, yes.

MALE SPEAKER: Someone else has suggested trying to do that survey on all the stakeholders and compare. I don't know if that can be commissionable, but that would be really interesting.

DR. STRAIN: Dave, did you have a comment?

MALE SPEAKER: Yes, include employers.

DR. STRAIN: What's that?

MALE SPEAKER: Include employers, please.

DR. STRAIN: Oh, employers. I thought you said, include lawyers, and I thought that was --

(Laughter.)

DR. STRAIN: Employers, yes. Thank you. Yes, George?

DR. WOODY: Would it be useful to separate what would maybe improve the patient but wouldn't be acceptable to the employer? Like impaired healthcare professionals, you really want them to be abstinent, or airplane pilots.

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So there are certain social situations where you could say, well, the patient is better, but it's not good enough for whatever that person is doing. Maybe there are two different dimensions there. I don't know how they interact with decisions.

Adjournment

DR. STRAIN: It resonates with Connie's points from yesterday as well about the motivations as well and the particulars of the population.

So let me thank all of you for yesterday and today. I think it's been a really fruitful conversation and dialogue. I feel very intellectually engaged. I wish I could single out each of you to thank you by name, but we'd probably be here for about another half-hour.

I think the value of something like this is that almost everybody in the room was both a participant in the audience, but also a presenter, so it makes it for a small but very fruitful dialogue, I think, and I appreciate that.

This is a process that likely doesn't end

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

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

(Applause.)

(Whereupon, the meeting was adjourned.)

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