

ACTION
Measures of Outcome for Stimulant Trials (MOST)

March 25, 2015

A Matter of Record
(301) 890-4188

ACTTION
Measures of Outcome for Stimulant Trials (MOST)

March 25, 2015

L*4343*L*		Page 1			Page 3
1	ACTTION		1	C O N T E N T S (continued)	
2			2	AGENDA ITEM	PAGE
3			3	The Conundrum of Changes in Use Versus	
4			4	Abstinence as Endpoints	
5	MEASURES OF OUTCOME FOR STIMULANT TRIALS (MOST)		5	Kathleen Carroll, PhD	153
6			6	Discussant	
7			7	Celia Winchell, MD	175
8			8	Prior and On-Going Efforts to Evaluate	
9			9	Clinical Benefit in Stimulant Trials	
10			10	Based Upon Past Studies	
11			11	David McCann, PhD	196
12	Wednesday, March 25, 2015		12	Presenters	
13			13	George Woody, MD	198
14			14	Brian Kiluk, PhD	212
15			15	Shengan Lai, MPH	232
16	Hilton Rockville Hotel and Executive Meeting Center		16	Ivan Montoya, MD, MPH	244
17	Rockville, Maryland		17	Discussant	
18			18	Phil Skolnick, PhD, DSc	262
19			19	Q&A - Group Discussion	267
20			20	Lessons Learned from other Addiction Trials	
21			21	Rachel Skeete, MD	271
22			22	Q&A - Group Discussion	296
			Page 2		Page 4
1	C O N T E N T S		1	C O N T E N T S (continued)	
2	AGENDA ITEM	PAGE	2	AGENDA ITEM	PAGE
3	Welcome and Introductions		3	What Research is Needed?	
4	Goals of Meeting		4	Wrap Up for Day	
5	Eric Strain, MD	5	5	Eric Strain, MD	326
6	Approach to Outcome Measure Development or		6	Adjournment	330
7	Selection: A Regulatory Perspective		7		
8	Ashley Slagle, MS, PhD	11	8		
9	Experience in Developing a Tool Using the		9		
10	CSSA as a Model		10		
11	Kyle Kampman, MD	37	11		
12	Q&A - Group Discussion	60	12		
13	Discussant		13		
14	Eric Strain, MD	67	14		
15	An Overview to the Experience in		15		
16	Developing an Outcome for Alcohol Studies		16		
17	Raye Litten, PhD	96	17		
18	Discussant		18		
19	Dan Falk, PhD	129	19		
20	Q&A - Group Discussion	143	20		
21			21		
22			22		

Page 5

1 P R O C E E D I N G S
2 Welcoming and Introductions
3 DR. STRAIN: Let me introduce myself. I'm
4 Eric Strain, and I have the dubious distinction of
5 chairing this meeting, and I want to welcome you
6 all to it. This is the Measures of Outcome for
7 Stimulant Trials meeting. And I'm going to explain
8 a little bit of background to it over the next
9 couple of minutes, but won't take long.
10 Before I get started, let me say
11 that -- actually, Bob Dworkin and I are co-chairing
12 this meeting, but Bob -- I think I can tell you
13 this. Bob has a kidney stone that he developed in
14 San Francisco and is not allowed to travel at this
15 point. I think he's getting a procedure done or
16 he's going to be evaluated for a potential
17 procedure.
18 So it's just really striking the extent that
19 some people will go to, to avoid coming to a
20 meeting I think. That's why Bob is not going to be
21 here today or tomorrow. And he sends his regrets.
22 He really did wish he could be here.

Page 6

1 A few housekeeping things, just standard
2 things. Please sign on [sic] to your cell phones.
3 The microphones here are voice activated, so please
4 speak into them if you do have a comment to make.
5 And I hope that people will engage in discussion
6 over the course of the next couple of days.
7 This meeting is being recorded. There will
8 be a transcript generated that's put on the ACTTION
9 website, so that you're aware of that. That's been
10 pretty routine for these meetings. And we will
11 have breaks that actually will be in this room
12 right over here to my left, to your right. So
13 they're going to be setting up coffee and things in
14 that room a little bit later this morning, so we
15 won't need to go back down the hall to the other
16 room to get replenished. Lunch will be held in the
17 Roosevelt Room located in the lobby level. We'll
18 explain that to you later
19 Check out is at noon tomorrow, and taxis can
20 be ordered for your return to the airport if you're
21 flying. And you can check in with Valorie.
22 Valorie, you want to wave your hand? If you

Page 7

1 haven't met Valorie in the back, if you have any
2 questions about those sorts of things -- and you
3 should have signed in when you came in this
4 morning. There was a sign-in sheet at the front
5 desk, right outside the door here.
6 Let me just give you a few orienting things
7 about this meeting. You should have received this,
8 but just to remind you, the goals of this meeting
9 are to review work that's been conducted validating
10 outcome measures for clinical trials of
11 stimulant-use disorders and to review related
12 target substances that have successfully developed
13 clinically meaningful outcome measures for
14 substance-use disorders. And finally, to identify
15 research agenda for the development of a tool and
16 related outcome measures that would be clinically
17 meaningful for stimulant-use disorder clinical
18 trials.
19 Those were the things that were defined to
20 us. And the structure of the meeting is that we
21 decided at the beginning we wanted to keep this
22 relatively small, somewhere between 30, 45 people

Page 8

1 max, so that's where we're at. I think we'll have
2 about 35 or 38 people. Some people will be
3 arriving later this morning. There are a couple of
4 people who will be here for tomorrow only.
5 The presentations, as you probably see with
6 the agenda, tend to be -- there are presentations
7 with a moderator, and then there's a discussant
8 afterward who will hopefully bring together and
9 draw out some of the salient points from the
10 presentations. And as I mentioned before, we are
11 recording the proceedings of the meeting.
12 MALE SPEAKER: Will slides be available?
13 DR. STRAIN: I think they are. I think the
14 slides go up on the website afterwards. Yes.
15 Some people have asked me -- and I have
16 asked -- how does this all work? This is sponsored
17 by ACTTION, which actually comes out as AAA-CTTION,
18 because there's a bunch of A's and T's in ACTTION,
19 which is the Analgesic, Anesthetic, and Addiction
20 Clinical Trial Translations, Innovations,
21 Opportunities and Networks program. I'm not sure
22 if Bob Dworkin or Dennis Turk -- one of them loved

Page 9

1 acronyms -- hence, MOST -- and ACTTION is a
2 public-private cooperation that works to optimize
3 clinical trials methodologies, and has included
4 academicians, people from the FDA, people from NIH,
5 as well as industry.
6 Its historically worked in the area of
7 analgesics and of pain, but they've recently taken
8 interest in the area of addictions. They had a
9 meeting looking at the use of terminology,
10 especially misuse terminology, and produced a paper
11 out of that. The primary mode of ACTTION -- and I
12 couldn't resist that pun -- is through expert panel
13 meetings and reports, such as what we're doing
14 here.
15 This is really run out of the University of
16 Rochester primarily and comes from funding from a
17 variety of federal as well as private sources that
18 seeks to produce something that will move the field
19 forward, for example, in terms of either
20 definitions of terminology or defining research
21 needs of the field.
22 The planned outcome for this meeting is a

Page 10

1 paper and a peer-reviewed literature that reports
2 on the outcomes, so it might be on the current
3 state of the affairs, the needs, the research
4 agenda, and going forward. And Brian Kiluk, who
5 can wave his hands, will be taking the lead on
6 writing up the results of this meeting. And that's
7 very in keeping with other ACTTION efforts.
8 So let me stop there. Any questions about
9 any of that?
10 (No response.)
11 DR. STRAIN: I think it's pretty
12 straightforward I hope.
13 Again, the meeting is structured with time
14 for discussion, time for reflection. I realize we
15 all may not have the answers, but I hope that we
16 can at least help to formulate questions and ideas
17 as to what needs to be done to help us get those
18 answers.
19 Let me see if there anything else I didn't
20 touch on. I think the only other thing is a
21 housekeeping thing, bathrooms. Bathrooms are down
22 the hall and to the left. Other than that, I think

Page 11

1 we're set to go.
2 So I would like to, next then, introduce
3 Ashley Slagle from the FDA, who's going to be
4 talking about approach to outcome measure
5 development or selection, a regulatory perspective.
6 Ashley?
7 Oh. And I should mention, I'll serve as the
8 discussant for this pair of talks since Bob
9 Dworkin's not available.
10 Presentation - Ashley Slagle
11 DR. SLAGLE: Good morning. Well, thank you
12 very much. I appreciate the invitation to speak
13 today. I'd like to give a little bit of background
14 and sort of set the stage for the discussion today
15 to share a regulatory perspective on the approach
16 to outcome measure development or selection. Of
17 course, the views expressed in this presentation
18 are my own and don't necessarily represent an
19 official FDA position.
20 Before we get into the details of measure
21 selection or development, I want to step back just
22 a little bit and think about the broader context of

Page 12

1 what we're trying to do in clinical trials. So
2 ultimately, we seek to evaluate treatment benefit;
3 that is, that a drug has some positive impact on
4 something that is important to patients: so how
5 long they live, how they feel, or function in daily
6 life. We then have to weigh those benefits
7 demonstrated and quantified in clinical trials with
8 known risks of the products in order to make drug
9 approval and labeling decisions.
10 We use outcome assessments to determine
11 whether or not a drug has been shown to provide
12 benefits to patients. One of the most important
13 aspects of drug development is how treatment
14 benefit, or sometimes referred to as clinical
15 benefit, is measured.
16 There are different types of outcome
17 assessments can be used to evaluate treatment
18 benefit. Of course, there's survival, but in many
19 contexts, survival may not be an appropriate
20 endpoint in a clinical trial, either because the
21 condition does not impact survival or because the
22 trials would need to be prohibitively large or long

Page 13

1 in order to detect survival benefits. So we often
2 turn to other types of outcome assessments.
3 Then there are clinical outcome assessments
4 of which there are four types: performance outcome
5 measures, and then outcome measures that are
6 reported by either clinicians, other observers, or
7 patients themselves. So it's important to note
8 that what separates clinical outcome assessments
9 from the other types of assessments are that they
10 rely on human judgment, motivation, or
11 participation.
12 So it might be that we're interested in
13 symptoms in a population that can report for
14 themselves. In this case, a patient reported
15 outcome assessment would be most appropriate. If
16 clinical judgment is needed to interpret an
17 observation, then a clinician reported outcome
18 assessment is most appropriate.
19 If an observable behavior in daily life is
20 being assessed in a population that can't report
21 for themselves, then an observer reported outcome
22 assessment would be appropriate. In some cases, we

Page 14

1 want to observe an actual demonstration of some
2 activity in the clinic, and in that case, a
3 performance outcome measure could be used.
4 So of course patient reported outcomes have
5 gained increasing attention over recent years, and
6 this is really a good thing because including
7 patient reported outcomes in clinical trials is
8 really useful to help us understand directly how
9 products impact how patients feel and function in
10 daily life. But keep in mind that there are other
11 types of clinical outcome assessments that are also
12 very important and can be considered for use in
13 trials. And then there are surrogates, which are
14 usually biomarkers that are intended to be used as
15 a substitute for how a patient feels, functions, or
16 survives.
17 Let's talk a little bit more about treatment
18 benefit. We think about treatment benefit in terms
19 of direct evidence and indirect evidence. Direct
20 evidence of treatment benefit is derived from
21 studies with endpoints that measure survival or how
22 patients feel or function in daily life. Indirect

Page 15

1 evidence of treatment benefit is derived from
2 studies with endpoints that measure other things
3 that are related to how patients survive, feel, or
4 function.
5 It might be helpful to think in terms of a
6 continuum of direct and indirect evidence of
7 treatment benefit. Direct evidence of treatment
8 benefit is gained from actually measuring what is
9 meaningful to patients in their daily lives.
10 For indirect evidence of treatment benefit
11 that does not actually measure the clinical benefit
12 directly, we need to have some evidence of the link
13 between the indirect assessment and the meaningful
14 benefit. So depending on how indirect something
15 is, the more evidence we might need to understand
16 that link.
17 For example, we consider performance
18 measures like the 6-minute walk test to be somewhat
19 indirect because they are not measuring how people
20 feel or function in their daily life, but are
21 intended to closely approximate how patients feel
22 or function in daily life. With these types of

Page 16

1 performance measures, it's important to understand
2 what the performance test is actually measuring and
3 what it is intended to represent. So what does a
4 score change on this indirect measure mean in terms
5 of meaningful treatment benefit in patient's daily
6 life.
7 Biomarkers are at the far indirect side of
8 the continuum, so therefore, we need very strong
9 evidence showing that the biomarkers predict some
10 clinical benefit; again, how patients feel,
11 function, or survive.
12 Surrogates within existing and
13 well-established link or prediction of clinical
14 benefit can support endpoints that are used in
15 traditional approval. So an example would be
16 something like blood pressure. Biomarkers or
17 surrogates without that existing evidence that they
18 are linked to meaningful clinical benefit, but are
19 reasonably likely to predict clinical benefit,
20 might be able to support approval through the
21 accelerated approval pathway with the requirement
22 that post-approval studies are completed to then

<p style="text-align: right;">Page 17</p> <p>1 confirm that link between the biomarker and the 2 expected clinical benefit. 3 We want to include the patient perspective 4 and evaluate patient reported efficacy outcomes in 5 clinical trials. How do we determine what's best 6 to measure? So we need to consider within our 7 selected patient population what concepts are 8 relevant to how patients feel and function. 9 For drug approval and labeling, we also need 10 to think about how closely related those things are 11 that we might measure to the disease and the 12 treatment. This slide helps to define those things 13 that might be more proximal to the condition and 14 treatment, like poor symptoms and aspects of 15 functioning, and those things that are more distal 16 like health related quality of life. 17 This doesn't mean that the more distal 18 concepts are less important. It just means that 19 there are many more variables that might impact 20 those concepts in addition to the disease and the 21 treatment. So the farther we move to the right on 22 this diagram, the harder it becomes to detect a</p>	<p style="text-align: right;">Page 19</p> <p>1 aspects of quality of life that are closely related 2 to the condition and treatment, like symptoms or 3 proximal daily functioning impacts, be the target 4 of endpoints and clinical trials, rather than the 5 broader concepts that are of course important but 6 are harder to measure, interpret, and to show a 7 treatment effect on. 8 From the regulatory perspective, it's 9 necessary that drug developers document substantial 10 evidence of treatment benefit from adequate and 11 well-controlled clinical trials. The regulations 12 also specifically indicate that the methods of 13 assessment of a subject's response should be 14 well-defined and reliable. So this is important. 15 It means that well defined and reliable become the 16 key criteria by which the FDA evaluates outcome 17 assessments to document evidence of treatment 18 benefit. 19 So when is a clinical outcome assessment 20 well defined and reliable and appropriate for use 21 in adequate and well-controlled studies? Well, 22 when we're measuring the right thing in the right</p>
<p style="text-align: right;">Page 18</p> <p>1 treatment difference or to interpret any treatment 2 difference that is identified when you measure 3 these things. 4 Of course, the distal concepts are 5 considered for measurement in clinical trials to 6 support labeling claims. We need to ensure that 7 the variables that contribute to these concepts are 8 also measured so that we can interpret trial 9 results. For example, if we wish to measure 10 health-related quality of life, we need to make 11 sure to assess symptoms, adverse events and 12 toxicities, and all of the impacts that can 13 contribute to health-related quality of life, 14 including general psychological functioning, 15 physical functioning, social functioning, and so 16 on. 17 Measuring these more distal concepts becomes 18 increasingly difficult, and especially in patients 19 with multiple co-morbidities that might also impact 20 things like health status and quality of life that 21 might be unaffected by our treatment under study. 22 So that's why we often recommend that more specific</p>	<p style="text-align: right;">Page 20</p> <p>1 way, in that population, and that the score that 2 quantifies that thing that we're measuring does so 3 accurately and reliably so that the effects that 4 are seen in the outcome assessment can be 5 interpreted as clear treatment benefit. 6 We refer to the FDA patient reported 7 outcome, or PRO guidance, that describes good 8 measurement principles that might be considered to 9 evaluate whether a measurement is well defined and 10 reliable. This guidance was developed specifically 11 for patient reported outcomes, but many of the 12 principles are appropriate and apply to any 13 clinical outcome assessment type. 14 This guidance provides an optimal approach 15 to patient reported outcome development, but we 16 understand that flexibility and judgment are needed 17 in order to both meet the regulatory standards as 18 well as the practical demands of drug development. 19 Specifically, when we evaluate whether an 20 assessment is well defined and reliable, we 21 evaluate the tool's measurement properties. First 22 and foremost, we consider content validity. After</p>

<p style="text-align: right;">Page 21</p> <p>1 content validity is established, then we consider 2 other measurement properties, including construct 3 validity, reliability, ability to detect change, 4 and then guidelines for interpreting meaningful 5 change. 6 So what do I mean by content validity? We 7 often use this term "content validity," and I think 8 eyes glaze over sometimes. So I want to just talk 9 a little bit about specifically what we mean. It 10 means what are we measuring? Is that the right 11 thing to measure in that population? Does the 12 patient understand the items and respond in the way 13 intended? And then when we combine all of the 14 items from a questionnaire into one score, what 15 does that score represent? 16 As regulators, we put a big emphasis on 17 content validity because we need to ensure that 18 when we see score change on an assessment, we can 19 determine what that score change means. And 20 importantly, that we can describe that score change 21 in labeling in terms of meaningful treatment 22 benefit in a way that it's not potentially false or</p>	<p style="text-align: right;">Page 23</p> <p>1 quantified risks and benefits to make approval 2 decisions. But this is also where patient input 3 can be very useful to help us understand what is a 4 meaningful change, amount of change on an 5 assessment, and how do patients weigh those risks 6 and benefits? 7 It's possible that for some things, a cohort 8 of patients with one condition might think very 9 differently about what are meaningful changes than 10 a cohort of patients with another condition. So we 11 need to understand and incorporate these 12 considerations. 13 We've developed a couple of diagrams to help 14 facilitate assessment development or selection. 15 The first is a Roadmap to Patient-Focused Outcome 16 Measurement in Clinical Trials, and this is really 17 intended to illustrate how someone might embark on 18 a sound and orderly instrument selection or 19 development pathway, beginning with the clinical 20 context in which the instrument is intended to be 21 used. 22 This is not intended to be a hurdle or a</p>
<p style="text-align: right;">Page 22</p> <p>1 misleading. 2 So we do recommend involving patients, using 3 focus groups or individual interviews, to help 4 develop the assessments that are planned for use in 5 clinical trials. And this can help ensure that 6 we're measuring the right things and to help us 7 figure out the best way to ask the questions in the 8 trials. 9 Another key consideration is how to 10 interpret what is meaningful change on an outcome 11 assessment. So often statistically significant 12 changes alone are not fully interpretable. So if 13 we see a very small change in a score that is 14 statistically significant, we have to think about 15 whether that amount of improvement is meaningful to 16 the patient population, and weigh the amount of 17 improvement or benefit against risk. 18 So we really need to think very carefully 19 when weighing risks and benefits of drugs. And of 20 course, these aren't unusual decisions. It's 21 really the job of the FDA to incorporate our 22 regulations, science, and judgment to weigh</p>	<p style="text-align: right;">Page 24</p> <p>1 checklist. I know there's a lot of information on 2 here. It really is intended to be helpful. It's 3 meant to be a tool that organizes a lot of the 4 things that drug developers are already thinking 5 about, and some things that sometimes they forget 6 to think about. But it really can help inform drug 7 development programs and outcome assessments. I'm 8 not going to go through it in detail. I just 9 wanted to alert you to the existence of this tool 10 on our website, and then drive home a couple of key 11 points from the diagram. 12 First, it's really important that adequate 13 attention is given to the first two columns. So 14 understanding the condition and conceptualizing 15 treatment benefit before beginning to think about 16 selecting or developing an outcome measure. So 17 this is a common pitfall that we do see. Trial 18 designers and instrument developers haven't paid 19 adequate attention to these things before selecting 20 an outcome assessment, and this can be really 21 problematic for trials. 22 So we encourage drug developers to discuss</p>

<p style="text-align: right;">Page 25</p> <p>1 outcome assessments early in the drug development 2 program so we can provide advice early enough to 3 help avoid some of the pitfalls that we've seen in 4 the past and improve the likelihood of a successful 5 use of outcome assessments.</p> <p>6 There are two elements from the roadmap that 7 I want to highlight that are important when 8 conceptualizing treatment benefit. It's important 9 that we think about what is important to measure 10 and be sure that we measure that appropriate for a 11 given context or context of use of the assessment.</p> <p>12 So we've tried to put together a list of 13 common elements that are part of the context of use 14 that might impact decisions about the assessment of 15 treatment benefit. And this list is not perfectly 16 comprehensive, nor will every element apply to 17 every drug development program, but it's useful to 18 give some thought to these elements. Consider the 19 disease definitions: the patient subpopulations, 20 clinical trial design and objectives, and the 21 clinical practice in study settings.</p> <p>22 So within the study design objective</p>	<p style="text-align: right;">Page 27</p> <p>1 about the drug product and labeling. These 2 assessments will still need appropriate attention, 3 as they could be the basis for labeling claims that 4 may be found, for example, in Section 14, the 5 clinical studies section of labeling. All the 6 assessments need to be well defined and reliable.</p> <p>7 Exploratory endpoints might be hypothesis 8 generating, might be used as additional supportive 9 evidence to help interpret the findings from 10 primary and secondary endpoints. But these 11 assessments supporting exploratory endpoints will 12 not be the basis for labeling claims. So these 13 assessments might not need to meet the same level 14 of evidence and documentation to justify their use 15 in clinical trials.</p> <p>16 Selecting what to measure and how to place 17 that in an endpoint hierarchy are important 18 considerations. Sometimes multiple measures and 19 endpoints might be used to provide the needed 20 information for approval.</p> <p>21 For example, on a recent drug development 22 program for ruxolitinib, a treatment of</p>
<p style="text-align: right;">Page 26</p> <p>1 headings, we include the bullets endpoint 2 definition and endpoint positioning. This is also 3 important in the regulatory setting and can impact 4 our choice of outcome assessments to support 5 endpoints, as well as the level of evidence needed 6 to support the selection of an outcome assessment.</p> <p>7 Note that outcome assessments and endpoints are not 8 synonymous, but the score of an outcome assessment 9 is used to develop an endpoint definition.</p> <p>10 We also think about the following categories 11 in the hierarchy of endpoints. They are primary, 12 secondary, and exploratory. For primary endpoints 13 that are meant to support drug approval decisions, 14 a higher level of evidence is needed to support the 15 selection or development of a particular outcome 16 assessment that forms the basis of the primary 17 endpoint, and then the indication statement and 18 labeling.</p> <p>19 Secondary endpoints are generally meant to 20 support the findings from the primary endpoint and 21 can help us better interpret the primary endpoint, 22 or to learn and to be able to communicate more</p>	<p style="text-align: right;">Page 28</p> <p>1 myelofibrosis, the primary endpoint was a reduction 2 in spleen size. So is shrinking a patient's spleen 3 true clinical benefit? Well, ruxolitinib also 4 demonstrated reduced total symptom score on the 5 Myelofibrosis Symptom Assessment form, which is a 6 patient reported outcome assessment that was used 7 to support a key secondary endpoint.</p> <p>8 So in addition to the reduction in 9 radiographic spleen volume, there was also an 10 improvement in patient's symptoms. So this total 11 symptom score was very helpful in correlating the 12 anti-tumor effect with improvements in how patients 13 were feeling and their symptoms. And so 14 ruxolitinib, or Jakafi, was granted traditional 15 approval rather than accelerated approval.</p> <p>16 In addition to the roadmap that helps to 17 conceptualize treatment benefit, the second diagram 18 on our website is the clinical outcome assessment 19 wheel and spokes diagram. This diagram identifies 20 the key components of the documentation that would 21 need to be submitted to CDER to support the use of 22 clinical outcome assessment.</p>

Page 29

1 It really represents the general iterative
2 process of developing a clinical outcome
3 assessment. And I think it's important to note
4 that this type of work has been going on for years
5 in the social sciences, and it's been more recently
6 that we're now bringing this into the world of drug
7 development.

8 This is a high level view of the wheel and
9 spokes diagram, and a more detailed version is
10 available on our website. For our purposes today,
11 though, I'm not going to walk through this, but I
12 do encourage you to take a look at the website.

13 The first spoke shows the need to identify
14 the context of use and the concept of interest, so
15 what are you measuring and what's the clinical
16 context?

17 In spoke 2, you're drafting the instrument
18 and evaluating content validity. And so, this is
19 where patient interviews, or interviews with
20 clinicians, literature, research, can be useful,
21 developing the items, and ensuring that you're
22 measuring what you intend to measure, and that the

Page 30

1 score really represents what you believe it
2 represents.

3 In spoke 3, this is the cross-sectional
4 evaluation of other measurement properties. So
5 after you've established content validity, then you
6 can evaluate cross-sectionally construct validity
7 and maybe some test/retest reliability. And then
8 spoke 4 is the longer, bigger, longitudinal
9 evaluation of the measurement properties, and
10 looking at the instrument's ability to detect
11 change and then establishing guidelines for
12 interpreting change.

13 The final spoke 5 is included if there needs
14 to be modifications to the instrument. So if
15 you're using an existing instrument in, say, a new
16 context of use, and you may need to make some
17 adjustments to the instrument to be appropriate for
18 that new context of use, spoke 5 represents that
19 potential.

20 I want to share just a few more
21 considerations about outcome assessments, including
22 patient reported outcomes. It's important to

Page 31

1 remember that available assessments are not all
2 adequate for use as clinical outcome assessments to
3 evaluate efficacy in trials.

4 So there's no such thing as an instrument
5 that is "validated" for all purposes. Some
6 measures may be used for diagnostic purposes,
7 prognostic purposes, used to select patients for
8 participation in clinical trials, used for
9 epidemiologic or population studies to better
10 understand characteristics or the natural history
11 of the condition, or used to assist in clinical
12 practice decision-making. But assessments used for
13 these other purposes are often not appropriate for
14 use as outcome assessments in clinical trials, at
15 least not without some modifications.

16 So we've seen challenges across various
17 development programs and understand the nuances of
18 outcome measurement within a regulatory context, so
19 we'd like, to the extent that we can, to share our
20 learnings with drug developers to help ensure the
21 highest likelihood of being able to detect
22 meaningful treatment benefit within trials to bring

Page 32

1 good drugs to market, and then to provide patients
2 and other stakeholders with important information
3 about those drugs and how patients feel and
4 function in daily life.

5 We have two pathways to provide advice to
6 those who are interested in outcome assessment
7 development for clinical trials, first within the
8 context of individual drug development programs.
9 So we encourage sponsors to begin these discussions
10 within their individual drug development program as
11 early as possible, even at the pre-IND stage if
12 possible; again, so that if any work needs to be
13 done on the proposed instruments, there's time
14 within what we know are very tight development
15 timelines.

16 The second pathway is outside of any
17 individual drug development program, and this is
18 through our drug development tool, or DDT,
19 qualification process. And this program, we can
20 work with outcome assessment developers to develop
21 and qualify assessments that are intended for use
22 across multiple drug development programs. So we

Page 33

1 work with many stakeholders in this pathway,
2 including consortia, patient groups, individual
3 academic investigators, and drug developers within
4 the program to help develop and qualify publicly
5 available outcome assessment tools.
6 We do have a guidance that describes the
7 drug development tool qualification process.
8 Outcome assessments that are used in clinical
9 trials are not required to be qualified through
10 this program, but we do believe that when
11 assessments are developed in consultation with
12 CDER, and then ultimately qualified through this
13 program, this will help to encourage drug companies
14 to pursue drug development in these areas because
15 the companies can be confident that FDA agrees with
16 the content and the measurement properties of a
17 tool, thus lowering their risk.
18 So here's the link to our website that I
19 mentioned a couple of times. I really do encourage
20 you to take a look. And with that, I thank you,
21 and I look forward to the discussion.
22 (Applause.)

Page 34

1 DR. STRAIN: Do you want to take one or
2 two -- we could take one or two questions now,
3 though we'll have question time as well after this
4 pair of talks.
5 Let me go back actually, if I can then.
6 First of all, it was a great talk. Thank you.
7 Very methodical, and I liked how it laid everything
8 out. Let me pose the question, but let you
9 contemplate it while Dr. Kampman speaks.
10 What I'll be curious to hear about is your
11 thoughts about how you take this structure and look
12 at stimulant clinical trials, and what we need to
13 do to move forward in that context, especially
14 given the reliance and the addictions field on
15 surrogate measures, as outcome measures so often
16 for clinical trials. So maybe I'll plant that seed
17 of a question.
18 DR. SILVERMAN: I have a question there,
19 too, I could add. I wonder --
20 DR. STRAIN: Can you state your name?
21 DR. SILVERMAN: Oh, I'm Ken Silverman.
22 DR. STRAIN: For the recording.

Page 35

1 DR. SILVERMAN: Okay. I do research with
2 incentives. I'm not attentive to the FDA concerns
3 as I probably should be. But I've always
4 considered the objective measures of a urinalysis
5 to be the best outcome measure for our trials. But
6 the FDA apparently, it sounds like, considers them
7 less -- I don't know -- you need stronger evidence
8 if you use those surrogate measures than if you
9 used some self-report.
10 Could you just comment on that?
11 DR. SLAGLE: Yes. Well, I think there are
12 trade-offs. So the objective measures are easier
13 to measure in some cases, and they're "objective,"
14 so you feel like you can trust the results. Some
15 people are a little less comfortable with the
16 subjective measures; for example, patient reported
17 outcomes.
18 But within our regulatory context, we are
19 looking -- we have to identify treatment benefit,
20 which is how patients, feel, function, or survive.
21 And these surrogate measures, while sometimes
22 easier to measure, don't always directly translate

Page 36

1 into how patients or function in daily life, or
2 survive. So we need evidence that shows that this
3 objective thing that you're measuring actually
4 means something to the patient in their daily life.
5 So I wouldn't say that FDA doesn't -- we use
6 surrogates in multiple conditions because there's
7 existing evidence that tells us that this actually
8 means something; it's meaningful to patients.
9 Does that help answer the question?
10 DR. SILVERMAN: Yes. Not sure I like the
11 answer.
12 (Laughter.)
13 DR. SLAGLE: Well, just because you can
14 impact some biologic process doesn't necessarily
15 mean that it's doing anything beneficial to the
16 patient. And so that's what we have to guard
17 against, that we're not just changing something
18 that we can measure without actually doing anything
19 beneficial for the patient.
20 DR. STRAIN: So let me introduce Dr. Kyle
21 Kampman, who's going to be speaking now on
22 experience in developing a tool using the CSSA as a

Page 37

1 model. Dr. Kampman?
2 Presentation - Kyle Kampman
3 DR. KAMPMAN: Good morning. I'm going to
4 talk to you today a CSSA, the Cocaine Selective
5 Severity Assessment, which is a measure of cocaine
6 withdrawal. Now, the purpose of my talk, as I
7 understand it, is to use the CSSA as an example of
8 instrument development. I do not believe that the
9 CSSA is the ideal instrument to measure efficacy in
10 cocaine pharmacotherapy trials. I just wanted to
11 give that disclaimer. But what it does is it
12 measures clinical phenomenon that seems to have
13 implications in treatment outcome in outpatient
14 cocaine-dependent patients, cocaine-dependent
15 patients undergoing outpatient treatment.
16 So that's what it does. So what we're going
17 to do for the next 20 minutes is talk a little bit
18 about how this instrument came about. So what
19 we're going to do is I'm going to introduce you to
20 the CSSA, tell you where it came from, why we
21 developed it, talk about what it measures, go
22 through some of the basic reliability and validity

Page 38

1 testing that we did with it initially, and then
2 talk about the subsequent testing we've done with
3 it and the usefulness that we found for it in our
4 clinical trials.
5 The CSSA, you've got a copy with you, in
6 front of you, at your desktop, and it's a measure
7 of cocaine withdrawal. It has 18 items, each one
8 measured on a zero to 7 scale. And the signs and
9 symptoms measured include things like appetite and
10 sleep changes, cocaine craving, depressed mood,
11 anxiety, irritability, lethargy, inattention,
12 paranoia, and heart rate changes.
13 So if you do the math and you consider that
14 two scales are mutually exclusive, your maximum
15 score is 112. People generally don't score that
16 high. On the whole, you get average scores in most
17 of your treatment trials somewhere between 25 and
18 35. That's the scale.
19 So where did it come from? This scale was
20 written by Joe Volpicelli at the Penn Center for
21 the Study of Addictions. And he was my mentor, and
22 I took over the testing of it shortly after he

Page 39

1 wrote it. And it's modeled on the Selective
2 Severity Assessment, which is a tool that measures
3 alcohol withdrawal symptoms. It's an old tool. It
4 was first published in 1973. There are a couple
5 versions, 30-item version, 11-item version.
6 Joe loved this tool. And he basically
7 modeled it -- and those of you who are familiar
8 with it will recognize the roots of the CSSA in the
9 ASSA.
10 Anyway, Joe had this tool, and what he
11 basically did, to begin with, is to comb the
12 literature and look for symptoms of cocaine
13 withdrawal as were reported by other investigators.
14 And then he supplemented that with the signs and
15 symptoms that the patients were reporting who came
16 to us at Penn.
17 Joe was a pioneer in the outpatient
18 detoxification of alcoholics, and that's why he was
19 in love with these scales. And he believed that
20 cocaine-dependent patients, like alcoholics, were
21 negatively reinforced to continue their cocaine use
22 by the withdrawal symptoms. So his ideal was to

Page 40

1 develop a medication -- first of all, to identify
2 patients who had these severe cocaine withdrawal
3 symptoms and identify a medication that could
4 produce the symptoms and help them do better in
5 treatment, or at the very least, identify a
6 subgroup of patients who may have needed some more
7 supportive psychotherapy or a more intense
8 environment to get themselves clean. So that was
9 our intention in the development of it.
10 Just to refresh the memories of some of you
11 here and to introduce you to something maybe many
12 of the younger people don't understand, during the
13 late 1980s, cocaine withdrawal was kind of a big
14 deal. It was very interesting to clinicians. It
15 was a time during which cocaine-dependent patients
16 were flooding our emergency rooms and our treatment
17 centers.
18 They came with a constellation of symptoms
19 that were really quite similar. They were usually
20 depressed, sometimes very depressed, sometimes
21 suicidal, often psychotic, primarily paranoid
22 delusions. They had appetite changes. They had

Page 41

1 sleep changes. They were irritable and restless.
2 And they were a mess.
3 Clinicians at the time tried to get these
4 symptoms together and form clinical syndromes.
5 Probably the most famous of these you'll see up
6 here is the Gawin and Kleber Three Stage Withdrawal
7 Syndrome, with the crash, the withdrawal, and the
8 extinction phase. So people tried to put all these
9 things together.
10 Other investigators, Bill Weddington, Sally
11 Satel, and myself, really couldn't find a
12 three-stage withdrawal syndrome. Basically, what
13 we found is that patients came in with maximum
14 withdrawal symptoms at the beginning of treatment,
15 and they linearly declined as they got abstinent
16 over the course of about 11 to 14 days.
17 Cocaine withdrawal is not medically
18 significant. No one's going to get DT's or
19 seizures from this. What really is important about
20 cocaine withdrawal is the effect that it has on
21 treatment outcome. Patients with more severe
22 cocaine withdrawal symptoms just don't do well in

Page 42

1 treatment. They don't get clean, and more often
2 than not, they drop out. So that's why we got
3 interested in studying this particular phenomenon.
4 So that leads you to wonder, why do patients
5 with more severe cocaine withdrawals do so crummy
6 in treatment? Well, clearly, they could just
7 simply be treating their withdrawal symptoms by
8 returning to cocaine use. But we thought it might
9 be more than that. We thought that these cocaine
10 withdrawal symptoms were the clinical manifestation
11 of the underlying neurobiologic changes that were
12 occurring in the brain as part of the addictive
13 process.
14 Part of what made us believe that were these
15 studies that were starting to come out, showing
16 that cocaine withdrawal symptoms actually increased
17 the high that patients experienced from
18 experimentally administered cocaine doses. And the
19 first of these trials just showed the isolated
20 symptoms -- for instance, depression or
21 irritability -- in patients actually predicted a
22 better high or an increase in the subjective

Page 43

1 effects of experimentally administered cocaine.
2 Of course, these are two biggies in cocaine
3 withdrawal symptomatology. It's not the entire
4 syndrome, but it's the beginning. So Mehmet
5 Sofuoglu went ahead and took it a step further and
6 showed that patients who actually met criteria for
7 DSM-IV cocaine withdrawal syndrome actually had
8 more subjective effects from experimentally
9 administered cocaine.
10 In this case, he took 34 cocaine-dependent
11 patients who had DSM-IV cocaine withdrawal, and he
12 compared them to 10 cocaine-dependent patients who
13 did not meet criteria for withdrawal, and he gave
14 them cocaine. And among the other outcomes
15 recorded were high and the effects of the last
16 dose. And he measured that over 15 minutes, and
17 what he found was patients who made criteria for
18 cocaine-withdrawal syndrome reported a greater high
19 from cocaine and reported a greater effect of their
20 last dose of cocaine.
21 So maybe patients with cocaine withdrawal
22 syndrome simply get a better high from cocaine, and

Page 44

1 that's part of the reason why these patients are so
2 difficult to treat.
3 The human laboratory data combined with our
4 clinical experience, really led us to believe that
5 cocaine withdrawal was the tip of the iceberg, sort
6 of the clinical manifestation of these underlying
7 brain changes associated with cocaine dependence
8 that included things like craving and hedonic
9 dysregulation. And that is really why we became
10 interested in measuring cocaine withdrawal and
11 trying to -- or developing this scale.
12 So that's why we did it, and this is what it
13 turned out to be. This is the CSSA. As I said,
14 it's sitting on a desk in front of you. It's got
15 the 18 items. It's an interviewer administer,
16 which may be a weakness. We could actually easily
17 convert this to a self-report scale, which would
18 probably make it a whole lot more useable, but we
19 haven't gotten around to doing that. We haven't
20 done the reliability of the validity testing of the
21 self-report.
22 So what remains, a clinician administered

<p style="text-align: right;">Page 45</p> <p>1 instrument, two craving scales, intensity and 2 frequency. And mainly when we use it as a 3 predictor of outcome, we're looking at a total 4 score as one score, although we have looked at 5 individual items, and interestingly, the 6 two -- well maybe not so much. It would be 7 predicted that the two craving scales would be 8 predictive of outcomes. But what we actually found 9 was bradycardia was almost as predictive as craving 10 or the whole scale as a predictor of outcome. 11 Think about that.</p> <p>12 I am not a psychometrician. I am a 13 psychiatrist, trained clinically. And Joe 14 Volpicelli, when I was a young fellow, took this 15 instrument, threw it on my lap, and said, "Kyle, go 16 do initial reliability and validity test." And I 17 said, "Joe, what's that?" And Joe said, "Go see 18 Arthur Alterman," and so that's what I did. Arthur 19 Alterman is a brilliant psychometrician at our 20 center, and he taught me whatever I know about 21 psychometrics. And I'm very grateful to his 22 lessons, which were sometimes harsh, but still</p>	<p style="text-align: right;">Page 47</p> <p>1 DSM-IV criteria for cocaine, which are all 2 depressed mood, lethargy, increased appetite, 3 increased sleep, and irritability. So that's 4 pretty good.</p> <p>5 We also wanted to measure whether or not our 6 instrument coincided with other instruments of 7 addiction severity. So one would guess that if one 8 has more severe cocaine dependence, then one would 9 have worse cocaine withdrawal symptoms.</p> <p>10 So we looked at the ASI, and we found that 11 we got very good individual item correlations with 12 ASI severity measures. So for instance, scores on 13 the CSSA correlated very well with days of cocaine 14 use in the past 30 from the ASI, longer lifetime 15 histories of cocaine use, and higher ASI severity 16 scores for drug problems. So the patients who had 17 more severe cocaine dependence tend to score higher 18 on the scale.</p> <p>19 We found that it was specific to cocaine 20 withdrawal. It wasn't just some non-specific 21 measure of addicts coming in for treatment being 22 miserable. And we demonstrated that by showing the</p>
<p style="text-align: right;">Page 46</p> <p>1 very, very useful. Those of you who know Arthur 2 will understand that.</p> <p>3 So what we did was, very simply, we did 4 test/retest reliability. We did interrater 5 reliability. We measured internal consistency, and 6 concurrent validity and predictive validity.</p> <p>7 Now, this I consider the boring stuff, and 8 I'm not going to talk about it today, aside from 9 saying that the instrument has really good 10 test/retest reliability and very good interrater 11 reliability. Its internal consistency is 12 acceptable. If you do factor analysis on the 13 instrument, it comes into two factors. Craving is 14 a factor in and of itself, and everything else 15 settles out as another factor. But there is pretty 16 good item total correlations. But I'm going to 17 talk a little bit more about the interesting stuff 18 to me, which is the concurrent validity and the 19 predictive validity.</p> <p>20 Concurrent validity. The individual items 21 on the CSSA that have the highest scores just 22 happen to be those items that are part of the</p>	<p style="text-align: right;">Page 48</p> <p>1 patients who came in with cocaine dependence and 2 were newly abstinent from cocaine or were cocaine- 3 and alcohol-dependent patients newly abstinent from 4 cocaine scored higher on the CSSA than our plain 5 alcohol-dependent patients. So it seemed to be 6 specific to cocaine.</p> <p>7 Finally, if this is in fact a scale that 8 measures withdrawal, one would expect the scale to 9 improve as patients became abstinent. And that's 10 in fact what you see. And as I mentioned before, 11 it's sort of a linear decline over time, and it 12 takes about 11 to 14 days for patients to come down 13 to baseline on their CSSA. And what's not shown 14 and what I do have data to show is that patients 15 who don't get abstinent don't have declines in 16 their CSSA with repeated measures. So it does seem 17 to behave like it's measuring cocaine withdrawal.</p> <p>18 The most interesting thing about cocaine 19 withdrawal to us, when we first started looking at 20 it, was its ability to predict treatment outcome. 21 Initially, we measured treatment outcome in three 22 pretty different settings. One was a cocaine</p>

Page 49

1 psychotherapy trial conducted at the University of
2 Pennsylvania, and the second is from the IOP, or
3 basic outpatient treatment, at the Philadelphia VA.
4 And then the third context we studied in were
5 medication trials being conducted at the University
6 of Pennsylvania.

7 This is data from the first psychotherapy
8 trial, was 87 patients. And what we measured here
9 was who completed 30 days of treatment looking at
10 patients with high and low CSSA. So in this case,
11 the cut-off for this was 24, so scores above 24
12 were high; scores below were low. And again,
13 patients with low scores on the CSSA were much more
14 likely to complete the first 30 days of treatment.
15 So it seemed to have a nice predictive validity in
16 that.

17 Now, when we took it down to the Day
18 Hospital, we ran into a little bit of a glitch. It
19 turns out that if you have very severe
20 Access 1 -- I guess we don't say Access 1 anymore.
21 If you have really severe psychiatric severity, you
22 tend to have really high scores on the CSSA, and

Page 50

1 they tend not to get a whole lot better. So if
2 you've got a bad schizophrenic, a bad bipolar, a
3 bad patient with PTSD, it may reduce the predictive
4 validity. And that's what we found in this
5 particular trial.

6 So to get this really pretty outcome of
7 prediction of completion of 30 days of treatment at
8 the Day Hospital, we had to exclude patients with
9 severe psychiatric illness, which really doesn't
10 make a lot of difference to us in our clinical
11 trials, since we routinely exclude those patients
12 anyway, but it does have implications for use in
13 general.

14 So that's one of the weaknesses of the CSSA
15 is that it may not necessarily be predictive in
16 patients with more severe co-morbid psychiatric
17 illness. And the cut-off on this was a little bit
18 higher. It was 37, was what we defined. And
19 you're going to see a pattern here. Again, scores
20 in the upper 20's to 30's tend to be the high
21 scores that predict. And if you want to look at
22 just the percentage of subjects, it's generally the

Page 51

1 upper one-third. Patients who have scored in the
2 upper one-third on the CSSA tend to be the ones
3 that have more problems in treatment.

4 Finally, medication trials. This was a
5 bunch of open trials, I think 3 or 4 open trials,
6 76 patients who participated in those. And what we
7 were measuring in this case is 3 weeks of
8 continuance abstinence at any point during those
9 brief trials. And again, we see a huge difference.
10 Cut-off score in this case is 21, but again, it's
11 just pretty consistent that if you have low scores
12 on the CSSA, you're much more likely to do well.

13 What are the advantages of being at a center
14 like the University of Pennsylvania, aside from
15 having Chuck O'Brien and Arthur Alterman and Tom
16 McClellan to help you, is that you can take your
17 instrument and you can put it into every single
18 clinical trial that gets done at the center, which
19 I did. So every -- with the exception of some of
20 the multicenter trials -- it won't allow me to do
21 that -- I will stick the CSSA into every single
22 cocaine trial that's been ongoing for the past

Page 52

1 20 years. That's a lot of trials.

2 What we did is we decided to go ahead and
3 put the data together from as many of these trials
4 as we could and identify predictors in cocaine
5 dependence treatment. What it turned out to be
6 were 7 fairly large clinical trials, all of which
7 were about 7 to 12 weeks in duration. We excluded
8 the alcohol, the comorbid alcohol-dependent
9 patients. Had I included them, I could have
10 probably tripled the end, but we looked only at
11 the cocaine-dependent patients.

12 We had outcome measures. And the beautiful
13 thing is we're at 10, so everybody gets the ASI as
14 well as the CSSA. We got urines 2 or 3 times
15 weekly, and of course we get timeline follow-back
16 self-report on everybody that comes through. So
17 for predictor variables for outcome, we had, as I
18 said, the ASI urine drug screens, and we had the
19 CSSA on all these folks.

20 For outcomes, success and treatment, we
21 arbitrarily selected 3, 3 weeks of continuance
22 abstinence at any point during the trial. This is

Page 53

1 urine's negative, none missing. So it was a hard
2 abstinence measure.
3 We also looked at 50 percent reduction in
4 ASI composite drug scores. Chuck likes that one,
5 so we used that. That seems to be a reasonable
6 measure of improvement. And then finally, we also
7 looked at no self-reported cocaine use during the
8 last 4 weeks of the trial, just to get rid of the
9 whole idea of urines; let's just see what the folks
10 tell us. And we used that as outcome measure.
11 What we ended up with was our usual sample
12 of folks. Now this trial was actually done a
13 few -- the trials were done a few years ago, so the
14 age actually has increased. Our average age right
15 now runs about 49 to 50 years old among our
16 cocaine-dependent patients. It's an aging
17 population. But we gathered up about 402 of these
18 guys, and as usual, they are primarily African
19 American men who smoked crack cocaine. Days of
20 cocaine use, 13. That's pretty standard, about
21 \$600 of cocaine in the month prior with an ASI
22 composite drug score of .23 and a baseline CSSA of

Page 54

1 27. So that's sort of average.
2 We took all of our predictors together, and
3 if you look at the 3 outcomes here, the most
4 consistent predictors of outcome when we threw
5 them into the regression were initial urine drug
6 screen and initial CSSA scores, both of which came
7 out to be significant in the regression model
8 independently. So they don't overlap. They're
9 different. They measure different things. But
10 these are the two things that best predict outcomes
11 in our clinical trials.
12 What about predicting medication response?
13 Can we use baseline CSSA scores to identify
14 patients who might respond better to medications?
15 And we were excited about this one in the
16 beginning. This is amantadine. This is a medicine
17 that we thought was going to treat cocaine
18 withdrawal symptoms, and it was the first trial I
19 ran at Penn. And the trial as a whole was
20 negative, but when we went back and we looked, and
21 we separated out patients with high and low CSSA
22 scores, again, using a two-thirds/one-third

Page 55

1 cut-off, the patients with high scores in the CSSA
2 seemed to have a wonderful response to amantadine
3 in the number of clean urines. So that got us
4 really excited.
5 Unfortunately, this is a really small
6 sample. This is a 60-patient study on the top
7 there, so there are 20 people in this group. So
8 when we went back to replicate it, it didn't
9 replicate, and we have of course long since given
10 up on amantadine. But I just thought I'd throw that
11 in for historical purposes.
12 Propranolol is another drug that I studied
13 early on in my career, which seemed to have a
14 differential response to patients with more severe
15 withdrawal symptoms, which again sort of made sense
16 to us. And this is, you again take the patients
17 with the top one-third on their baseline CSSA,
18 which I think was a score of 28 in this case, and
19 you just look at treatment retention or urinary
20 benzoylecgonine levels. This is actually
21 quantitative urinary benzoylecgonine levels, which
22 we actually did measure and use as an outcome, in

Page 56

1 the past. But in any event, if you got
2 propranolol, you're more likely to be retained in
3 treatment, and you had lower overall urinary
4 benzoylecgonine levels. So that's great.
5 This we partially replicated in the
6 subsequent trial of propranolol in that we found
7 that propranolol among patients who actually took
8 their propranolol and had high CSSA scores actually
9 did look a little bit better than placebo, nothing
10 to write home about, and I don't think we're going
11 to pursue propranolol as a medication going
12 forward, but it was replicated.
13 Now, the interesting thing about propranolol
14 is this is the one and only medicine that I have
15 ever studied that showed a differential change in
16 CSSA scores during the trial compared to placebo.
17 So propranolol actually lowered CSSA scores during
18 the trial, and it's the only one of the medications
19 I've studied so far that actually does that.
20 Now, most recently, we looked at topiramate,
21 and we've done two trials of topiramate at our
22 center. Bankole Johnson has a positive trial

Page 57

1 there. So actually there's three positive trials
2 of topiramate out there in the record, and we have
3 two of them. And this is our data from our second
4 trial, which was cocaine- and alcohol-dependent
5 patients, 177 subjects, 300 milligrams of
6 topiramate. And in the main trial, we found that
7 topiramate was associated with greater end-of-study
8 abstinence compared to placebo, so that was good.
9 So we went back and we looked at baseline
10 predictors of topiramate success, and this is the
11 only thing that we found. Patients with high
12 scores on the CSSA did better with topiramate. And
13 what we did was we divided the sample into
14 tertiles, so we've got your low CSSA scores, your
15 medium scores, and your high scores. And we only
16 saw a topiramate effect in patients with high
17 scores, which was CSSA above 18.
18 All right. That's the good part. Now,
19 although we have really nice predictive validity in
20 initial CSSA scores, what the CSSA falls down in is
21 in outcome measures. The fact that we haven't yet
22 found a medication that actually predicts a

Page 58

1 differential response to placebo in reducing these
2 scores. So what you see in clinical trials is that
3 the mean CSSA scores tend to decline over time in
4 all our trials. That's pretty much universal.
5 This is actually probably not even an
6 exhaustive list, but these are just the ones I
7 thought of when I was putting together and checked.
8 None of these medications actually showed a
9 difference in CSSA over time, so that was kind of
10 disappointing, with the exceptions I said of
11 propranolol. So as an outcome measure, maybe not
12 so good.
13 What do we know about the CSSA? CSSA is a
14 good predictor of outcome in outpatient
15 cocaine-dependent treatment. Aside from urine drug
16 screens, it's probably the best predictor. So what
17 do we use it for primarily? We use it as an earned
18 variable to make sure that our poor prognosis
19 patients are equally distributed between a placebo
20 and the active group, and that's something that we
21 do. We earn pretty much everybody in our cocaine
22 trials on urine drug screen on the day of

Page 59

1 randomization and their CSSA score on the day of
2 randomization.
3 The CSSA may identify subgroups that are
4 responsive to particular medications. Propranolol
5 is an example. Topiramate may be a better example.
6 Then finally, no medication tested thus far has
7 shown a differential response in reducing CSSA
8 scores consistently. Propranolol did it once, but
9 it didn't do it in the second trial.
10 Finally, I just want to make a plug for NIDA
11 centers, wonderful things. Trying to do this kind
12 of work outside of the context of a NIDA center
13 would have been extremely difficult. Not having
14 all those people funded in the same building with
15 me to help me; not having the ability to insert my
16 instrument into all the trials being done at the
17 center, and not to have the funding and the ability
18 to do all these secondary analyses and get all
19 these patients published, again, it would be very,
20 very difficult. So I'm extremely grateful to NIDA
21 for allowing us to have the center for all the
22 years that we've had it and continue to have it

Page 60

1 because it does support things like that.
2 With that, I'll stop.
3 (Applause.)
4 Q&A - Group Discussion
5 DR. STRAIN: Maybe we could take a couple
6 minutes for questions.
7 DR. KAMPMAN: Sure.
8 DR. STRAIN: And I'm actually going to
9 start. Is the CSSA copyrighted?
10 DR. KAMPMAN: No, in the public domain.
11 DR. STRAIN: Okay. It's an important point
12 simply because as we move to electronic medical
13 records, not just for clinical care, but for the
14 interface of clinical care with research, we're
15 getting push back for copyrighted instruments like
16 the CINA, for example, with opioid clinical trials,
17 which is copyrighted. So then the lawyers descend
18 upon us.
19 Do we have lawyers in the room?
20 (Laughter.)
21 DR. STRAIN: So the lawyers descend upon us
22 and tell us that essentially we can't use those

Page 61

1 copyrighted instruments. So I'm very glad to hear
2 the CSSA is not copyrighted, and I'd encourage you
3 to continue in that venue.
4 DR. KAMPMAN: We want it used.
5 DR. STRAIN: Yeah. Good. I had also just
6 one other question before we go to the discussant.
7 What do you think is the next step in the CSSA
8 development?
9 DR. KAMPMAN: The CSSA was sort of put out
10 there, and I got interested in finding medications
11 and accepted it for what it was. The instrument
12 has never been modified, improved in any way. This
13 is basically what Joe Volpicelli gave me back in
14 1992. We could fix up some of the items. It
15 certainly would be better as a self-report. That's
16 one of the biggest complaints I get from people.
17 Why isn't this self-report? This doesn't make any
18 sense. You don't need to have a research tech.
19 Ask these people these questions. So that would be
20 one of the things we would do.
21 DR. STRAIN: Thanks.
22 Other questions? Yes, Kathy?

Page 62

1 DR. CARROLL: Thinking about how it might be
2 developed as an outcome measure, have you done
3 anything looking at change across time? And is
4 there any evidence that if people kind of go from
5 that high level above 21 to somewhere below it,
6 some set point, that that predicts how they do in
7 the long-term?
8 DR. KAMPMAN: No. We've looked at it mainly
9 as a predictor --
10 DR. CARROLL: As a predictor, but not as
11 a --
12 DR. KAMPMAN: Not as over time. What we've
13 looked at more as a predictor is change in urine
14 drug screens, abstinence during the first two
15 weeks. Cocaine trials are like cigarette trials.
16 The best predictor of who's going to do well in
17 your trial is what happens during the first two
18 weeks, but we haven't done that with the CSSA. The
19 CSSA just kind of goes down over time.
20 Yeah, George?
21 DR. STRAIN: Ivan was waiting, and then
22 George.

Page 63

1 DR. KAMPMAN: Oh, I'm sorry.
2 DR. MONTOYA: I just have a question. Maybe
3 I missed it.
4 DR. STRAIN: Identify yourself for the
5 recording.
6 DR. MONTOYA: Ivan Montoya from NIDA.
7 What's the sensitivity and specificity of the --
8 DR. KAMPMAN: Sensitivity for the CSSA is
9 really, really good. It approaches like 80-90
10 percent. The specificity stinks, mainly
11 because -- and that is if you're predicting poor
12 outcome. Because so many people do poorly in our
13 cocaine trials, the sensitivity is very high and
14 the specificity is pretty low. So it identifies
15 people who are going to do crappy really well. It
16 doesn't necessarily identify people who are going
17 to do well.
18 DR. STRAIN: George?
19 DR. WOODY: George Woody from Penn. It's a
20 question for the FDA. Many of the drugs are
21 illegal, and arrests in illegal activities is one
22 of the ASI factors. How does that count in our

Page 64

1 outcome measures? Because you can show decreases
2 in arrests and crime and various things in some
3 studies.
4 DR. HERTZ: This is Sharon Hertz. I'm with
5 the division. And I'm not sure I understand your
6 question fully because when you're assessing a drug
7 to treat addiction, what we want to know is that
8 people stop using the drug. The fact that there is
9 an activity of illegal behavior associated with
10 drug use is clearly a bad effect that's associated
11 with using drugs, but -- are you trying to ask if
12 it would be a suitable surrogate?
13 DR. WOODY: That's just the question, is
14 that in the various outcomes, that wasn't
15 mentioned, but it is part of the ASI. And of
16 course, that was studied pretty heavily with
17 methadone. That was one of the things with
18 methadone, that it reduced crime and police -- so I
19 was just curious.
20 DR. HERTZ: Right. So it's an important
21 element. It could be an interesting secondary
22 measure. I'm not sure that it would have

Page 65

1 necessarily labeling value.
2 DR. WINCHELL: I'm Celia Winchell, also with
3 the FDA. I can't speak into the microphone and
4 look at Dr. Woody at the same time, so I'm going to
5 apologize to Dr. Woody and speak into the
6 microphone.
7 DR. WOODY: That's fine.
8 DR. WINCHELL: There are a lot of adverse
9 consequences of being involved, addicted to various
10 substances, and criminality is certainly one of
11 them. But we think it's probably unrealistic to
12 run a clinical trial long enough that you could
13 directly measure impacts such as criminality,
14 although a broad basket of adverse consequences of
15 drug addiction, that's kind of the direction that
16 we looked at when we were exploring what patterns
17 of alcohol use behavior, other than ceasing alcohol
18 use altogether, could translate to clinical benefit
19 for patients.
20 There were batteries of a variety of alcohol
21 associated consequences, which include -- I mean,
22 legal problems such as driving while intoxicated.

Page 66

1 One doesn't so much get arrested for possession.
2 And though that was part of the battery of
3 consequences that was evaluated against various
4 patterns of alcohol use, conceivably among the many
5 bad things that could happen to a person as a
6 result of his or her involvement with drugs,
7 criminality could be one aspect that you would look
8 at long-term, but it doesn't seem as a practical
9 endpoint for a clinical trial.
10 DR. SLAGLE: This is Ashley Slagle from the
11 FDA also. I think criminality is one of those
12 things that is more distally related to the
13 treatment and the condition, so it's a downstream
14 effect. If you treat the -- if the patients become
15 abstinent, because of that, criminality is reduced
16 longer term like Celia said.
17 There are also other things that contribute
18 to criminality, so psychosocial support and all of
19 these other variables that contribute. So it's a
20 little bit harder to interpret a change on
21 criminality without also being able to understand
22 that there's abstinence or that the drug use has

Page 67

1 been reduced.
2 Discussant - Eric Strain
3 DR. STRAIN: Let me interject here, and I
4 want to switch hats and become Bob Dworkin for a
5 couple of minutes and summarize the two talks
6 because I think we are moving into some questions,
7 and I've got questions as well, certainly, broader
8 about it.
9 But before we do that, let me thank both the
10 speakers, first of all. I thought they were great
11 talks. I think they nicely bookend each other in
12 the sense that Ashley's talk kind of giving us a
13 real structure and a way to think about the
14 methodology and about what are the parameters
15 related to this topic. I'm looking forward to
16 looking over your slides again. They were rich
17 slides, I thought, that really helped to give a
18 structure to this. So I greatly appreciated it.
19 One of the things that I noted from your
20 talk, Ashley, that I think I'll probably come back
21 to if I have time for questions, is this concept of
22 how the patients feel, function, or survive. I

Page 68

1 think that's a very intriguing thing to consider
2 when we're in the addictions field because it's
3 different from what we usually think about. And
4 this resonates also with Ken Silverman's comment
5 about urine test results, which I think we'll
6 probably come back to some more while we're here.
7 I greatly appreciated, as well, your points
8 about -- all points, but about assessments being
9 well defined and reliable. And I thought that
10 nicely resonated with Kyle's talk, which I'll talk
11 about in a moment, where he was looking at both the
12 validity and reliability aspects of the CSSA.
13 I think that you also touched on the concept
14 of what is a meaningful change on a measure, and
15 meaningful change compared to risk. And risk
16 didn't really -- you didn't really dive into risk a
17 lot, and I think that may be an opportunity as well
18 for us to think about and to have some discussion
19 about because there are risks inherent in
20 stimulant-use disorders. So change needs to be
21 interpreted in the context of that risk, which is
22 something to consider.

Page 69

1 I thought, as well, the discussion on -- you
2 touched on benefits, both direct and indirect, and
3 the outcome assessments. Both patient related,
4 clinical related, and surrogate measures all were
5 intriguing points and things that may lead to
6 further discussion by us.
7 Your outline of how to assess an instrument
8 led I think nicely to Kyle's talk about the CSSA,
9 this instrument that's been around -- I didn't
10 realize it's been around now for 22 or 23 years.
11 It was fun an interesting to hear about the history
12 of it as well. I didn't realize that Joe
13 Volpicelli had originated it out of the ASSA.
14 Kyle was careful to caution us about what
15 this instrument is, and that it's not -- in some
16 ways, it sounds to me like -- and I don't mean this
17 in a disrespectful way, but you kind of backed into
18 this as something that perhaps took on more of a
19 life of its own than you initially thought it might
20 as an instrument although it has resulted in you
21 getting multiple papers out of it, which is nota a
22 bad thing if you're in an academic medical center.

Page 70

1 There was this intriguing point about its
2 content, especially with respect to bradycardia.
3 And I thought you were going to draw something out
4 there about the propranolol effects and bradycardia
5 perhaps, if there was something that resonated
6 there, and maybe you'll want to comment on that at
7 some point.
8 There also, though, is this feeling with
9 the -- so I appreciated that you went through and
10 discussed a little bit about the steps that you
11 went through in test/retest, and interrater,
12 internal reliability, internal consistency, and
13 then concurrent and predictive validity.
14 I think the important thing to recognize out
15 of this discussion or this presentation is that
16 this has not been developed as an outcome measure.
17 It's really not been a robust outcome measure, but
18 it has shown some value in being predictive, which
19 is interesting and intriguing. And if anything, I
20 think in your free time, which I'm sure you have
21 lots of, it would be interesting to think about how
22 to take the instrument and make a next generation

Page 71

1 of it, it seems to me, to try to further refine it
2 and see if there could be further value to it in
3 some way, perhaps either as a more robust predictor
4 with a specific score rather than a somewhat
5 floating cut-off score that seems to vary across
6 clinical trials, or with a further refinement of
7 the content, or as a self-report measure, of
8 course, which would be valuable.
9 Those are my initial thoughts about these
10 two talks. Oh. And I just want to acknowledge
11 that Kyle in his talk also talked about cocaine
12 withdrawal and the -- I appreciated the historical
13 context of that, that three-stage model that Gawin
14 and Kleber showed, which I don't think anybody ever
15 was able to substantiate, but it got them a paper
16 in the Archives of General Psychiatry at the time.
17 But there was this constellation of patients with
18 cocaine withdrawal, certainly, that was
19 interesting.
20 The only other thing that I thought and we
21 may want to come back to is I was intrigued that
22 the high CSSA scores were associated with better

Page 72

1 outcomes in your amantadine clinical trial, if I
2 got that right. And that seemed a little
3 paradoxical to me in that -- I think I've got this
4 right -- in the modafinil studies, lower -- isn't
5 it the case that the positive signals in the
6 modafinil clinical trials have been associated with
7 lower rates of methamphetamine use?
8 DR. KAMPMAN: Yes. We could not get the
9 CSSA to predict outcomes in modafinil, which was
10 very disappointing to us. We really thought it
11 would, but it did not.
12 DR. STRAIN: Yes. So there's something a
13 little paradoxical there.
14 Let me stop there, and maybe we can open it
15 up for discussion because I think there's a lot of
16 potential areas to discuss. So Sharon and then
17 Steven.
18 DR. HERTZ: Thanks. This is Sharon Hertz
19 with FDA. So I'm interested in a couple of points
20 about whether or not the CSSA can be used as an
21 outcome measure. It seems to me that because we
22 don't really have treatments that we've identified

Page 73

1 as being particularly useful, that I'm not sure the
2 failure of CSSA in those studies necessarily means
3 it's not going to be a good measure once we
4 actually find something that works. So I'm not
5 sure that I have any concern about that lack of a
6 good outcome yet since the drugs have failed us and
7 perhaps not the instrument.

8 But my question is, the predictive measure
9 of the CSSA seems very useful when you're initially
10 assessing somebody in a state of withdrawal. And I
11 think that -- my question is, how confident are we
12 that drugs that are used to treat the
13 addiction -- I'm having trouble quite making this
14 connection, and that's the question I have.

15 How would one connect the withdrawal period
16 and the long-term success for avoiding relapse?

17 DR. KAMPMAN: We conceive medications now,
18 at least when we're studying them, as medications
19 that are essentially helpful for abstinence
20 initiation versus those that are effective for
21 relapse prevention, and the two may be completely
22 different.

Page 74

1 Now, just treating withdrawal we know in
2 alcohol doesn't help long-term because people just
3 relapse. So the only advantage of treating cocaine
4 withdrawal symptoms, if you're really concerned
5 about that, is to stop this sudden drop out in
6 treatment. And that's really what we thought about
7 in the beginning. Even when we were doing clinical
8 trials for cocaine dependence, we would get 30 or
9 40 percent of our patients to be retained in an
10 8-week trial. That was success. That was crazy.

11 So we were kind of hoping that we would
12 treat the withdrawal symptoms, they'd stay in
13 treatment, and then we would find another medicine
14 that might help them, or psychosocial treatment
15 engagement would help them down the road. This is
16 just to get people engaged and get them initially
17 abstinent.

18 DR. STRAIN: Steve?

19 DR. SPARENBORG: Kyle, thanks much for the
20 good explanation of the CSSA. Ashley's
21 presentation about the underlying meaning, when she
22 talked about this underlying meaning of what you're

Page 75

1 looking at, this particular questionnaire or
2 whatever, does the CSSA correlate in any way to
3 measured or self-reported 30-day prior to baseline
4 cocaine use, severity? And if it does, what does
5 that mean? And if it doesn't, what does that mean?

6 DR. KAMPMAN: Yes, it does. That's one of
7 the ASI variables that correlates pretty well with
8 baseline CSSA scores. It's 30 days -- the number
9 of days of cocaine use in the prior 30 days. So we
10 always attribute that to patients who use more
11 severely should have more severe withdrawal
12 symptoms. So that does correlate, and that we
13 agree with.

14 Could you use that measure as a surrogate of
15 CSSA scores? Yes. They don't work as well. We've
16 put those into the regression models, and days of
17 cocaine use will stay for a while but will fall
18 out, whereas CSSA scores will remain the same.

19 Interesting that you brought that up because
20 another story of topiramate -- I'm sorry. I'm
21 stuck on topiramate. But another study of
22 topiramate done by my partners at Columbia, who

Page 76

1 we're collaborating with in a replication trial,
2 found that patients who used more frequently in the
3 30 days prior to entering a trial actually were the
4 ones that responded to the combination of
5 topiramate and Adderall, which kind of harkens back
6 to my finding of high CSSA scores predicting a good
7 outcome with topiramate. Just thought I'd throw
8 that out there.

9 DR. SPARENBORG: Just one last comment. I
10 think it's important for us to try to strengthen
11 the relationship between self-report and any more
12 objective measure of drug use, and I think this is
13 very important for us to consider during this
14 meeting.

15 DR. KAMPMAN: Thanks.

16 DR. STRAIN: David?

17 DR. McCANN: Dave McCann from NIDA. First I
18 want to echo the thanks on both of the
19 presentations. They were wonderful. Part of what
20 goes through my mind is what we might be talking
21 about at the next meeting of this group that might
22 be on the next agenda. And before I forget, I just

Page 77

1 want to mention that stratification factors for
2 clinical trial design is something that we should
3 definitely talk about.
4 I hadn't considered the CSSA as something we
5 should look at, but it certainly sounds good. The
6 problem is, when we sketch out a protocol and run
7 it by our statisticians, they don't like to have
8 too many stratification factors. We have to start
9 out asking for three so they will compromise and
10 take two. We've looked at things like alcohol
11 dependence, whether the last urine during screening
12 is clean or dirty. CSSA would be a third one we'd
13 add on there. It's tough to get those
14 statisticians to work with three of them.
15 I don't want to get into a long discussion
16 here, but at a future meeting, I think that this is
17 something we need to think about. If we're limited
18 to two, what are the best two? The other thing
19 would be how do we convince statisticians to use
20 three because -- to me, if you see three factors
21 that are highly predictive of outcome, is it better
22 to totally ignore one so that you can have a great

Page 78

1 balance of the other two, or to try all three and
2 come close with all three? That's something we
3 need to talk about.
4 But getting back to the CSSA --
5 DR. STRAIN: So now we've dissed lawyers and
6 statisticians.
7 (Laughter.)
8 DR. McCANN: So a question about the CSSA;
9 there is a question in here. To what extent is
10 this really withdrawal? If you bring somebody
11 inpatient with high CSSA scores, and you give them
12 cocaine, now they have almost no score?
13 DR. KAMPMAN: Have I ever done an inpatient
14 withdrawal test with the CSSA? No. What has been
15 the findings of cocaine withdrawal among patients
16 who are brought in to inpatient settings, it goes
17 away, pretty much, and you don't get a lot of
18 symptoms inpatient.
19 In fact, when I wrote the initial paper, I
20 had to take every reference to withdrawal out of
21 it. If you look at my initial reliability of
22 validity testing, there is no cocaine withdrawal

Page 79

1 written there because I couldn't get it pass the
2 editors because at the time, no one believed that
3 cocaine withdrawal existed. And that was mainly
4 Weddington and Satel's two papers.
5 I think that if you put patients inpatient,
6 you reduce their craving significantly, and that is
7 a large part of the CSSA, which is why you get I
8 think much lower scores. But you still will get
9 some withdrawal that may not be as pronounced as
10 you get on an outpatient.
11 DR. STRAIN: Yes?
12 DR. FALK: Dan Falk, NIAAA. From the CSSA
13 presentation, I got that it's not a great outcome
14 measure, but it could be a good moderator of
15 treatment effect. I guess my question is maybe for
16 the FDA, Ashley maybe. I don't know if anyone
17 would necessarily want to go for the CSSA as a PRO
18 patient reported outcome, but maybe as a moderator
19 they'd want to put it in a phase 3 trial perhaps to
20 say that, well, we think that the treatment effect
21 might vary as a function of their CSSA score.
22 Is there anything special that needs to be

Page 80

1 done from a PRO perspective or from maybe an FDA
2 perspective on creating subgroups or validating
3 this instrument for moderator purposes?
4 DR. SLAGLE: My group typically focuses on
5 outcome assessments, but I think that gets back to
6 the question that David had about the
7 stratification and whether there's a benefit to
8 really doing that with other variables that you can
9 use. I'm not sure if my clinical colleagues have
10 any additional thoughts on this, using the CSSA as
11 a moderator in trials rather than an outcome.
12 DR. WINCHELL: So if I understand correctly,
13 Dan, your question was should it turn out that this
14 tool or a tool like this was actually very helpful
15 to distinguish between patients who really would
16 benefit from medication treatment and potentially
17 patients who wouldn't, and therefore could be used
18 maybe in an enrichment strategy, would any further
19 work on that tool need to be done for it to be
20 appropriate for use in a registration trial. So
21 that we would say in the label, this medication is
22 beneficial for the subset of the population who

Page 81

1 have this diagnosis and meet this other criterion.
2 I would think it would have to be at least
3 something that we had taken a look at and
4 thought -- I mean, it couldn't be something
5 completely not vetted at all. I'm not sure what
6 the process would be for that, but it would be
7 incorporated as almost a diagnostic measure, the
8 person has a condition that will be responsive to
9 this medication. And maybe we kind of -- we're
10 used to looking at that type of thing in the
11 context of an NDA. We've got things like that.
12 DR. FALK: Thanks.
13 DR. HERTZ: This is Sharon Hertz. I think
14 that the work that was maybe alluded to that
15 there's already been some interest in having this
16 developed as a PRO, so just whatever it would take
17 to transition the instrument, whatever the basic
18 work would be, could be that type of
19 psychometric -- and we use the term "psychometric
20 conversion" because it sounds good in my head. I
21 don't know if it's a term.
22 (Laughter.)

Page 83

1 interviewer-based instrument is not something that
2 may be used clinically as much a self-report
3 instrument.
4 Somebody in the back was -- go on, please,
5 Laurie.
6 MS. BURKE: I think that --
7 DR. STRAIN: You want to identify yourself
8 for the --
9 MS. BURKE: I'm Laurie Burke, and I
10 am -- what am I today? University of Maryland or I
11 also am LORA Group, whichever. I am wanting to
12 perhaps ask -- keep a focus on what exactly -- the
13 CSSA measures and the write-ups as it measures
14 cocaine withdrawal signs and symptoms.
15 I think that in the discussion, it would be
16 really useful to make sure that we keep our eye on
17 that. I mean, there was discussion about how it
18 doesn't really measure the long-term abstinence
19 because it doesn't measure that. It measures signs
20 and symptoms. But how is that related?
21 I think we need to go back to Ashley's
22 presentation of exactly what are we trying to make

Page 82

1 DR. HERTZ: But whatever that is, yes. The
2 value of something as a tool to help select
3 patients is whether it's available to clinicians,
4 is it something they're likely and able to use. So
5 the easier it is to have someone use the tool,
6 particularly if it becomes appropriately
7 transitioned to a PRO, it certainly could have some
8 promise there.
9 DR. STRAIN: So just to clarify -- because
10 one of the outcomes of this meeting is what should
11 we -- are there things that the field should work
12 on. So Dan, I appreciate your question in that
13 context because this could at least a beta version
14 of something that could be developed, is what I
15 hear, that may be of value either as a
16 stratification or as a moderator, although it may
17 not be this particular instrument, I guess.
18 I'm thinking because it's an interviewer
19 rated instrument, it's not a -- quite
20 honestly -- it's 18 items I think.
21 DR. KAMPMAN: Yes.
22 DR. STRAIN: Yes. An 18-item

Page 84

1 this measure do in a clinical trial. It's hard to
2 identify the value of this measure unless we know
3 exactly what we want to be able to conclude at the
4 end of the day by the score that's generated.
5 If it's cocaine -- and I want to compare
6 this with depression. In psychiatry, there are
7 depression signs and symptoms that the clinician
8 observes and comes up with a conclusion of the
9 diagnosis of depression. This seems to me very
10 similar, where there is a definition of cocaine
11 addiction -- or what is the DSM diagnostic
12 category?
13 DR. STRAIN: Use disorder.
14 MS. BURKE: Use disorder. And within that,
15 you identify things, the signs and symptoms, which
16 are also included in the CSSA.
17 In the development of this instrument or of
18 the alcohol instrument that this is derived from,
19 was there any actual interview of patients to make
20 sure that they are agreeing that the signs and
21 symptoms here are inclusive of all the most
22 important things in that course that cocaine

Page 85

1 addicts experience?
2 I think that would be an important first
3 step, to first making sure that you have not just
4 the diagnostics of signs and symptoms, but the
5 things that actually are experienced by the
6 patient, which is getting to the important thing
7 about what do patients actually experience, feel
8 and function in their daily life.
9 My question is, has that been done to any
10 extent? And if not, how could that be a next step
11 for the development of this for an outcome
12 assessment?
13 DR. KAMPMAN: We did not do focus groups,
14 but what we had was a busy clinic with nurse
15 practitioners, cocaine-dependent patients, and Joe
16 Volpicelli. Although some of the items in the
17 instrument came from literature review, a great
18 number of them came from what our patients were
19 reporting to us. So, no. We did not do focus
20 groups.
21 DR. STRAIN: Connie, and then I'm going to
22 ask a question, then Ashley.

Page 86

1 DR. WEISNER: Connie Weisner from Kaiser
2 Permanente and UCSF. I think that this moves a
3 little bit more to the outcome part, but
4 working -- doing research in a health plan that has
5 a very -- we find that our cocaine patients are
6 very heterogeneous. We use the ASI in our
7 instruments. And that question for each of the
8 domains that says how important to you is treatment
9 for your drug problem, how important is it for your
10 legal problem, how important is it for your
11 employment problem, those people, those
12 cocaine-dependent people, or other
13 stimulant-dependent people, who are there on a
14 legal referral say it's extremely important for
15 their legal problem. Treatment is not
16 important -- very important for their cocaine
17 problem.
18 If they're there on an employment mandate,
19 it's the same. They're there to fix their -- it's
20 extremely important to fix their employment
21 problem, not extremely important -- so the
22 job -- the way the clinicians see their job is to

Page 87

1 make this connection for people that if they stop
2 using cocaine, their employment problem will get
3 better and so forth.
4 I'll talk more about this tomorrow, but kind
5 of teasing apart what patients want out of
6 treatment and what stakeholders want out of
7 treatment, that sort of sometimes disconnects.
8 DR. STRAIN: Thanks. Actually, my question
9 is very congruent with that comment, so I really
10 appreciate it. I want to go back to the FDA on
11 this, and maybe I've just gotten hooked on this,
12 but how patients feel, function, or survive, that
13 statement. And I think that's a quote, right?
14 Have I got that?
15 (Laughter.)
16 DR. STRAIN: And it's feel, function, "or"
17 survive. It's not "and survive." So you'll accept
18 feel, function, or survive. Am I being like a
19 lawyer now?
20 (Laughter.)
21 FEMALE SPEAKER: Or a priest. I don't know.
22 DR. STRAIN: Yes. Bless you.

Page 88

1 So you didn't agree or disagree on the "or"
2 question, but let me move on. It's an interesting
3 thing. I think, in addictions, if we add a
4 medication trial, and we had an outcome that
5 produced improved functioning but didn't
6 necessarily substantially impact drug use, would
7 the FDA find that persuasive as an efficacious
8 medication?
9 Let me further elaborate. I can see all the
10 FDA people actually move towards their microphones.
11 DR. HERTZ: Actually, I would like to answer
12 that by asking us to focus on other kinds of
13 questions because we're really not here to ask
14 about what is necessary to get a drug approved.
15 We're here to find out how to evaluate this area.
16 And we're really -- our participation is to sort of
17 provide information, but I would like to not answer
18 that question.
19 So what I would do is I would like to take
20 that question and turn it back to all of you.
21 Would you find a drug that improves function
22 without affecting drug use to be something that the

Page 89

1 clinical group finds important and would be helpful
2 to the community for whatever reason? And then
3 that argument, if it was to be something used in
4 drug development, could then be brought through the
5 proper channels for discussion.
6 So it's not what's important to us in terms
7 of these outcomes. It's what important -- and this
8 is a pretty esteemed group of people within this
9 field. So what's important to you, and then how
10 can we assist through these mechanisms to make sure
11 that the instruments are available to support that
12 work, and how it then intersects with specific
13 product development.
14 DR. STRAIN: And I fully appreciate and
15 respect the answer. The reason I ask it, not as
16 to -- I'm not trying to bait you into something or
17 the FDA into that. What I'm trying to do is, I'm
18 trying to figure out should we look at developing
19 an instrument as an outcome measure that emphasizes
20 function.
21 This goes back to Ken Silverman's question
22 from like an hour or an hour and a half ago, which

Page 90

1 is we've been as a field obsessed with drug
2 results, urine results, I think, as sort of our
3 standard for an outcome measure. But it's
4 interesting -- and let me riff on this for a
5 moment.
6 It's interesting to think about something
7 like a functional outcome because I found myself
8 thinking, what if you take somebody with a chronic
9 condition like rheumatoid arthritis and say, we're
10 going to work on a medication that looks at
11 functional outcome rather than cure to rheumatoid
12 arthritis? That probably would be something that's
13 got real value to that patient population. Well,
14 it does. I mean, we've got medications that treat
15 the symptoms and improve functioning without
16 undressing the underlying disease state.
17 So I've not really thought about
18 stimulant-use disorders as something where we
19 should focus on outcome measures that look at
20 function. I've always looked at it as let's focus
21 upon the drug use itself.
22 I'm kind of thinking aloud and digesting

Page 91

1 this idea, but it was a really intriguing idea to
2 think about it in other clinical conditions.
3 David?
4 DR. McCANN: Kelly can go ahead.
5 DR. DUNN: Just to echo, not dysfunction but
6 also how patients feel.
7 DR. STRAIN: Yes, function, feel, or
8 survive. Yes.
9 MALE SPEAKER: The question, function, feel,
10 or survive. The question, function, feel, or
11 survive. So let's say you could find a drug that
12 would help with something like that, but did not
13 decrease cocaine use. That's really the kind of
14 question. I'm trying think what parallel there
15 might be in another addiction disorder. How about
16 naloxone? I mean, you don't use it to treat
17 addiction, but it has great benefit for the
18 patients.
19 It's worth looking at these issues. It may
20 not be an addiction treatment. It may be something
21 else that's beneficial for the patient.
22 DR. STRAIN: And I'm not -- just to be

Page 92

1 clear, I'm not advocating it as the only thing, but
2 in sort of a menu of things that we should be
3 thinking about in terms of outcome measures, the
4 development of outcome measures. Should there be
5 this slice that we should be thinking about, which
6 may be disentangled from the drug use slice in some
7 ways.
8 Laurie? Was somebody else before Laurie?
9 No? Okay. Laurie.
10 MS. BURKE: Well, I think that this
11 conversation -- and I'm not part of your expertise
12 here in terms of treatment of addiction disorders.
13 But I think that going back to what Ashley
14 presented in that roadmap is going to be really
15 useful to helping you sort out the answer to this
16 conundrum that you're pointing out. Because what
17 you measure and what you develop an outcome measure
18 for is going to completely depend on all of that
19 background information in column 1: what the
20 patient population looks like; what they're seeking
21 in terms of treatment; what the community is
22 desiring in terms of their treatment; what other

Page 93

1 treatments are available; what they do when they
2 don't have an successful treatment; the healthcare
3 environment that exists; how they're identified;
4 how they're self-identified.
5 I think having that to inform then your
6 column 2 of how you're going to actually set up a
7 trial, what are the objections of your trial, is it
8 going to be just signs and symptoms; and it might
9 be valuable to have a treatment that just gets them
10 through that initial withdrawal signs and symptoms
11 base. And then have an extension study to look at
12 other outcomes.
13 The design of your study is going to
14 determine what you really want to find out in the
15 context of the treatment that you want to test. I
16 look at all of the negative studies, and like
17 Sharon said, you can take that as we have no
18 treatments that are effective or you can take that
19 as we don't have a measure to know whether there
20 were little effects that were useful here. We
21 don't know either way because the outcome measure
22 that we're using is rather blunt. It's better for

Page 94

1 a diagnostic. It's not specific to the symptoms
2 syndrome that the patients are experiencing.
3 There's one more thing I wanted to say; and
4 the fact that it worked with patients who had very
5 high scores at baseline. That also tells you that
6 the sensitivity is not there -- I mean, we don't
7 know. That's another research question, can the
8 measure be better to measure change in those that
9 have less severe symptoms at baseline?
10 Perhaps your research objective would be
11 just to study those people with high symptoms at
12 baseline and exclude others from your trial, just
13 to start with, just to try to figure out the whole
14 outcome versus the treatment effect issue, and the
15 whole enrichment trial kind of ideal. I don't know
16 if that would be acceptable to the division or not.
17 But I think that in order to answer the
18 question about what should we do, proceed which
19 direction, with this outcome measure, you really
20 have to put together that background and that
21 difficult thinking about what's your context of
22 use, what's your clinical trial design, entry

Page 95

1 criteria, and also then design what the thing is
2 that's useful to measure as opposed to just putting
3 in the tools that are readily available.
4 I think that's the whole purpose of impact
5 and action, is to get people thinking. So I don't
6 know. What is the low-hanging fruit in terms of
7 the context of use and that background information?
8 And I'm sure this room has all the
9 possibilities -- all of that information to able to
10 put together some sort of a research agenda or a
11 priority for the initial foray into developing a
12 measure for a certain context of use and the thing
13 that you want to measure in that context. And that
14 would be my question. What is that, is the most
15 important thing.
16 DR. STRAIN: We're running into our break
17 time. And I think those are great questions. I
18 think those are the meta-questions that we're
19 struggling with here. Let me encourage people to
20 continue the discussion while we break, but I do
21 want to respect the break. I also want to thank
22 our two speakers from this morning. And let's

Page 96

1 reconvene in here in about 10 or so minutes if we
2 could. I think that's what we have. And Laurie
3 will be certainly resuming those questions over the
4 course of the day.
5 Thanks. Thank you guys.
6 (Whereupon, a recess was taken.)
7 DR. STRAIN: We're now going to hear from
8 Raye Litten, who's going to provide us an overview
9 to the experience and developing an outcome for
10 alcohol studies. Without further ado, Raye.
11 Presentation - Raye Litten
12 DR. LITTEN: Thank you. And thank you very
13 much, Eric. It's a pleasure for me to be here
14 today. What I'm going to present is an exploration
15 on our part here at NIAAA on endpoints, and really
16 focusing more on pivotal clinical trials that treat
17 alcohol use disorder.
18 First, I'd just like to mention key
19 organizations that are really kind of dedicated to
20 improving the methodology of clinical trials. And
21 we're hoping by improving the methodology of
22 clinical trials, we can increase our sensitivity to

Page 97

1 detect a difference in our medication during a
2 clinical trial. I'll mention our NIAAA team, Dan
3 Falk, Joanne Ferig, and Megan Ryan. And they
4 oversee the human studies and medications
5 development.

6 This is really a great team. They really
7 work well together. Megan and Joanne are both
8 here, as well as Dan who will be our discussant on
9 this. I'll just mention the ACTIVE Group. This is
10 another acronym. Don't even ask me what it stands
11 for. I've forgotten at this point. Being in the
12 government, we have so many acronyms. But what
13 really gets confusing is when they use the same
14 acronym for different organizations, then that
15 really kind of gets confusing.

16 But this group has been meeting for years.
17 It's kind of unique. It has the FDA present. At
18 times we have the EMA, which is the European
19 counterpart of the FDA, regulatory affairs. We
20 have pharmaceutical companies, anywhere from six to
21 eight, and some of these are European companies.
22 We have academic researchers. Some of them are

Page 98

1 international researchers. We have NIAAA present.
2 Dan and I primarily attend these meetings. We also
3 have NIDA. Dave McCann is a regular participant,
4 and also from the academic side, Chuck O'Brien
5 comes to all these meetings also.

6 With that, I'd like to talk about first, FDA
7 has put out a draft guidance. And I can tell you
8 the field's very happy and excited about them
9 putting this out. This is certainly the first one
10 put out in the alcohol field, and maybe even the
11 first one put out in the addiction field.

12 Basically, they have made recommendations to
13 use two endpoints. You don't have to justify using
14 these endpoints. The first one is, of course, the
15 old gold standard percent subjects abstinent.
16 That's usually the endpoint that used for other
17 drugs of addiction. But the FDA has also added now
18 percent subject with no heavy drinking days.
19 That's a mouthful. Sometimes I abbreviate this
20 PSNHDD.

21 Basically, it's pretty simple. It's
22 basically just the number of heavy drinking days,

Page 99

1 no heavy drinking days divided by the total number
2 of subjects during treatment. Again, just to
3 remind you, a heavy drinking day is 4 or more
4 drinks per drinking day for women and 5 or more
5 drinks per drinking day for men. Also to remind
6 you, no heavy drinking days includes abstinence as
7 well as low-risk drinking. And low-risk drinking
8 is those who didn't meet the heavy drinking.

9 So the question is, what evidence was
10 provided for consideration of this percent subjects
11 with no heavy drinking days as a primary endpoint?
12 This really came from three different types of data
13 sets: clinical trials, treatment settings, as well
14 as epidemiologic studies. And I'm going to talk
15 just briefly about each one of those and just kind
16 of highlight some of the studies that have been
17 done for those.

18 Before I get into the analysis that we did,
19 primarily Dan and our group did, the combined
20 trial, which most of you are probably familiar
21 with -- it was a 4-month treatment study, 1-year
22 follow-up. It's very large. In fact, it was the

Page 100

1 largest one we ever conducted. It was 1383.
2 It's a great data set to work from. In
3 fact, I've given it out now to 36 different
4 research groups around the world, and we still get
5 a lot of publications from that combined data set.

6 At randomization, they were required to have
7 anywhere from 3 to 21 days abstinence, and these
8 were the medications and the behavioral therapies.

9 The other thing I just want to introduce you
10 to briefly is this Drinker Inventory of
11 Consequences. These are basically the
12 alcohol-related consequences. It's given the
13 acronym DRINC, with a C, and that was developed by
14 Bill Miller a long time ago. And Kathy Carroll
15 looking, "Yeah, I remember that." And it was
16 developed for a project match.

17 Basically, in our analysis, we used a 37
18 item or the four subscales: physical, social
19 responsibility, interpersonal, and impulse control.
20 It actually has another subscale, intrapersonal,
21 which makes it 45 items. We thought that wasn't
22 quite as important for what we wanted to look at.

Page 101

1 Though, to be quite honest, if we did include it,
2 it didn't make any difference in our results.
3 Let me just go through first the data here.
4 This is -- again, the Y-axis is the drink scores.
5 And of course, the higher the drink score, it means
6 more consequences you had. We took the last
7 2 months of treatment -- that's actually where we
8 found the biggest effect of naltrexone combined.
9 You can see the red here are those who had
10 no heavy drinking days, and they had a value round
11 2.5, whereas those who had any heavy drinking days
12 had an average of 13.7. So you can see they were
13 suffering a lot more consequences. And we thought,
14 well, it would be nice. Let's just follow up on
15 these patients to see if this last. And 2 and a
16 half months later, still a big difference between
17 the two; even at 9 months, and a year later. It
18 was certainly a big difference between the two.
19 We also thought it would be interesting,
20 well, you know, since no heavy drinking days,
21 consist of abstinence and low-risk drinking, it
22 would be interesting did they drink; did they

Page 102

1 differ much. So we looked at the DRINK scores
2 here. The light blue is the abstinence, and the
3 darker blue is the low-risk drinkers. Of course,
4 the yellow again is the heavy drinkers.
5 You can see at the end of treatment that
6 they were very close in terms of their
7 consequences. And again, follow up two and a half
8 months later, it did go up a little bit, but
9 certainly they were pretty close. And it's
10 definitely different from the heavy drinking.
11 As you go up further, of course they no
12 longer got the treatment. They slight increased,
13 but still they were fairly close together. So
14 generally that's a trend we find. A low risk may
15 be a little bit worse than the abstainers in terms
16 of returning to drinking for long term.
17 We also just looked at the other one instead
18 of the consequences, what about if they took a
19 drink on a drinking day? How many drinks did they
20 have? Again, at treatment -- of course, the
21 abstinence didn't have any drinks than the
22 treatment. Those at low risk only had 2.4 drinks

Page 103

1 when they did drink. And those who had any heavy
2 drinking averaged 8.2. And you can see as we
3 follow up later, they weren't too far apart, the
4 abstinent group and the low risk. It's a little
5 bit higher, but certainly different from the heavy.
6 And this sort of continued all the way out to 9 or
7 12 months. Also, I might mention they did some
8 analysis on Project MATCH, and we really found
9 pretty much the same results in these clinical
10 trials.
11 Now, let me just briefly just review some of
12 the data we found in the treatment setting. We
13 worked with Connie Weisner, who's here today. This
14 is Connie's data and her group. What they did was
15 they took two data sets and roughly 995 patients.
16 And what we did was after they were initiated in
17 treatment, we looked at them 6 months after the
18 initiated treatment. And then we classified them
19 into three groups: the abstinent group, the low-
20 risk drinkers, and the heavy drinkers. Again, we
21 went back 30 days, so it was at month 6.
22 Then we wanted to know, okay, what did they

Page 104

1 look like 6 months later, say 12 months after the
2 initiation of treatment. And we looked at their
3 drinking as well as their consequence, and also
4 looked up to 5 years looking at their treatment
5 utilization and cost. I just want to now give you
6 a summary of it, and I'm sure Connie can go into a
7 lot more detail about those analyses. We actually
8 ended up getting two publications out of it.
9 This is the bottom line on this. Again, we
10 compared low risk to abstinent group, and then
11 heavy drinking to the abstinent. Again, they were
12 determined 6 months at their initiation of
13 treatment. Then we looked at them at 12 months.
14 We found that going back to drinking was greater in
15 the low risk than the abstinent, but it was much
16 greater in the heavy drinking. In fact, the
17 drinking was closer to the abstinent group, and
18 this really did separate out a lot more in the
19 heavy group.
20 We looked at consequences, particularly the
21 psychiatric, family, social problems, and they
22 were somewhat similar to the abstinent group, the

Page 105

1 low risk, where the heavy drinking was higher,
2 significant higher than the abstinent group. We
3 also then looked over a 5-year period treatment
4 utilization, particularly looking at inpatient and
5 emergency room, and we found they were similar, low
6 risk to the abstinent group. But it was
7 significant higher in the heavy drinking. And then
8 finally, we looked at the treatment cost against
9 similar in the low risk but higher in the heavy
10 drinking compared to the abstinent group.
11 Let me just review one other set of data
12 that was looked at. These are just results of two
13 epi studies. One was by Tom Greenfield. And this
14 is something we did a contract for him to do this.
15 He did it actually on two of his national alcohol
16 surveys. He's actually published the first one on
17 general population, but the FDA was really more
18 interested in these treated or concerned drinkers.
19 Tom told me he's working on that paper.
20 Sometimes he needs a little pushing. He did say he
21 added another survey to it. But this is what he
22 found so far, was that basically that those who had

Page 106

1 low volume drinking and did not any heavy drinking
2 days, had a low risk for alcohol dependence and
3 abuse. If they had any heavy drinking day, you
4 really did see that go up.
5 Finally, we looked at the NESARC data, which
6 is something NIAAA supported. It's a big one, over
7 40,000. These are just some results that Deborah
8 Dawson and Bridget Grant and that group came up
9 with. And basically, what they found was subjects
10 with no heavy drinking days carried a much lower
11 risk for alcohol dependence and alcohol use
12 disorder symptoms than those who experienced heavy
13 drinking.
14 There were actually even some more data that
15 I'm not presenting I think that Celia had in her
16 draft. But really, if you look at the summary of
17 this, if you look at no heavy drinking versus heavy
18 drinking, no heavy drinking decreased the risk for
19 relapse to heavy drinking, dependence,
20 consequences, treatment utilization, cost, compared
21 to those who had heavy drinking. And even looking
22 at abstinence versus low risk, versus heavy

Page 107

1 drinking, the relapse to drinking dependence for
2 heavy drinking was much greater than the low risk.
3 And it was somewhat greater, though, than the
4 abstinent group.
5 In terms of consequences, the heavy drinking
6 was different than the low risk and pretty much the
7 same, what we found so far, with the abstinent
8 group, as well as treatment utilization and cost
9 the same. The heavy drinking was greater than the
10 low risk and pretty close to the abstinent.
11 So if you integrate all this data together,
12 it really had the FDA and their
13 guidance -- basically were saying that patients who
14 never exceeded the heavy drinking limits had
15 minimal alcohol-related consequences and were much
16 likely to relapse at follow-up -- less likely.
17 Thank you, Dan.
18 See, this is why it's good to have Dan
19 around. We work so well as a team that when I get
20 off track, they always get me back on again.
21 A lot of our investigators and other people
22 were saying, okay, you've got this no percent

Page 108

1 subject to no heavy drinking days. How sensitive
2 is this? We tried to go out and see if we could
3 analyze this. I know we've looked at -- our
4 group's looked at at least a dozen data sets from
5 12 or so multisite clinical trials for alcohol. We
6 particularly looked at the ones where we actually
7 found an effect.
8 Yeah, it's hard to believe. We were not
9 positive in our trials. But all we said, if you're
10 positive in all your trials, you'll never believe
11 us. So it's always good to have a couple negatives
12 in there. It kind of gives you credibility.
13 Anyway, we found that so far from what we've
14 seen, it's not quite as sensitive outcome measures,
15 which isn't surprising. And particularly the
16 number of heavy drinking days, average seems to be
17 a little more sensitive. But it was certainly
18 significant in 5 alcohol clinical trials. And when
19 we tested this in this outcome measure, we found
20 that it was only really significant in two of the
21 trials.
22 I want to give you some examples here, going

Page 109

1 back to a COMBINE trial, where we did find it was
2 sensitive, and look at one like the varenicline
3 trial, which was less sensitive. And we're going
4 to compare this with the continuous outcome
5 measures, which I'm going to show you. And then
6 I'm going to compare it with the abstinent outcome
7 measure. So I'm going to do that.

8 This is the COMBINE study, again, the
9 continuous measures, the really popular one, the
10 average number of percent heavy drinking days,
11 drinks per day, drinks per drinking day, and
12 percent days absent. And they all showed a
13 significant effect. By the way, this was the last
14 two months of treatment, is where we got a bigger
15 effect, though we did find similar results if you
16 go back three months. And if you look at the
17 dichotomous measures, percent subjects no heavy
18 drinking day, we were picking up a significant
19 difference in that. Percent abstinence, we didn't
20 quite pick up a difference in that.

21 But I want to talk a little bit more about
22 these dichotomous measures and introduce the

Page 110

1 concept of grace period to you. A grace period is
2 a period of the trial where the outcome is not
3 considered in the analysis because the measured
4 treatment effects is not thought to be
5 representative of the full potential of the drug
6 and the pattern of drinking may still be unstable.

7 In other words, you may have a 6-month
8 trial. You might fail 3 months. You could have a
9 grace period because things weren't settled down.
10 The drug may not be working yet or the pattern of
11 drinking wasn't stable enough to get that. And
12 that's also in the draft guidance that the FDA put
13 up, that you can have a grace period. But you had
14 to defend what your grace period is going to be.

15 With that, let me go through and first talk
16 about total abstinence. Here is percent subjects
17 with total abstinence. The blue is the naltrexone,
18 and the yellow is the placebo. This first one here
19 on the left is of the whole trial, the first
20 4 months of treatment. And you can see, with the
21 effect size around .07, it wasn't significant.

22 Just looking at the last 3 months of

Page 111

1 treatment, this separated a little bit more. The
2 effect size went up a little bit. It still wasn't
3 significant. At the last 2 months, maybe a little
4 bit better. And the last month, you hit the
5 jackpot. We actually found a significant
6 difference in that between the naltrexone and
7 placebo.

8 Now, let's look at the percent subjects with
9 no heavy drinking days. The percentage, again if
10 you take the full stud -- and again, the blue is
11 naltrexone, the yellow placebo -- there was a
12 separation, effect size around .13, but it wasn't
13 significant. If you go back and look at the last
14 3 months, we were getting significant; .17 started
15 to become significant. The last 2 months was even
16 more, and the last month gave us the biggest effect
17 and had the biggest significance.

18 Again, just to compare, the red here is the
19 effect size with the total abstinence. You can see
20 that over the duration, the effect size was more
21 with the percent subjects with no heavy drinking
22 days than it was abstinence. So at least in this

Page 112

1 study, it appeared that the percent subjects with
2 no heavy drinking was more sensitive than the total
3 abstinence.

4 Now I'd like to talk about our varenicline
5 trial. This was a multisite trial that we did,
6 that we published. It was a 3-month trial.
7 Alcohol, we had about 198 subjects. An interesting
8 randomization, we didn't require any abstinence. I
9 don't think that matters too much because we're
10 getting positive effects and negative with both
11 abstinence or non-abstinence. What matter is we
12 noticed the placebo effect will be smaller,
13 particularly the first couple of months, than the
14 abstinent. Six months is usually the required
15 trial for a pivotal trial. And we're not quite
16 sure how that would play out over six months. We
17 do find the placebo rate does go up each month for
18 those who were drinking up to randomization.

19 Anyway, the results, what we found was that
20 there was a significant reduction on many of the
21 continuous measures. It was not significant in the
22 dichotomous measures. And just to go in a little

Page 113

1 more detail, these were the continuous measures.
2 Again, this was taken over 12 weeks. It was
3 actually week 2 through 13. We had a first week
4 titration. We found a significant effect for
5 percent to heavy drinking days, which was, by the
6 way, our primary outcome measure for this one.
7 This was a proof of concept trial; proof of concept
8 trial, you can do anything you want.
9 Drinks per day, we found an effect, drinks
10 per drinking day. Interesting, percent days
11 abstinent, we did not find an effect. And we
12 looked at the dichotomous measure, and we didn't
13 find an effect for either one of those two.
14 I'd like now just to discuss these two
15 measures in terms of grace periods. Again, this is
16 the percent subjects who are abstinent. These
17 values are over the whole maintenance period.
18 There was no difference, no effect size, and the
19 values were smaller, too. I think if you remember
20 COMBINE, they were around 17 percent, somewhere
21 like that.
22 If you look at the last 2 months, the values

Page 114

1 actually go up, and you start seeing a separation,
2 that it's not significant. And the last month,
3 though, you really did start seeing separation
4 between the varenicline and the placebo. It's
5 close to significance if it wasn't. So if this was
6 carried out a little bit longer, maybe 4 or
7 5 months, we might have been able to pick up a
8 significant difference here.
9 Again, just to compare the effect size, the
10 red here is total abstinence, and this is percent
11 subjects with no heavy drinking. You can see that,
12 again, in this study, it appears that the percent
13 subjects no heavy drinking days was a little more
14 sensitive to that.
15 In summary, as an endpoint, it's probably
16 not as sensitive as some of these continuous
17 outcome measures. It appears to be more sensitive
18 than abstinence, though we have to really check
19 this with more trials, just the ones we've seen so
20 far. It appears you definitely need a grace period
21 if you're going to show significance in these
22 dichotomous measures.

Page 115

1 Now, when we first had this present subjects
2 with no drinking, people were coming to us and
3 saying, "Well, what are you doing?" I said, "Blame
4 Dan. He's first author on this." But we said
5 okay. What would happen if you had one heavy
6 drinking day, or 2, or 3, or 5, or 10, or whatever?
7 Because people say they relapse. Why don't you
8 allow some heavy drinking? So we said, okay.
9 Let's look and see what happens if you allow heavy
10 drinking, and what will that do to the difference
11 between the two.
12 To do that, we decided to do an analysis
13 called, a Cumulative Proportion of Responder
14 Analysis. That has been around. It's been used
15 for other medical disorders for pain. In fact, the
16 FDA has actually even used it in their insert
17 package for pain. But it's never been done in
18 alcohol, and I'm not sure if it's even been done in
19 addiction, this type of analysis.
20 So what is it? Well, it represents a
21 proportion of responders over the entire range of
22 possible cut-off on the graphs. You can take the

Page 116

1 number of heavy drinking days and create all kinds
2 of different situations, zero heavy drinking, 1, 2,
3 or whatever.
4 Instead of explaining all this, let me just
5 show you what it looks like in the graph. This is
6 really a simple graph or else I've looked at it so
7 many times, it looks simple. I'm not sure. But I
8 think it is pretty simple.
9 What it is here, on the X-axis is the number
10 of heavy drinking days allowed. You go from here,
11 zero heavy drinking, or you could allow up to 1, 2,
12 10, 20. Again, this was I think the last 3 months
13 of treatment here. So you could theoretically have
14 up to 90 days of heavy drinking, though nobody
15 really did that.
16 What this purple is here are the placebo
17 values, and it tells you the proportion who had no
18 say, no heavy drinking here. And the blue here is
19 the naltrexone values. The red is the effect size
20 between the two values, and that's the effect size
21 here.
22 So let's start with zero, which is no heavy

Page 117

1 drinking days, which is the outcome measure. And
2 going back 3 months, the placebo had roughly
3 30 percent and the naltrexone, about 38. But they
4 had an effect size slightly under .2. So if you
5 add 1 or 2 -- say 2 heavy drinking days, if you
6 allow that, we notice that the effect size goes up
7 a little bit here, over .2. And it seems to peak
8 around somewhere between 10 heavy drinking days,
9 allowing 10 heavy drinking days, or allowing 20
10 heavy drinking days does seem to be the optimal.
11 And then it seems to go down from there.
12 So you say, well, why not allow 10 heavy
13 drinking days or whatever. Well, there is a price
14 to pay for that. If you're allowing more heavy
15 drinking days, the consequences are going to
16 increase. And this is an example where we plotted
17 the number of heavy drinking days with the drink
18 score. And you can see, even going up 1 heavy
19 drinking day -- and again, I think these are the
20 past 8 weeks in this one. But anyway, just jumping
21 up to 1 heavy drinking day, you do get an increase
22 in consequences, and it goes up, as it should if it

Page 118

1 was a good measure. As you drink more, you get
2 more consequences with that.
3 So you'd sort of have to justify, if we were
4 doing 10 heavy drinking days, what is the clinical
5 benefit of doing that. Plus the fact it may be a
6 little weird if you had that in your package
7 insert, and a physician said, "Well, if I can get
8 you to 10 heavy drinking days, this drug's going to
9 really work." It may not make a lot of sense. But
10 what might make sense, if you do these in different
11 categories and say you can reduce one category to
12 another.
13 That's sort of a lead-in to my next part, is
14 what new analyses are being conducted to possibly
15 expand the primary endpoints for alcohol clinical
16 trials? We're really thinking about three areas
17 here that we're trying to develop and validate.
18 One is can we validate and show clinical relevance
19 in reduction of continuous drinking outcome?
20 Secondly, can we develop categories of drinking
21 levels and patterns? And third, can we develop
22 some non-drinking outcomes that are sensitive?

Page 119

1 So with that, we're looking -- by the way,
2 this is something in progress right now, but I'm
3 going to give you an update where we're at on this
4 and what we're thinking. And this is really the
5 data sets we're really interested in. Jurgen Rehm
6 has this chronic disease. He has a lot of data on
7 that where you have amount of drinking and the risk
8 for chronic disease. He has at least 15 or more
9 that he's done on that, and I'm going to describe
10 that in a second.
11 Certainly, our clinical trials are COMBINE,
12 MATCH, and what we call the NCIG trials. We have a
13 network of sites that we do clinical trials. We
14 finished four already and starting a fifth one.
15 Also, the NESARC -- in fact, there's new NESARC
16 data that just got completed, or study just got
17 completed, as well as perhaps even looking at some
18 other large epidemiological surveys. We're also
19 interested in Connie Weisner. We like her data
20 sets, and perhaps even some other HMO research
21 networks.
22 Let me just move on and talk about what

Page 120

1 we're thinking about this continuous drinking
2 outcome. If you're going to validate this, we
3 think there are a lot of things you could validate
4 it; certainly the alcohol-related consequences,
5 treatment utilization, treatment cost. Maybe some
6 others we haven't thought of.
7 What we have done, we know that a Rehm study
8 has done a lot of analysis on amount of alcohol
9 consumed and various chronic diseases. And these
10 are long-term. These are what Ashley would say is
11 a distal. Rehm has sent us equations so that we
12 could plot these, where we could plot these with
13 the amount of drinking versus the risk of these
14 various diseases. And this is an example, some
15 curves we got for cancer of the upper digestive
16 tract and the lower.
17 Let me just take this a step further. For
18 example, suppose we take the one for mouth and oral
19 cancer. And this is the amount of alcohol
20 consumed, and this is the relative risk of the
21 disease. Then we took our varenicline study, and
22 what we found was in the treatment, the varenicline

Page 121

1 group was down to 4.4 drinks a day, and the placebo
2 was 5.4. So it's a difference of 1 drink. And you
3 might say, well, one drink doesn't seem like much.
4 I always like to think, well, maybe if you take it
5 per week, that's 7 drinks a week, or if you take it
6 per year, that's 365 drinks a year. So that sounds
7 a little more impressive than 1.
8 Anyway, if you take this graph here and put
9 where the placebo would be, at the 5.4 drinks per
10 day, and the varenicline at 4.4, and look at the
11 risk factor, the placebo has a risk factor of 4.4,
12 and the varenicline has it at 3.5. So by reducing
13 one drink, you reduce the risk factor from 4.4 to
14 3.5. Is that significant? Well, maybe.
15 Rehm has now, though, integrated all this
16 data and has now put it into a table. This was
17 just recently published. And to be honest, we're
18 still studying this, and we want to study in a lot
19 more detail. But basically, what he has
20 done -- and it's really neat -- he has taken the
21 amount of alcohol consumption per year, and then he
22 has made a table where you get a number of events

Page 122

1 per 100,000 patients.
2 For example, he has 15,000 to 18,000 grams
3 of alcohol per year, and he has a risk of
4 development of ischemic heart disease, stroke,
5 traffic injuries, other injuries, cirrhosis,
6 pancreas, and so forth. So he's developed these
7 tables, and he's also developed tables for heavy
8 drinking, the number of heavy drinking days per
9 year.
10 Now, what's interesting about this is that
11 Lundbeck got approval in Europe for nalmefene, and
12 they did this in three very large clinical trials.
13 And they were using a continuous measure of
14 reduction in drinking and reduction in heavy
15 drinking. But to show that there was a clinical
16 benefit, the EMA actually allowed those tables.
17 This is an example. The difference between
18 nalmefene and placebo, as an average, was around
19 one drink a day, and that's somewhat of a
20 conservative value. But with that, looking at
21 these tables, they found that it was 692 fewer
22 alcohol trivial diseases or injuries per 100,000

Page 123

1 alcohol-dependent patients. And he's done this
2 with other different categories. For heavy
3 drinking, he found -- it was pretty conservative,
4 but he found that they had 3 heavy drinking days
5 less a month, the difference between nalmefene and
6 placebo, and then they had 941 fewer diseases and
7 injuries and so forth.
8 We're still studying this, and Dan's going
9 to talk a little bit more about this in his
10 discussion. But we had to also know that there are
11 weaknesses in getting this data. So we're
12 evaluating this in how they came up with these
13 tables, right now.
14 The other thing we're interested in is
15 developing risk categories for alcohol intake and
16 can we establish categories describing the risks-
17 benefits at different levels of drinking and maybe
18 patterns of drinking, sort of similar to what's
19 been done in clinical categories developed for
20 blood pressure, cholesterol, for diabetes. This is
21 an example of blood pressure. You could find that.
22 They may even have a stage 3 now. I'm not sure.

Page 124

1 They keep changing this a little bit. But normal,
2 pre-hypertension, stage 1, stage 2, where the blood
3 pressure goes up.
4 The question we had asked, well, can we
5 develop these, too? Dan and I sat around one
6 afternoon and made up this table, so it is kind of
7 made up. You have abstinence, low-risk drinking.
8 In fact, you might even have two different levels
9 of low-risk drinking. And then you have that break
10 off with no heavy to heavy drinking, where you have
11 high risk. Perhaps you have different stages:
12 low, moderate, and severe. But the challenge we
13 have to do is to fill this in. These have to be
14 filled in with clinical relevance from different
15 types of data sets, to fill this in to give it some
16 meeting.
17 I think doing something like this would be
18 extremely valuable, not only to regulatory
19 agencies, pharmaceutical companies, and
20 researchers. I think this would be very useful to
21 patients, be very useful for clinicians, and also
22 third payers. Insurance companies would like to

<p style="text-align: right;">Page 125</p> <p>1 see if you're going from one category to another, 2 what is the advantage of doing that? How is that 3 saving you money? 4 Pharmaceutical companies, whenever you go to 5 a pharmaceutical company, the first thing they want 6 to know is -- well, first the thing is, can we make 7 money off of it? But then they say, well, what is 8 the clinical benefit of how you do these studies? 9 And they won't even begin to do any drug 10 development until they do that. And I know pharma 11 people, Amy and others, could vouch for that. 12 Anyway, that's something we're thinking 13 about. I'll just mention, though, the WHO has 14 different criteria that they develop. I had to 15 tell you though, there's probably not a lot of 16 validation for how they came up with these numbers, 17 to be honest. But it's interesting that the EMA 18 has accepted the fact that one of the outcomes 19 could be if you reduce two categories. And most of 20 them come in high or very high. So if they went 21 from very high to medium or low, it would count as 22 a success, or if you come in high, you could be</p>	<p style="text-align: right;">Page 127</p> <p>1 we're very lucky because she's here today. Amy 2 Duhig was very much involved with that program. Of 3 course, she can answer any questions. 4 What Amy and the group came up -- by the 5 way, they lost interest, really, so they gave us 6 the data to go to the FDA to see if we could -- and 7 I've submitted something to Ashley, and I know 8 she'll get back to me soon on that. I have a full 9 plate, believe me, but people are asking me about 10 it. 11 Anyway, they called this IMBIBE, and it's 15 12 items. We actually did this, IMBIBE, in our 13 varenicline study. Just to show you some 14 analysis -- by the way, we didn't get a difference 15 between placebo and varenicline on the IMBIBE. 16 What we did was take the last month of 17 treatment -- actually, varenicline seemed to 18 work -- got stronger as it got further down the 19 trial. It took at least halfway through before we 20 really began to see some effects with it. But 21 anyway, this is the number of heavy drinking days 22 versus the score. And as predicted, as you had</p>
<p style="text-align: right;">Page 126</p> <p>1 down to low or abstinence. 2 I'm just about done. But anyway, there is 3 some indication that people could use something 4 like that. 5 The last thing -- and we'll finish up 6 here -- is just on these non-drinking outcome 7 measures. So far, we haven't found them to be 8 generally as sensitive as drinking measures, or 9 they're certainly not more sensitive for sure. We 10 are interested, though, in trying to validate, 11 through the FDA, two of them. One is the 12 alcohol-related consequence, the other one craving, 13 which we haven't really started yet. We might even 14 have to change the name from craving to urge or 15 something. 16 But the alcohol-related consequence, Lily 17 started validating the drink. This is something 18 Bill Miller made up, sort of like what Joe 19 Volpicelli did. So they really started to validate 20 this. They interviewed patients, researchers. 21 They did factor analysis with COMBINE, MATCH. The 22 person who's really in charge of this at the time,</p>	<p style="text-align: right;">Page 128</p> <p>1 more heavy drinking days, it did go up. 2 So we thought, it would be fun if we took 3 the average value of the placebo at the end of 4 treatment -- so the average placebo, the last 5 4 weeks averaged around 12.5 heavy drinking days, 6 and the average value for the varenicline the last 7 4 weeks was around 8.5. So it did go down a little 8 bit. But I think it's pretty obvious why we didn't 9 get a significant difference between the two. Now, 10 if the drinking had gone down in here, we might 11 have been able to pick up a significant effect. 12 We also really continue to look at this. 13 We're looking at individual items and how they vary 14 with alcohol consumption. These are the ones that 15 vary the most. I would tell you what they were, 16 except I can't read them from here. But anyway, 17 we're looking at that. We're also doing a lot of 18 exploratory analysis with NESARC and some of the 19 other data sets to see if we can find consequences 20 that are really sensitive to the various drinking 21 outcomes and patterns. 22 Basically in summary, I think we're making</p>

Page 129

1 progress. We've still got a long ways to go, in
2 developing and evaluating new sensitive and
3 clinical relevant alcohol outcomes. These are the
4 three categories right now we're looking at. And
5 we're hoping of course for any new approaches over
6 the next decade.

7 So with that, I think I'd like to introduce
8 my colleague, Dan Falk, who will now tell you -- I
9 don't know if it's the dirty side of this, but will
10 tell you things aren't easy to do, but he's going
11 to tell you the nuts and bolts about how to do
12 these types of analyses.

13 (Applause.)

14 Presentation - Dan Falk

15 DR. FALK: Hi. I'm Dan Falk, NIAAA. So I
16 just thought I'd talk briefly about some key issues
17 just to dovetail on what Raye was talking about.

18 First, just backing up what makes a good
19 outcome measure, and then we're going to talk about
20 sensitivity of alternative drinking outcomes, as
21 well as the non-drinking outcomes. We'll talk more
22 details -- the devil's in the details -- when it

Page 130

1 comes to validating these outcomes. There are a
2 lot of data issues. And what are the most
3 important validating outcomes, how do we decide
4 upon them, how do we integrate the results. And
5 then I'll try to jump off for challenges for -- I
6 know what you all care about most are stimulant
7 trials.

8 This is kind of what we think makes a good
9 outcome measure. First, it's got to be clinically
10 meaningful. So if it's response variable or
11 dichotomous outcome, it should set a threshold by
12 which a clinician might judge a patient to be well
13 or have gotten better. It should be able to be
14 achieved by a sizeable proportion of subjects, and
15 that's not always easy.

16 In the topiramate trial, we found that no
17 subjects achieved abstinence in the full
18 maintenance period, and only 5 percent in the
19 topiramate group. So it's kind of questionable
20 whether it's a good outcome for all populations or
21 trials.

22 Number 3, it should be validated or

Page 131

1 correlated with other informative outcomes, so
2 that's the bulk of the work that Raye has been
3 talking about. You can validate against
4 alcohol-related consequences, physical health
5 markers like blood pressure, global indicators of
6 well being like the SF12. And then
7 finally -- well, then next, it should be sensitive
8 to the effective medication. I mean, that's
9 obvious, but that's critical.

10 We tend to get really excited, thinking
11 about all these potential outcome measures we can
12 come up with, but are they going to be sensitive?
13 Well, let's see. So they should be at least as
14 sensitive as other outcome measures or at least no
15 less sensitive.

16 Then finally, and very importantly, it
17 should have the support of the key stakeholders
18 because we've learned in the active group that
19 we're part of, different stakeholders have very
20 different perceptions on what's important.

21 So first off, the sensitivity of alternate
22 drinking and non-drinking outcomes. A lot of

Page 132

1 people will come up with these outcome, but I say
2 be careful what you wish for. You might get it.
3 Some of these are not as sensitive. These
4 alternative drinking outcomes can be less
5 sensitive.

6 This was what Raye was talking about. This
7 was the EMA, the FDA equivalent in Europe, came up
8 with this reduction in drinking by two or more
9 levels, from baseline to treatment. So you can go
10 from very high to medium low. Abstinence, that's a
11 two-shift or from high. These are most of where
12 our people are coming in our clinical trials. You
13 can go to low or abstinent.

14 But the real question is, is it sensitive?
15 This was in COMBINE. You've seen all this before,
16 and I just added this at the bottom. It's
17 significant, but the treatment effects are a little
18 less than percent subjects, no heavy drinking days
19 and less than the continuous outcomes. Now, we
20 still have to test it in other trials, but it may
21 diminish some enthusiasm. I'm not sure.

22 Also, there are other dichotomous endpoints

Page 133

1 that can be proposed, and the EMA proposed several
2 more. They proposed a proportion of subjects with
3 a reduction in alcohol of actually 50, 70,
4 90 percent or 100 percent. A hundred percent is
5 total abstinence.
6 So we're borrowing from our friend the
7 Cumulative Proportion Responder Curve here. This
8 is from a topiramate trial. This was in one of our
9 papers. So Raye introduced how to read this. But
10 basically, on the right-hand side where it says a
11 hundred percent reduction, that's total abstinence.
12 You get a treatment effect of about .43, let's say.
13 The other arrows, that's the 90 percent
14 right there, that's 75, and that's 50. What you
15 see, there's some fluctuation there. Ninety
16 percent of the treatment effects drops; kind of
17 picks up a little bit with 75 percent. But then by
18 50 percent reduction, it goes down to about .3. So
19 you do go from .43 to about .3, so you do lose some
20 treatment effect there by going to this more
21 lenient -- let's call it more lenient responder
22 definition.

Page 134

1 This is just one more of these. The X-axis
2 is drinks per day. On the right side where it says
3 zero drinks per day, that's total abstinence. This
4 is in the topiramate trial. Again, with total
5 abstinence, you get .43. What happens if
6 you -- let's say you wanted to create a dichotomous
7 outcome at 5 drinks per day. These people that
8 enter these trials have maybe 8 to 9 drinks per day
9 when they come in. So you might think, well, 5
10 might be pretty good. They're cutting back to
11 about 5 drinks per day. Let's call that a good
12 outcome if they have 5 or less.
13 But if you did that, you would see that the
14 treatment effect would kind of plummet there from
15 .43 to about .17 or something. So you kind of have
16 to be careful what you wish for because you could
17 get it if you choose these more lenient outcomes.
18 Let's talk about non-drinking outcomes.
19 These were all drinking outcomes. What about the
20 non-drinking outcomes? FDA has expressed in their
21 guidance that drinking is really a surrogate for
22 the non-drinking outcomes, and we've heard that a

Page 135

1 little bit this morning. The aim of treatment is
2 often expressed as an effort to modify drinking
3 behavior, but the actual desired effect is
4 improvement in physical and social consequences, in
5 the non-drinking outcomes.
6 So we would love to measure the non-drinking
7 outcomes in our trials and have them be
8 significant. That would be wonderful. We wouldn't
9 even have to bother probably validating the
10 drinking ones, right? But the problem is that they
11 may have limited sensitivity or at least variable,
12 and that's what Raye I think was alluding to there.
13 LoCastro et al. in 2009 looked at COMBINE,
14 and he basically found -- these are all secondary
15 outcomes, all non-drinking outcomes. There's a
16 wide variety here. And most of them were not
17 significant, with exception of a couple here, SF12
18 health score and maybe a WHO, environmental. But
19 actually, they concluded -- they did so many tests
20 that after they controlled for multiplicity, they
21 found that none of these were significant. We did
22 a couple more analyses on the drink score; again,

Page 136

1 not significant, and blood pressure wasn't
2 significant either.
3 So that's the challenges, that we can't find
4 significant things. In other trials, I think
5 Bankole Johnson in the topiramate trial found that
6 craving and drink score, the consequences were
7 significant. This is just one trial, a large one.
8 So that's our challenge here, is that we can't
9 really find significance in these. That's why we
10 have to validate the drinking outcomes. And that
11 brings us to the issues of the devil's in the
12 details when you're validating drinking outcomes.
13 The validation of our drinking outcomes is
14 really only as good as the data against which we
15 validated. And each of these data sets here at the
16 top have strengths and weaknesses in terms of -- so
17 here's our drinking outcome. Well, the Rehm data
18 tends to just look at total alcohol consumption,
19 but we know there's a lot of other drinking outcome
20 measures we might want to validate, like the number
21 of heavy drinking days, the percent drinking days.
22 That's not here in these data. But we do get it in

Page 137

1 our clinical trial data, where we have very -- we
2 use the timeline follow-back. We can calculate any
3 kind of outcome we want from the daily records of
4 drinking.
5 NESARC has pretty good, and the Kaiser has
6 pretty good drinking as well. In terms of the
7 consequences, there's chronic and acute
8 consequences. The Rehm data is very good with
9 chronic. In our trials, we don't have any real
10 chronic data that we collect. Even if we did, it
11 would probably be too short of a duration to
12 collect it. But NESARC has a nice -- they measure
13 chronic and acute pretty well, and so does Kaiser.
14 We do measure in our trials acute consequences very
15 well with the drink instrument.
16 In terms of study design, ideally, you'd
17 want a longitudinal study design. When you look at
18 the drinking outcomes at wave 1 or time period 1,
19 you look to see how it predicts consequences later
20 on. And that's the strongest test, and that's what
21 Ashley was talking about. That was one of her
22 spokes, was a longitudinal validation, and that

Page 138

1 seemed to come after doing maybe a cross-sectional
2 one.
3 The cross-sectional -- the Rehm
4 data -- we're trying to understand how they churn
5 the numbers out in the Rehm data, but it seems to
6 be a little more cross-sectional, but that needs to
7 be confirmed. But at least with these other data
8 sets, it's more longitudinal.
9 This is blood pressure. The question is
10 which outcomes do we validate and against what
11 consequences? This is blood pressure. They've got
12 it pretty easy in some way. They have two outcome
13 measures, systolic/diastolic, and they're going to
14 kind of crunch these numbers, maybe come up with
15 the cut-offs, 140/90. And those are going to be
16 validated against these consequences, which are
17 kind of limited.
18 This one comes from their most recent 2014
19 and the JNC, committee, which develops the blood
20 pressure guidelines. So they said that this is
21 what they look for as outcomes to validate blood
22 pressure. It's basically just cardiovascular

Page 139

1 health outcomes and kidney, renal outcomes.
2 But what's it like for drinking? We have at
3 least 7 to 10 different types of drinking outcomes
4 we might want to -- these are continuous measures.
5 And then we're going to slice and dice them an
6 infinite amount of ways just with the number of
7 heavy drinking days. You could have no heavy
8 drinking days, 1, 2, up to 3, 5, 10, whatever you
9 want. But then we're going to have to validate
10 these against -- there could be like 65
11 consequences that -- because alcohol's a dirty
12 drug. It affects all these physical, these health
13 related aspects, as well as the drink has 45 items
14 in these 5 classes. We've got interpersonal,
15 economic, employment, all these other consequences.
16 So it's really a challenge. This is the
17 challenging question, as I see it, is how do we
18 integrate the data? How are we going to validate a
19 given clinical trial result on a continuous
20 outcome? First off. And then how are we going to
21 create and validate a responder definition given
22 the myriad consequences by which to validate them?

Page 140

1 In the very limited -- it's a simple
2 example. I only picked two outcome measures, two
3 health consequences. They're both cancers. One is
4 occurring a little higher up in your mouth. The
5 other one's occurring a little lower in your
6 esophagus. And you have the alcohol consumption,
7 the outcome measure you'd like to validate, and the
8 relative risk.
9 What you notice that's different about these
10 is that the slope of the risk curve is different.
11 This is steeper here than this one, which means
12 that, basically, you start seeing risks occurring
13 with lower levels of drinking.
14 Let's take the blue. We're going to
15 validate a clinical trial result. That's what Raye
16 was talking about when you're comparing placebo and
17 medication on the actual outcome that you achieved
18 in your clinical trial. We said 4 here, 4 drinks
19 per day, in placebo; a 1 drink difference
20 corresponds to 1 relative risk unit different,
21 let's say, on this outcome. But on another
22 outcome, really there may be very little relative

Page 141

1 risk difference in the clinical trial result we
2 see.
3 So the question is, well, which outcome do
4 we use? Now, this is only 2 outcomes. There are
5 going to be 65 of these curves even in ideal state
6 that we would eventually develop. How do we know
7 which ones to look that? Do we pick the one with
8 the steepest curve if we want to be really
9 conservative with what we're doing? We want to
10 minimize any risks, so maybe we take the one with
11 the steepest curve.
12 Now, if we want to create and validate a
13 responder definition, we could decide a priori, we
14 will not accept any amount of alcohol in our
15 responder definition that increases from zero to a
16 relative risk of 2. So we're doing to cap at
17 a priori at a relative risk of 2. If this
18 responder definition is going to increase our
19 relative risk more than 2, forget it.
20 So let's say that's how we're going to do it
21 a priori. Now, do we choose 2? Do we choose 1.5?
22 Do we choose 3? We'd have to have a debate about

Page 142

1 that. But if you did, you'd see that the relative
2 risk of 2 does translate to different amounts of
3 alcohol consumption that you'd make your cut-offs.
4 I don't think we have an answer to this, but
5 I do know in the blood pressure -- I was trying to
6 read how they came to consensus. They had big
7 meetings. I think they invited 50 -- I don't know.
8 I didn't tally up all the numbers of experts. It
9 looked like 20 to 50, and they had special -- I met
10 the people, NHLBI, that set up these meetings.
11 They actually hired a special consultant who was
12 expert in achieving consensus, get these people
13 together, herd the cats, and try to come up
14 with -- and they reviewed -- each expert reviewed
15 the meta-analyses. But they didn't have the
16 challenge that we had. I don't think they had as
17 many outcome measures, and they did not have as
18 many consequences to look at.
19 Now this brings us to the challenges for you
20 all for the stimulant trials. I don't know much
21 about stimulant trials, but this is what our
22 understanding is. I don't think you have timeline

Page 143

1 follow-back like we do, where you measure daily
2 quantity. Do you have daily quantity of -- no. So
3 that's correct. There's not daily quantity of I
4 guess cocaine amount consumed.
5 Okay. Two minutes. That's fine. So maybe
6 you only have frequency like percentage of days
7 that are abstinent or maybe just total abstinence,
8 right? But if you only have frequency, you need to
9 evaluate the clinical relevance, develop sensitive
10 non-substance, intake endpoints like the
11 health -- all these different kinds of
12 consequences. But definitely before going through
13 the process of picking the ones you like, make sure
14 that they're sensitive, and try to testing as many
15 clinical trials as you can.
16 That's our very low level of advice. We're
17 not experts, but that's kind of where we're at. So
18 that's it.
19 (Applause.)
20 Q&A - Group Discussion
21 DR. STRAIN: If it's all right, I'd suggest
22 that we maybe start lunch a little later. We've

Page 144

1 got plenty of time for lunch, and you can all eat
2 fast, because I think these were really a great
3 pair of studies.
4 Raye, do you want to come up as well? I
5 think it would be useful to take a couple minutes
6 to see if there are any questions people have
7 because this is such a -- as sort of a model for
8 stimulants, this seems like a critical opportunity
9 to look at it.
10 George?
11 DR. WOODY: George Woody. One of the slides
12 said GGT, but I had the impression that liver
13 enzymes are a pretty sensitive measure of change,
14 but I didn't see that coming up too much in any of
15 these studies.
16 DR. LITTEN: Yes. George, we generally do
17 use biomarkers in our trial. The liver enzymes
18 just aren't very sensitive. We're more, though,
19 excited about these new alcohol metabolites:
20 ethanol, glucuronide, and phosphatidyl ethanol,
21 particularly because they're more direct
22 metabolites.

Page 145

1 But when you use biomarkers, there are
2 limitations to them. You have to know what the
3 limitations are. First of all, biomarkers aren't
4 going to tell you so much how much. It's always
5 yes/no. And you have to know exactly how much you
6 think they're measuring. For example, ethanol
7 glucuronide will measure up to one drink, but it
8 has a very small window of assessment within maybe
9 one, three or four days, depending how much you've
10 drank. Phosphatidyl is a little bit different.
11 That will stick around maybe two or three weeks,
12 maybe four weeks, but you probably had to drink
13 more to get that elevated. So you could sort of
14 use those in combination.
15 Also, for example, too, it depends on not
16 just how much you were drinking a day. Say you
17 have phosphatidyl, and you need 3 or 4 of 5 drinks
18 to elevate it. It depends on how quickly you did
19 those drinks because if you did it over, say, 12
20 hours -- in fact, if you had maybe a drink an hour,
21 it may not be elevated. Remember, it's measuring
22 the amount that's in your blood. But if you drank

Page 146

1 it over, say, a two-hour period, then it would be
2 elevated more.
3 So you really have to take into account all
4 this. What I think is most exciting for us, and
5 the one we're really trying to get is these alcohol
6 sensors. SCRAM I think has done a great job with
7 that. It's used in the criminal justice system
8 quite a bit. It's around your ankle. But it
9 measures drinking in real time. It's not quite as
10 quantitative as we would like for it to be in terms
11 of blood alcohol levels. But we put out special
12 announcements to improve the technology of that, to
13 make it cheaper, maybe easier to where more
14 quantitative.
15 Of course, if we start using this, too, we
16 probably have to change our outcome measures, and
17 change it instead of drinks is how much blood
18 alcohol you have because it's really a measure of
19 blood alcohol, not the number of drinks. And as
20 you know, the number of drinks and the amount of
21 blood alcohol you get varies quite a bit, depending
22 on the size of the person, whether they have any

Page 147

1 food in their stomach, of the enzymes vary that
2 break it down among individuals.
3 So these are all things worth thinking about
4 in terms of biomarkers. We do like to use
5 biomarkers -- and I think the FDA likes for us to
6 include them in our trial -- more as validation.
7 If we report and self-report that you have a
8 reduction in drinking or whatever, it's nice to
9 have that validated by biomarkers. But you have to
10 realize the limitations of those.
11 DR. STRAIN: Other questions? Thanks. Ken?
12 DR. SILVERMAN: This is Ken Silverman. Two
13 terrific presentations. Thanks very much for
14 those. I shouldn't be hung up on this, but I'm
15 hung up on the FDA issues that Eric elaborated on,
16 that you want to show either that the medication
17 improves how long people live or whether how they
18 feel and function in daily life.
19 You guys described validation of the
20 drinking measures, which seems pretty good to me,
21 but you're focused on drinking as your outcome
22 measure, and you pick measures that are validated,

Page 148

1 like the drink responses, which seems pretty
2 sensible.
3 But I'm wondering, is the FDA -- is the
4 focus on how a patient feels and functions in daily
5 life, would that suggest that the drink should be
6 that the validation measures should be the primary
7 outcome measures? Have you given that some
8 thought?
9 DR. FALK: Yes, exactly. That's what I was
10 trying to show with that one slide with COMBINE,
11 where the drink, the consequences wasn't
12 statistically significant in drink. The effect
13 size was .11, whereas the drinking outcome was .21.
14 That's the problem. And the question is, why isn't
15 the consequences significant in our clinical
16 trials? Maybe it's too short of a period that
17 we're assessing the outcomes. Maybe it takes
18 longer before you finally move the dial in terms
19 of -- like some of the consequences are if you got
20 a DUI, or you got divorced or whatever. It could
21 a while, a lot of reduction before you see
22 improvements in some of these kinds of

Page 149

1 consequences.

2 DR. WOODY: Plus different people might show

3 different kinds of effects, different kinds of

4 consequences.

5 DR. STRAIN: Sorry?

6 DR. WOODY: Different people may have

7 different kinds of consequences, whereas everyone

8 might decrease drinking -- or more people may. A

9 large percentage, many people decrease drinking as

10 they do in our trials; they decrease cocaine use.

11 But the effect that that has on their lives varies

12 across the people a lot, so it's harder to --

13 DR. FALK: There's a lot more variability.

14 DR. LITTEN: And there could be a lag behind

15 this, too. The varenicline was 3 months. If we'd

16 done it 6 months, we'd might have been able to pick

17 up differences in consequences. And we have some

18 data that suggests that you do start seeing

19 consequences and follow more -- after the drinking

20 has occurred.

21 FEMALE SPEAKER: I think the other

22 thing -- real quick to follow up on that. I was

Page 150

1 part of the initial -- we took the drink at Lily.

2 And the idea was for us to have an endpoint that

3 would actually resonate with maybe clinicians, but

4 more towards the patient, like what benefits do I

5 actually receive if I reduce my drinking.

6 So we went through the FDA draft guidance

7 that had just come out I think it was in 2006, or

8 '07, or something like that. So we went back to

9 patients, and we took all the drink items, and we

10 asked them about the relevance, the importance, how

11 often they'd actually experienced those symptoms.

12 And we had to cut out those things that were

13 not -- that were going to take a super long time or

14 the really infrequent items, or things that just

15 really didn't matter.

16 So we came down with -- it was not perfect,

17 but came down with a shorter list, with the idea of

18 what is relevant and important and what could

19 potentially change. I don't think these trials

20 have never been powered based on the drink either.

21 I mean, you're powering based on your primary, and

22 then hoping that these tertiary or secondary

Page 151

1 outcomes then move.

2 Then also, the population that was -- we did

3 the qualitative interviews with about 60 patients,

4 and they were all outpatients, and they

5 were -- with the idea that this is an outpatient

6 drug, with people with not severe comorbidities

7 like would be included in your phase 3 studies, but

8 with the idea that at the end of the day, could you

9 demonstrate value to a patient who said these

10 things were important.

11 FEMALE SPEAKER: That's the IMBIBE?

12 FEMALE SPEAKER: That's the IMBIBE, yes. So

13 there are some gaps in there. And if it's just

14 based on the qualitative phase only, I'm not sure

15 that -- then Lily kind of abandoned it when their

16 drug -- so it was turfed over to you guys. But

17 there are so many issues associated with that.

18 DR. FALK: But even with IMBIBE when we

19 tested in varenicline, where we got nice treatment

20 effects, .3's on most of the drinking outcomes,

21 IMBIBE still wasn't -- it didn't improve our -- our

22 sensitivity wasn't significant. So even with some

Page 152

1 of these shorter duration consequences -- so it's

2 not clear. Maybe there's more variability. We'd

3 have to check the standard errors and just see if

4 there's more variability around consequence type

5 measures than drinking type measures.

6 DR. STRAIN: Connie, real quick, and then I

7 want to move on.

8 DR. WEISNER: I was just going to say, I

9 know it's a power issue, and we've talked about

10 this before, too. But I think we are often selling

11 our treatments short because the issue is that we

12 are finding you see the consequences improve that

13 are related to why the person came to treatment.

14 So unless you're measuring employment outcomes for

15 someone with an employer mandate or legal outcomes

16 for that, you're not seeing this. But again,

17 that's a real sample size issue.

18 DR. FALK: That's a good point. That's an

19 excellent point.

20 DR. STRAIN: So thank you. Yes, I know,

21 that granular level to it.

22 So I want to thank these two guys again.

Page 153

1 Thank you, NIAAA.
2 (Applause.)
3 DR. STRAIN: We're going to move on, but I
4 hope we can continue this discussion over lunch.
5 Kathy Carroll, you're up.
6 Presentation - Kathleen Carroll
7 DR. CARROLL: I'm delighted to be here
8 today. I want to thank ACTTION. And I really want
9 to thank NIDA and Medications Development, Dave
10 McCann and Ivan and Phil for spurring us to do this
11 work, where we've been slavishly following
12 Dr. Falk's work; a big fan! Big fan. This began
13 in about 2011 with a supplement. This is sort of a
14 two-parter.
15 When we began trying to figure out what's an
16 appropriate endpoint in stimulant trials, we came
17 up with a list of what we wanted. And what I'm
18 going to do today is talk a little bit about the
19 conundrums in selecting stimulant trials or 50
20 different ways to calculate urines. You think
21 you're doing it all the same way, and you're really
22 not. I've become an aficionado of reading things

Page 154

1 and reviewing and really looking at those numbers
2 because it's tricky.
3 Why do we need a sound and valid indicator?
4 I'm preaching to the choir. There's the choir.
5 But we really, really need this in stimulant abuse,
6 and especially as we're moving into primary care
7 medical settings because we can't yet talk about
8 what we do in a way that's convincing to clinicians
9 and payers and so forth. So we absolutely need
10 these things for meta-analyses.
11 We really do need to set and monitor
12 performance standards. I think something that gets
13 totally in the way of being able to move some of
14 these new treatments into the field is that the
15 field itself, the clinical field of stimulant
16 treatment, doesn't have outcomes. All they've got
17 is retention, and all they've got is group and
18 individual treatment.
19 So when we come in and say our little CBT
20 for CBT can give you a 30 or 40 percent difference
21 in three or more weeks of continuous abstinence,
22 nobody cares because they don't have a clue about

Page 155

1 their rate of three or more weeks of continuance
2 abstinence. They don't even collect urines. So we
3 should think about that, too, a clinical field that
4 does not collect urines and doesn't know.
5 It's complicated, so we really, really do
6 need this. And it's so fascinating. I was
7 fascinated when Raye was talking about the percent
8 of completely abstinent people in alcohol trials.
9 I mean, we should know that. We should know that
10 it's 7 to 9 percent, and we can do better than
11 that.
12 So anyway, this is something that I think is
13 really important. We need to be able to
14 compare -- let's all take comparisons across a
15 common standard and pull the clinical and research
16 fields together more.
17 What I'm going to do is talk about what
18 we've been doing in the last three or four years in
19 terms of working through desirable characteristics
20 of indicators. I'm going to talk about some of the
21 strengths and weaknesses of the common approaches
22 for approaching endpoint analyses -- it's really

Page 156

1 ugly, so the guy's coming back from looking at the
2 truth -- and then talk about our project where we
3 have taken four of our more recent randomized
4 clinical trials of cocaine use disorders and pooled
5 the data, tried to harmonize it, and then go
6 through what it said. So I'll just be talking
7 about how we approached it, and then later this
8 afternoon, Brian Kiluk will be talking about what
9 we actually found.
10 When we started this, we were also thinking
11 about this approach to what's clinical
12 significance, what's really meaningful. And if you
13 look in the general psychological literature, it's
14 always things that translate to complete
15 abstinence.
16 So if you look at change of two standard
17 deviations anti-depressant form or something like
18 that, or moving into normative functioning, that's
19 really complicated with cocaine users because, in
20 general, they come in with all kinds of variance in
21 their frequency of quantity of use. So anything
22 that is a change in two standard deviations of when

Page 157

1 they came in is almost always abstinence. It's a
2 huge standard deviation.
3 Reliable change indices, just looking at
4 reductions in frequencies doesn't work very much
5 because, again, we're not quite sure what's a safe
6 level or what's an appropriate level of cocaine
7 use. So this notion of return to healthy
8 functioning that Dan and Raye are talking about I
9 think is fascinating, and I think we're just now
10 getting to be able to have the data that can begin
11 to point us in that direction. And I hope that's
12 one of the goals of this meeting, too, what data
13 can begin to inform finding that endpoint for us.
14 This is what we're looking for in an
15 indicator, and there's a lot of overlap with what
16 Dan talked about. But we want also that's fairly
17 easy to calculate and interpret. I can tell you
18 that no clinician is really impressed with
19 hierarchical linear modelings and the differences
20 in the slopes. It may be great. It may use all
21 the data, but it's not real convincing.
22 So we want it to be psychometrically sound,

Page 158

1 reliable and replicable across trials. We were
2 joking about this last night, but low
3 susceptibility to missing data. You can set it up
4 perfectly, but almost all of our really great
5 measures are almost completely undone by missing
6 data, and we do tend to have a lot of it in our
7 trials.
8 We want something that's verifiable. It's
9 really nice if there's a biological indicator. And
10 we kind of want it to be independent from baseline
11 measures. If severity predicts everything -- and
12 we heard about that a little bit from Kyle, where
13 they come in predicts where they go. We're not
14 really adding much if it doesn't increase our
15 predictive power. It should be clearly sensitive
16 to treatment effects when we've got treatments.
17 They all cost something. Ideally, it
18 shouldn't cost a lot because we have to remember we
19 live in a field that doesn't collect urines. They
20 don't collect urines. We have to predict long-term
21 cocaine outcomes. That's obviously useful. It
22 should relate to indicators of good, long-term

Page 159

1 functioning however we define that in terms of work
2 and so forth.
3 It should be acceptable to the field, and it
4 should be easily interpreted and seen as useful by
5 clinicians, policymakers, and payers. So this is
6 kind of the grail quest for us. And it's going to
7 be hard, I think, to come up with something like
8 this, but it's lovely to begin.
9 We've been talking about this in different
10 kinds of ways, but when you talk to people in
11 general health care, they say, "Your outcome should
12 be easy." Success in treating substance users
13 should be some sort of durable period of
14 abstinence. They should be working -- that would
15 be nice -- or productive in some way, taking care
16 of the kids. They shouldn't be a burden on the
17 criminal justice system and involved in criminal
18 activity.
19 It's always complicated when you look at
20 healthcare utilization because a lot of times when
21 they come in to treatment, they're beginning to get
22 involved in preventative care and ideally using

Page 160

1 hospitalization and emergency rooms less, but not
2 always. I think the only treatment I know -- I was
3 thinking this -- is Ken Silverman's. You get your
4 guys working, and they're not involved in -- you've
5 got it. You probably have the measure of what
6 changes people with your workshop, your contingent
7 workshop.
8 But we also decided to be brave with this
9 and come up with this as a straw man indicator of
10 outcome in substance users. And we found across
11 our -- it's around 450 patients in this combined
12 data set, that this characterizes about 11 percent
13 of our population at the end of treatment, which is
14 really close to your percent of completely
15 abstinent, and 20 percent at the end of one-year
16 follow-up. I hope that's not lying, but that's
17 where it is.
18 I think it's useful -- it's sobering to have
19 this kind of straw man indicator. We often find we
20 can get cocaine use to change because that's
21 actually what we're targeting. Our treatments
22 don't necessarily target employment and criminal

Page 161

1 activity. I think the reasons that some of those
2 measures are insensitive are complicated, as we
3 were just talking about.

4 One of the things that Brian will talk about
5 just a little bit, too, is why not choose complete
6 abstinence from the beginning to the end of trial
7 for our folks, and this was interesting. It's a
8 relatively insensitive measure. It is difficult
9 for most people. It's about 14 percent in our
10 sample of 434.

11 One of the things that we found was that the
12 people who were completely abstinent from the
13 beginning of treatment for the full 12 or 8 weeks
14 were not those who actually had the best cocaine
15 use outcomes as they went through a one-year
16 follow-up. There's something odd about those
17 people. And perhaps if you've got a chronically
18 relapsing disorder maybe using a little bit once or
19 twice isn't the worst thing in the world and
20 learning from it.

21 Again, I've always wondered if you're
22 starting with people who are completely abstinent

Page 163

1 We pay them for their time doing assessments
2 and so forth, and I think we make research contexts
3 more supportive and willing to be there for the
4 patient than some clinical contexts are, sort of
5 the date, notes, data, and a lot of other data
6 suggests that in the clinical context, sticking
7 around is just about everything. And patients
8 leave treatment for different reasons. Some get
9 bored. Some don't like our treatment. Some of
10 them are around for eight weeks, aren't using, and
11 feel like they're cured; they're done.

12 There are philosophical things. If you're
13 only looking at retention, that's problematic
14 because is retention with an ineffective treatment
15 really all that meaningful? And again, we didn't
16 find that it was related to long-term cocaine
17 outcomes in our particular sample as well. So, oh
18 well.

19 Percent negative urines is the big one in
20 our field. We like it. It's widely used. It's
21 accepted. Most people believe in it because it is
22 less susceptible to the demand characteristics and

Page 162

1 and it's not a relapse prevention trial, what are
2 treating? They're already abstinent, so that's the
3 reason it may not be terribly sensitive. I like my
4 abstinence slide. It's hard. It's really hard.

5 So we went through, and we wrote this up in
6 a paper, but when we were approaching how to
7 quantify 15 or 16 different outcomes that we came
8 up with for this project, we just thought about
9 pros and cons for each of them. What's often used,
10 again, in the clinical literature is retention
11 because it's easy. It's really easy to calculate.
12 They're there or they're not, and you can get that
13 on everybody. They're there or they're not.

14 It certainly is an indicator of treatment
15 acceptability. It can be a really nice indicator
16 of differential attrition and data availability
17 across conditions, too, so there are reasons to
18 collect it. It certainly may be meaningful in some
19 context than others. In our research trials, we
20 find it doesn't predict a whole lot because there's
21 a lot going on in the research context that kind of
22 keeps people in.

Page 164

1 misrepresentation of our patients. With
2 quantitative urines, you're certainly able to
3 detect new episodes. And it can be wonderfully
4 accurate if you set it up right with the right
5 timing and there is no missing data. And then
6 when there are missing data, it's really where all
7 hell breaks loose in the field.

8 So timing really is critical. Is it twice a
9 week? Is it three times a week? What do you do
10 about overlaps? And we're going to let Kenzie talk
11 about that tomorrow.

12 This has all been said before, but just to
13 refresh us, for stimulants, it tends to get only
14 recent use only, so 3 to 5 days back. If you're
15 doing quantitative urines, especially 3 times a
16 week, it cost a lot. These kinds of measures are
17 very sensitive to missing data, especially with
18 differential attrition and assuming -- and it's all
19 depending on the assumptions that you make when the
20 data are missing, and I'll get to that in a minute.

21 It's also complicated because you've got
22 urines, and we tend to focus on just the cocaine

Page 165

1 dependence, but a lot of times, I think we're a
2 little less sensitive to as the stimulants go away,
3 what goes up? Does drinking go up? Does marijuana
4 use go up? Is that really a good outcome if you
5 get them to stop using cocaine and they're using
6 tons of marijuana, and alcohol, and other kinds of
7 things.
8 You can't backfill the information that you
9 came with the timeline follow-back. And again,
10 there were all kinds of problems with the
11 assumption that missing is positive. Well, okay.
12 I'll get to that in a minute.
13 Just to show how -- there are tons of
14 examples of this. Let's say you've got a 12-week
15 trial. As often happens, somebody's around for two
16 sessions. They give up one negative urine, and
17 then they drop out. So there's at least 50 ways
18 you could calculate urines for these guys.
19 So if you're based on the number submitted,
20 they're all clean. They were abstinent. That's a
21 winner. Hooray! If you based it on possible, it's
22 50 percent. If you based it on the expected with a

Page 166

1 one time a week collection schedule, it's
2 8 percent. If it was 3 times a week, it's
3 3 percent.
4 So you have to be really careful. And I
5 guarantee you that when we start harmonizing our
6 data sets, this is going to be a killer because
7 everybody does it differently. And we found that
8 even our data managers, who we all thought were
9 doing it the same way, do it slightly differently
10 because those assumptions are really important.
11 Longest consecutive weeks, 3 or more
12 consecutive urines, 3 or more weeks. This is a
13 really, really nice one, too, because I think when
14 you get it, it provides strong evidence of
15 meaningful abstinence. It has all the other
16 advantages of looking at urines. Again, timing on
17 this one is so critical. And this one's great,
18 too -- but it's really, really susceptible to the
19 missing data. If you're missing one in between,
20 you've got this urine, this urine, a missed urine,
21 and then another clean one? Is that three in a row
22 that's clean or what happened when -- when they're

Page 167

1 not around, they're usually using something. There
2 are reasons people don't submit urine.
3 It sounds great, hard to do. Percent days
4 abstinent through self-report. We do timeline
5 follow-back, and it's widely used. And it's
6 wonderful for approaching these kinds of things
7 because essentially what we have is frequency, not
8 quantity, of cocaine use for the 3 months before
9 somebody comes into our trial, the 8 to 12 weeks
10 they were in the trial, and then we have
11 another -- we have a whole year of data on people.
12 You can cut that data up any way you want.
13 It's really highly flexible for these kinds of
14 analyses. And you can also do these true
15 intention-to-treat analyses, which we've done with
16 cocaine users. So we tend to -- we get about
17 80 percent of everyone in the trial and actually do
18 go and find the people who dropped out, which is
19 really nice. And it turns out we can't make that
20 assumption that at the point of dropout,
21 everything's dirty. There are these different
22 trajectories after people drop out. Some people

Page 168

1 drop out because they're doing well. So you really
2 can't make those kinds of assumptions.
3 So our general approach has been to look at
4 our discrepancy rate of percent days abstinent and
5 self-report. Across all of our trials, it's about
6 8 to 12 percent. So if we collect 3,000 urines in
7 the course of a clinical trial and count the number
8 where the urine was positive in cases where the
9 patient did not report cocaine use 3 to 5 days
10 back, it's about 8 to 12 percent. So we've got to
11 have a 10 percent error rate.
12 Sometimes those errors are -- sometimes we
13 have -- we have liars, really consistent liars and
14 really bad liars.
15 (Laughter.)
16 DR. CARROLL: Really, if you look at these
17 things -- we're obsessive about this stuff. But
18 it's interesting. What's also interesting is that
19 rate is somewhat unusual. If you talk to other
20 investigators in the field, their rate of
21 discrepancy of 50 percent. It's really a
22 complicated thing.

Page 169

1 What are we doing that's differently? We
2 have great research assistance. The thing that
3 we're doing, our rate of discrepancy has gone down
4 since we've been using immediate test cups rather
5 than waiting a week to get the urine results, so
6 the patient can be encouraged to self-correct a
7 little bit. That's another complicated thing.
8 But percent days abstinent have all kinds of
9 problems as well with higher differential dropout.
10 The denominator gets really complicated as a
11 percent days of the 12 weeks of the time they were
12 in treatment. It's all about the denominators in
13 these kinds of analyses. And it's not always easy
14 to correct the urine data if the discrepancies are
15 really high. So you can certainly take was the
16 patient abstinent for three or more continuous
17 weeks and self-report. And if there's a dirty
18 urine in there, they're a no. But you can't
19 necessarily correct percent heavy days or percent
20 days of abstinence because you could get one or two
21 dirty urines. Is that 5 days? Is that 10? It's
22 really complicated.

Page 170

1 Maximum days of abstinence overall are in
2 the final 3-4 weeks. We're working at that.
3 That's been nice for us because it has been linked
4 to longer term cocaine use. It's potentially
5 verifiable if the urines are collected at adequate
6 interviews. You can play with this idea of grace
7 period. It's not clear to us yet, and we hope to
8 kind of get back to that.
9 So we seem to get a signal around this 3 or
10 more weeks of continuance abstinence that Frank
11 Gawin made up umpteen years ago. And it's not
12 clear if it matters to the end of treatment or at
13 some point during treatment. But again, it's
14 really complex when you've got missing data and
15 you've got discrepant urine, which we always do.
16 Are we counting? When you talk about end of
17 treatment, is it end of the patient's time in
18 treatment where you have more data or the end of
19 the actual trial where you have less data? It's
20 complicated.
21 Reduction in use, frequency and quantity.
22 This is something that I think we have to dive in a

Page 171

1 bunch of different ways. It is a nice alternative
2 to abstinence. It may be a more achievable target
3 for people. It's also nice because it's really
4 compatible with those lovely random aggression
5 models over time. It may be sensitive to
6 treatments that take a little more time for the
7 effects to emerge. You can get your grace period,
8 and you can also easily dichotomize that kind of
9 thing, too. So you can lay a percent reduction use
10 or the percent of people who get to a 75 percent or
11 a 50 percent reduction in use.
12 As we start playing with it, it's really,
13 really complex because we can't get really good
14 quantitative measures, especially with that
15 baseline period. We don't know what people were
16 doing, in general, the three months before they
17 came to us, and they don't remember real well
18 either. And then, when are you looking for that
19 reduction? Again, in the last weeks, over the
20 entire course? So we could easily get up to 50 or
21 60 different ways to cut the data here, and we
22 certainly don't want to do that.

Page 172

1 With stimulant users, some of the things we
2 tripped over, just defining what we want in
3 reduction is really complicated because the
4 patterns of use in stimulant users vary so widely.
5 We've got these huge bingers who can go forever
6 without using, and you get some low-level users,
7 maybe the people who are self-medicating and
8 attention problem, who use a little bit every day.
9 It's really, really hard -- this came up in
10 Dan's question. Getting these reliable estimations
11 of quantity is just really, really complex. We
12 don't have a standard unit of cocaine. It's an
13 illicit substance. Dealers don't exactly hand them
14 out in standard units. There's all kind of
15 adulterants. The potency varies. The language is
16 really, really complicated, and it can't convert to
17 a dollar value because there's sex for drugs.
18 People share drugs. It's illicit. It's tough.
19 Again, that's where quantitative urines really
20 help, but that's complicated, too.
21 One of the things that we really wanted to
22 do as we were jumping into the status, that was

<p style="text-align: right;">Page 173</p> <p>1 come up with a nice dichotomous indicator. We know 2 that they're not -- the continuous measures are 3 more powerful for all kinds of reasons, but we 4 guessed at what some reasonable candidates would 5 be, based on the lurcher in cocaine use, alcohol 6 use, smoking and so forth. So we looked at things 7 like complete abstinence, 3 or more weeks of 8 abstinence, end of treatment abstinence, reduction 9 of X percent. And then we had that little straw 10 man of good enough functioning. Are they abstinent 11 at the end of treatment? Are they working? Are 12 they not in jail, kind of thing.</p> <p>13 So this is the beginning of the paper that 14 Dr. Strain's journal was kind and generous enough 15 to take because it was so long. Essentially, what 16 we did was take 15 candidate indicators, the most 17 common continuous measures that are used in the 18 field, the dichotomous measures that I just went 19 through, and really talked about them in terms of 20 characteristics that were sort of inherent in the 21 outcome measurement itself, ease of computation, 22 cost, acceptability, and so forth.</p>	<p style="text-align: right;">Page 175</p> <p>1 bring up Celia for the discussion, and then we'll 2 take a few minutes for some questions, and then 3 break for lunch. But this has been really helpful, 4 and I appreciate the plug for my journal as well, 5 which is always appreciated.</p> <p>6 Discussant - Celia Winchell</p> <p>7 DR. WINCHELL: Hello. I'm Celia Winchell. 8 I'm the medical team leader for addiction products 9 at the FDA. I'm going to get us rapidly back on 10 track because I don't have any prepared remarks. 11 So I'll just take long enough to say that I greatly 12 appreciate Dr. Carroll and her group and the work 13 that they've been doing, not just the work that 14 they're doing to explore the data, but what a 15 wonderful job they've done in articulating the 16 problem, both here today and in the published 17 papers.</p> <p>18 If you have not read them, I very much 19 commend them and recommend that you take a look 20 because one of the major lessons I've learned the 21 hard way, through a few years -- it will be 20 this 22 summer -- of being involved in the review of</p>
<p style="text-align: right;">Page 174</p> <p>1 But some of these also -- some of the things 2 that we're really interested in are questions that 3 can be addressed with data, good empirical 4 questions, so relationship to one year cocaine use, 5 sensitivity to baseline variables and so forth. 6 Brian will be talking about that a little bit. We 7 just, I think, wanted to lay out the conundrums and 8 the complexity of doing this kind of work. But 9 it's been fascinating, though. And we are the 10 Knights of the Holy Grail.</p> <p>11 So far, doing this work has also been 12 really, really rewarding and interesting, too. So 13 we've produced a fair amount of data so far and 14 looking forward to do more. That's it.</p> <p>15 (Applause.)</p> <p>16 DR. STRAIN: Thanks, Kathleen. And thanks 17 to you also -- [inaudible - off mic.] I thought 18 that was Monty Python, actually.</p> <p>19 DR. CARROLL: It was Knights of the Holy 20 Grail.</p> <p>21 DR. STRAIN: Is it? Okay, good.</p> <p>22 I would like to, for the sake of timing,</p>	<p style="text-align: right;">Page 176</p> <p>1 protocols for these types of treatments, is that 2 there are a lot of great ideas that turn out to be 3 essentially impossible to operationalize. It's a 4 nice idea to say a 50 percent reduction from 5 baseline, but it's very hard to do.</p> <p>6 So when we think about what is the best 7 endpoint, we think about a lot of things, what 8 would be meaningful to people, what seems like a 9 good idea, and what can we do. Sensitivity to 10 missing data is very important. And the cost of 11 obtaining the data is also important, if we're 12 talking about development of drugs and what 13 industry would be willing to do.</p> <p>14 So if we pick an endpoint that is maybe less 15 sensitive, maybe you lose a little power with a 16 dichotomous endpoint, but you also inure yourself 17 to the difficulties in missing data, or you create 18 a situation where you can adjudicate all the 19 patients, or it's easier to collect the necessary 20 information, and you save some costs that way, and 21 that trade-off might be helpful.</p> <p>22 So as we think about what patterns of drug</p>

Page 177

1 use we can measure proximally that would be valid
2 surrogates for clinical benefit more distally, if
3 we assume we can't do a study long enough to
4 actually observe that clinical benefit, we can also
5 think about those challenges in the clinical trial,
6 the cost, and the difficulty of getting complete
7 ascertainment, and fold those into our discussions.
8 I'll stop there.

9 Q&A - Group Discussion

10 DR. STRAIN: So this talk and discussion is
11 open for questions or comments. I'm going to take
12 the prerogative to begin by just making one point.
13 Well maybe I'll make more than one point. I'm
14 really taken with the idea that the alcohol field
15 is sort of two or three steps ahead. So learning
16 from what's worked and what hasn't worked is
17 valuable from them.

18 In point of fact, Kathy when you made your
19 point about there's a variable use patterns in
20 stimulant users, I found myself thinking, well, oh,
21 gee, that's a problem. And then I thought, wait a
22 second. Alcoholics have variable patterns of use

Page 178

1 as well. So I think that actually, there yet
2 again, is another parallel there that may be useful
3 to capitalize on, and I wondered if you had any
4 thoughts on that page or the more general point of
5 what can be learned from the alcohol field as you
6 think about the stimulants.

7 DR. CARROLL: Yes. I think the most
8 important thing is following your lead, which is
9 being guided by the actual data, that you've had
10 COMBINE. The expert panel approach has been
11 useful. We always come up with these great ideas,
12 but it's going to be so important to just imply
13 empiricism to this. And I think that's the number
14 one thing. And we do have enough trials where we
15 can actually do this, and we can turn clinical
16 wisdom on its head a little bit. It turns out
17 complete abstinence may not be all its cracked up
18 to for the cocaine literature, and I think it
19 looked a little less sensitive for the alcohol
20 literature, too.

21 So can we find our equivalent of no -- I
22 think the approach will be the same, probably not

Page 179

1 the same variables. What's a heavy cocaine use
2 day? No binges are okay? Probably not. Marsden
3 did a trial in the UK where they used a clinically
4 significant -- I can't remember -- the RCI, and
5 then determined that people who reduced their
6 cocaine use 15 days a month was a success. But
7 there are still people using 15 days a month. Is
8 that really a success? It just gets so complicated
9 in our field.

10 DR. STRAIN: Thanks. Other questions or
11 thoughts?

12 DR. FALK: I just had a clarification
13 question. Sorry. This is Dan, NIAAA. When you
14 said urines are quantifiable, I'm really naive what
15 that means exactly.

16 DR. CARROLL: Our urines can be yes or no,
17 so that tells us something about how specified it
18 is, but you can also -- if you get adequate urines
19 and you do quantitative analyses, you can get I
20 think a nice reading in terms of the levels going
21 up or the levels going down, those kinds of things.
22 It sounds great, but it tends to be really

Page 180

1 complicated. And again, it's very expensive to do
2 it. But we can actually see.

3 DR. FALK: Do they tend to do that in most
4 trials? Is it very rare to do that kind of
5 quantitative -- in terms of the data that you're
6 going to find that you have when you look across
7 trials.

8 DR. CARROLL: It was very popular for a
9 while. Kenzie, you know better.

10 DR. PRESTON: I don't think that
11 quantitative analysis of urine results is very
12 common at all. People have done it and then
13 abandoned it. So I think the cost benefit hasn't
14 worked out very well.

15 DR. FALK: Okay.

16 MALE SPEAKER: I think the trials where
17 you've potentially toward a regulatory filing,
18 you'd probably find that it's been done in all of
19 those. That's the minority of the studies. Most
20 are done for publication.

21 DR. FALK: I guess where I'm going, I was
22 wondering what you can do with that quantifiable

Page 181

1 data. Can it become more like a continuous
2 variable, or is it sort of just more like -- I just
3 wonder -- I don't know; it's a kind of rhetorical
4 question -- what more can be done with that than
5 just having a yes/no.
6 DR. STRAIN: Kenzie, do you want to --
7 DR. PRESTON: One of the things my lab did
8 is -- what we found is a huge discrepancy between
9 positive urines and self-report, and so we did
10 quantitative analysis, and we saw that some
11 people's concentrations were going down. But
12 because the cut-offs were positive or pretty low,
13 and they're really designed to catch everybody, not
14 to distinguish level of use, that we developed an
15 algorithm to try to tell when people's positive was
16 due to some recent use or carryover because we were
17 testing three times a week. And in fact, we were
18 able to normalize it so that what appeared to be
19 the real rate of use was somewhere in between urine
20 positives and self-report.
21 You still have -- and I will show some
22 concentration data tomorrow. But the range for

Page 182

1 cocaine -- and we use a cocaine metabolite -- is
2 huge, so you have to -- if you just went with
3 concentration, you have to do transformation of the
4 data because you can end up in the hundreds of
5 thousands nanograms per mL, where the cut-off is
6 300.
7 DR. STRAIN: Dave, did you have a --
8 DR. McCANN: In listening to Raye and Dan's
9 presentation, and then these most recent ones, in a
10 way, we're trying to learn from the alcohol field
11 and use what the successes have been there to help
12 guide us. But there are some real important
13 differences that makes it difficult.
14 One of them, after having set through, is
15 the active meeting group, been meeting for seven
16 years now -- through seven years of meetings twice
17 a year. One of the nice things is, you guys have
18 effective medications. When you start asking how
19 sensitive is this endpoint, you've got data sets
20 with effective meds. And for cocaine addiction, we
21 just don't have that. That's a huge difference and
22 a huge challenge.

Page 183

1 But the other thing, when you consider a
2 non-abstinence endpoint, like no heavy drinking
3 days, that's something that now has been endorsed
4 by the FDA. Patients may go to their doctors and
5 say, I don't want to quit drinking, but I want to
6 reduce my drinking, and it's okay to have that as
7 the goal. But for cocaine addiction, where anytime
8 somebody buys cocaine on the street, it could be
9 anything. A dose could kill them acutely. It's a
10 very different situation.
11 This is a question that I would throw out
12 for the group. Can anybody imagine simply reduced
13 use as being something that a physician would say
14 people should work toward as opposed to, you need
15 to try to quit, and if you can't quit, if you can
16 reduce the use, you reduce it as much. But it
17 seems like the goal of quitting is always going to
18 be there for the physician and probably in our
19 clinical trials, too.
20 So if that's the case, it doesn't mean that
21 a non-abstinence endpoint won't be useful if in the
22 process of trying to quit, we find that a

Page 184

1 medication is able to substantially reduce use.
2 Potentially that could be useful. But I think we
3 need to think about the fact -- am I right in
4 saying it's a fact that it's always going to be the
5 goal to quit? And if that's a big difference, we
6 need to think about that in terms of how acceptable
7 is an endpoint.
8 DR. STRAIN: Thanks. Great. Connie and
9 then Ivan.
10 DR. WEISNER: Just a couple of quick points.
11 One is, on the health policy side, if you're
12 studying treatment populations, that can be
13 charged. Drug testing can be charged. It's like
14 for diabetes, you need to have your insulin tested.
15 So there's no reason for treatment programs to not
16 be doing your end test. Many have to anyway
17 because they have to give the stuff back to the
18 employer.
19 Also again, as Dan and Raye and the group
20 really know, we're not always so sure about how
21 patients are answering drinking questions either.
22 So when we do our expert in primary care, we just

Page 185

1 really have to have the drinking pictures on the
2 wall because people say something differently if
3 they really see what is a drink, what does a drink
4 look like and so forth. So again, isn't it just
5 the -- there's low fuzziness there, so I don't
6 think this research should stop because of that.
7 The last thing I would say, we're
8 still -- even on the alcohol side -- not looking at
9 reduced use by looking at treatments that reach
10 reduced use. We have abstinence-based treatments,
11 and then we look at reduced use. You know what we
12 might really -- there have been a few controlled
13 drinking studies in the past and so forth, but for
14 all of these things, you're right. We have to get
15 buy-in from physicians and other clinicians to look
16 at that. But until we really do that and really
17 develop some treatments that would be focused on
18 that, we can't answer some of these questions, but
19 it shouldn't stop us.
20 DR. STRAIN: Thanks. Ivan?
21 DR. MONTOYA: I have a question. I'd like
22 to know your opinion about -- the DSM-V has three

Page 186

1 categories of substance-use disorders: mild,
2 moderate, or severe.
3 DR. STRAIN: Can you try -- is he getting
4 picked up the mic?
5 DR. MONTOYA: Do you have some thoughts
6 about using those categories as treatment outcomes
7 and maybe trying in the future to test those
8 categories, if they mean anything? Because they
9 were just taken without any valuation, but they are
10 now part of the DSM-V.
11 Any one of you? Kathy, you have all this
12 analysis with different outcomes, but the DSM-V
13 outcome is --
14 DR. CARROLL: As a measure of severity.
15 Those weren't exactly empirically based.
16 DR. MONTOYA: Right.
17 DR. CARROLL: So we can go do that. And
18 again, it's generating the database. It was in
19 fashion for a while to repeat the skid at the end
20 of treatment to see how much movement there was in
21 time, but we didn't do that consistently enough in
22 this to do it. We sort of reinstated that. So we

Page 187

1 intend to do it, but we can't give you an answer
2 yet about how that maps out. By the time we get
3 the answer to that, they'll switch to DSM-VI, I'm
4 sure.
5 It took us 20 years of trials to get the 400
6 people that were clearly described with skids, and
7 we had a year of data on functioning and healthcare
8 utilization. It takes a long time to do it. I'm
9 not saying not do it. I was pointing out the
10 complications.
11 DR. STRAIN: Let me comment. But I think
12 it's an interesting idea going forward because it's
13 out there, and it's widely available, and could it
14 be used as a -- as we think about what should be
15 developed, it's a really appropriate and useful
16 question.
17 Raye?
18 DR. LITTEN: Just a question. In our
19 alcohol trials, we get people coming in that have a
20 goal of abstinence and a goal of just cutting back.
21 We sort of get a mixture. I was just wondering in
22 your trials, does everybody come in for a goal of

Page 188

1 abstinence or do some say I just want to cut back?
2 I was just wondering about that. It would seem to
3 me it might be -- just accept those that really
4 have a goal of abstinence.
5 DR. CARROLL: Right. Those 4 people, that
6 would be great. It's not a lot. One of the
7 advantages of the data set is that we actually had
8 those data. And I think it's -- most people
9 say -- it's 70 percent maybe; I would have to
10 look -- say that their intention and their
11 expectation would be to do that. In turns out to
12 be utterly unrelated to how they actually do. So
13 their stated goal and expectation prior to
14 participating in one of our trials -- it
15 predicts -- people are pushed in for all kinds
16 of -- the heterogeneity is really a complicated
17 thing.
18 DR. STRAIN: Goes back to Connie's point.
19 Kelly, you looked at -- was it the project
20 COMBINE that you looked at pre-treatment drinking
21 goal? Yes. And so it did predict, right?
22 DR. DUNN: It did, yes. Kind of the outcome

Page 189

1 of that paper was that it may be better within the
2 alcohol field to evaluate outcomes in the context
3 of the person's original goal, whether their goal
4 was to maintain abstinence or to just reduce their
5 use.
6 DR. STRAIN: Yes. So another stratification
7 variable, Dave.
8 DR. McCANN: I just thought of that.
9 DR. STRAIN: Yes. We're up to four.
10 DR. McCANN: You're reading my mind.
11 DR. STRAIN: Well, I'm a psychiatrist.
12 I have a question. I know that we're coming
13 up against lunch. It strikes me to go back -- if I
14 follow -- and I'm going to betray my naivete about
15 something here. But if I follow the logic of what
16 was done in the alcohol field, basically, you use
17 the drink as the measure of consequences to
18 establish the value of heavy drinking days as the
19 outcome measure of relevance. Correct?
20 That's critical, just to summarize, because
21 the fact of the matter is, the drink in a short
22 interval doesn't show a significant effect, but

Page 190

1 heavy drinking days does. But your logic is that
2 you've got too short a window in the studies for
3 the drink to show that.
4 Hey. The field has accepted it. You've got
5 a paper that's probably getting cited hundreds of
6 times, right?
7 MALE SPEAKER: I think Connie brought up a
8 good point, though. Maybe it's not just the
9 duration. I don't know if we really know why the
10 consequences are not significant. There could be a
11 variety of reasons.
12 DR. STRAIN: That was the preface to the
13 question, which is does the stimulant field need a
14 drink?
15 MALE SPEAKER: [Inaudible - off mic.]
16 DR. CARROLL: The short of it is there are
17 short inventory problems. You have the SIP [ph]
18 that we use.
19 MALE SPEAKER: I was going to talk with the
20 Lily folks about how IMBIBE was different than the
21 SIP, because the SIP was just kind of the shortened
22 version of the drink, basically, right. So how

Page 191

1 does the IMBIBE -- is it just a different empirical
2 process coming up with that as opposed to the
3 shortened, abbreviated version? Yes, we don't have
4 the consequences measure in stimulant trials.
5 I think to follow up on your point, though,
6 Eric, it also was largely based on the definition
7 of heavy drinking to begin with, of having
8 consequences, right? Dan, Raye, you guys weren't
9 the first ones to come up with heavy drinking day,
10 right? That there was an already established
11 definition for that meant something. And where
12 that cut-off criteria came from, I was going to
13 talk to you guys later about this. I'm a little
14 ignorant about that aspect of it; where did that
15 come from, and how is that somewhere we can use
16 that in a cocaine trial. I don't know if that's
17 impossible. Because it's largely dependent on how
18 the outcome was validated because there was a
19 definition of what's heavy drinking versus just
20 abstinence.
21 DR. LITTEN: I don't know. Maybe Raye -- I
22 wasn't around for that at all. I know 4 or 5

Page 192

1 drinks is probably, what, could be enough to get
2 somebody drunk enough to start experiencing acute
3 consequences perhaps. But I don't know if all the
4 drink items would be -- are necessarily
5 sensitive -- had that in mind that somebody had to
6 be drunk in order to get the consequence. I think
7 probably even a few drinks maybe could trip some of
8 the consequences. I'm not sure what the threshold
9 is.
10 MALE SPEAKER: Well, yes. That goes back.
11 It's sort of a long history how it sort of
12 developed. Even the late '60s, people were
13 suggesting a drink was around 5 drinks or 6 drinks.
14 I think Tom Vaver [ph], back in the late '80s -- I
15 think Hank Kranzler was part of that,
16 too -- pointed out the difference that seems to be
17 a good cut-off for problems.
18 Martha Sanchez, which Celia actually quoted
19 to, looked at a couple studies and found those who
20 had the 5 drinks had problems, those that didn't.
21 Then we started validating this 4 or 5 in
22 recent analysis that I showed today, and it just

Page 193

1 seemed to work out well. And I know Celia's been
2 looking at this, too.
3 DR. WINCHELL: So I'll just add that
4 different cut points were explored. There are some
5 unpublished analyses, regrettably unpublished
6 analyses, that involved sort of diving into the
7 MATCH data set and swimming around, and explored
8 various responder definitions, either based on
9 absolute cut-off, different levels, or percent days
10 abstinent, all kinds of different approaches, and
11 emerged with support for this particular endpoint.
12 Similarly, the analysis of the NAS data set
13 explored a whole lot of different cut points, and
14 kind of converged on this point, that we found
15 those two convergent lines of evidence supported
16 recommendations that we started making a few years
17 ago, and then additional lines of evidence
18 continued to support that from the managed care
19 data set and from the NESARC.
20 DR. STRAIN: Joanne, were you stretching?
21 DR. FERTIG: No, I have a question.
22 DR. STRAIN: Okay. Yes, then we'll break.

Page 194

1 DR. FERTIG: This is going to reveal my
2 naivete, and it's for Celia. Is it really likely
3 or possible that the FDA would approve anything
4 other than an abstinence outcome for an illegal
5 substance?
6 DR. WINCHELL: Well, I'm going to echo what
7 my boss said earlier today, which is --
8 DR. STRAIN: It's always good to echo your
9 boss.
10 DR. WINCHELL: -- we are here to listen to
11 what the field has to say. We also think that the
12 field needs to be aware of what providers, payers,
13 and policymakers think as well because, otherwise,
14 you just sort of wind up preaching only to the
15 choir. But we are here to learn from you.
16 DR. STRAIN: On that note, why don't we
17 break for lunch, and let's reconvene at about 1:25,
18 which means it will be 1:30. But if I say 1:30, it
19 will be 1:35. And lunch is back where breakfast
20 was, down this way. Don't any food in the hallway.
21 I remind you again.
22 (Laughter.)

Page 195

1 DR. STRAIN: Thanks, everyone. And thanks
2 to all the presenters this morning for a great
3 session.
4 (Whereupon, a lunch recess was taken.)
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

Page 196

1 A F T E R N O O N S E S S I O N
2 DR. STRAIN: So we're going to get started,
3 and I'm going to ask Dave McCann to come up. He's
4 going to be moderating this session, which will now
5 go until 3:00. And the title of this session is
6 Prior and Ongoing Efforts to Evaluate Clinical
7 Benefit in Stimulant Trials, Based on Past Studies.
8 So David, I turn it over to you. Thanks.
9 Moderator – David McCann
10 DR. McCANN: We're almost all back here I
11 guess. Within NIDA, we've been working, in a
12 stimulated work, evaluating potential endpoints for
13 a number of years, going back at least four or five
14 years. We had grant supplements available in 2011
15 and gave out three of those to work on existing
16 data sets to really try to go beyond abstinence as
17 an endpoint.
18 In the discussions we've had with the FDA
19 folks, abstinence, especially end-of-study
20 abstinence, being clean at the end of a trial, is
21 accepted as an endpoint. Now, we may still debate
22 how long the period of abstinence needs to be and

Page 197

1 how long the trial needs to be, but for a certain
2 period abstinence, we don't need to prove that it's
3 beneficial. It's accepted that it's beneficial.
4 It's when we get to something other than
5 abstinence, intermittent use or reduced use
6 endpoint, that the message we've gotten from Celia
7 and others at the FDA is we're open to hearing
8 about it, but we're data driven. You need to bring
9 us data that shows us that something other than
10 abstinence has a clinically meaningful benefit.
11 So that's the message that we tried to get
12 out to the field over the past few years, and we've
13 tried to support work to generate data that could
14 drive the FDA, pharmaceutical companies, payer, to
15 be convinced that something other than long-term
16 abstinence is an acceptable endpoint.
17 So out of the four presenters that are
18 coming here, three have worked through grant
19 funding, and Ivan Montoya along with Shou-Hua Li,
20 who's the statistician in our division, spent some
21 time looking at our previous contract supported
22 medication trials to try and pull out data that

Page 198

1 might show clinically meaningful benefit to
2 something other than long-term abstinence.
3 So we'll start out with George Woody.
4 Presentation - George Woody
5 DR. WOODY: Thanks for inviting me. I'm
6 going to present data from one of our NIDA
7 supplements. Unfortunately, I didn't put the grant
8 number or anything up there. It was a supplement
9 to our CTN node, the Delaware Valley Node, one of
10 the supplements that was just mentioned. Then at
11 the end, I'm going to put some data from a study of
12 naltrexone that we did in Iceland, very quickly.
13 The goal of our supplement was to do
14 secondary analysis of data from the NIDA Cocaine
15 Collaborative Psychotherapy Study. This was done a
16 number of years ago. Paul Crits-Christoph was the
17 PI, and the treatments were group drug counseling,
18 counseling plus cognitive therapy, counseling plus
19 supportive expressive therapy, or counseling alone.
20 The secondary analyses were guided by a
21 concept paper by David and Li, who demonstrated
22 that the number of weeks of abstinence during and

Page 199

1 after treatment shows differences in outcome
2 between treatments, even when previous analyses
3 found their differences. So the goal of this study
4 was to evaluate the merits of different methods of
5 measuring end of study -- measuring outcomes using
6 different ways to look at cocaine use, both during
7 this study and measures of overall functioning at
8 follow-up.
9 The design of the parent study, it was six
10 months of counseling with or without psychotherapy
11 treatment, a maximum of 24 group sessions. It was
12 group plus individual. Everybody got 12-step
13 oriented group therapy, and some got additional
14 individual therapy. The counselors were highly
15 screened. We screened them. I participated in
16 this study, trained them in drug counseling
17 according to the manual that's on the NIDA website.
18 Almost 500 patients were randomized. We assessed
19 drug use and overall functioning using the ASI
20 during treatment and up to 12 months after
21 randomization, and urines and self-report were used
22 to assess drug use.

Page 200

1 Here's the patient's sample, 50/50 occasion,
2 African American, most using crack; about a third
3 alcohol dependent; about a third with cocaine-
4 induced mood disorder. This is the attrition that
5 we had follow-up data of drug use, either urine
6 tests or self-reports on 85-90 percent of the
7 subjects. But they kept a little less than half of
8 their psychotherapy sessions, which is pretty much
9 like what we've gotten when we did psychotherapy in
10 the methadone program.
11 Here's our outcome, a surprising outcome.
12 As you see, the hypothesis, adding the extra
13 therapy would help, as we found out with a study in
14 the methadone program. But here, it was the drug
15 counseling that did the best. But everybody got
16 better. And actually surprising was the group drug
17 counseling alone. Excuse me. That's SE therapy.
18 But the group drug counseling alone did pretty
19 well, too. Percent of patients achieving 3 or more
20 months of abstinence; there you see it. Individual
21 drug counseling, again, had more in that group.
22 The questions were what measures during

Page 201

1 treatment cocaine use best predict end of treatment
2 functional outcomes, and drug-use outcomes at
3 follow-up, and functional outcomes at follow-up?
4 We were guided by what David had done. Basically,
5 what you see here, in this series of analyses, are
6 cocaine outcomes predicting 12-month follow-up
7 functioning. The significance, here you see
8 psychiatric -- and all these are fairly low. When
9 they're significant, they're fairly low effect
10 sizes so to speak.
11 But there you see psych was significant.
12 But the most consistent one, actually, was legal,
13 which is why I asked the question about legal
14 outcome earlier, which is not surprising because
15 cocaine's illegal. So those who are using more
16 would be more likely to have legal problems. Also,
17 the psych difference is not surprising because
18 cocaine is psychotoxic. It produces a lot of
19 psychiatric symptoms, so less use is usually
20 associated with less psychiatric.
21 Here we looked at predicting 12-month
22 drug-use outcomes, and basically what we found was

Page 202

1 drug use during treatment-predicted drug use had
2 outcomes, which is pretty much what a lot of people
3 had found. That's what it was.
4 Then we used some of the methods that David
5 McCann and Li developed. We looked at end-of-study
6 abstinence and number of -- 2 weeks here was the
7 threshold. And then we looked at number of beyond
8 threshold weeks of abstinence to see if that made
9 any difference, and basically it didn't.
10 If we looked at within-treatment cocaine
11 outcomes, predicting 12-month drug-use outcomes,
12 basically what you found was within treatment, no
13 matter how you looked at it. Any one of those
14 parameters within use predicted later use. And
15 that was significant in just about all the
16 measures. And if we looked at functional outcomes
17 as they related to these, basically there was
18 nothing predicted. There was just one
19 significance, and that was with employment. But
20 there were so many measures, that could have just
21 been an incidental finding.
22 What we concluded from that, from this

Page 203

1 study, within study, cocaine use measures
2 moderately associated with cocaine-injecting drug
3 use at 12 months. The abstinence measures actually
4 looked best here. And within-study cocaine use
5 wasn't associated with function at 1-year
6 follow-up. And end-of-study abstinence and weeks
7 beyond the threshold, established by David and Li,
8 associated with cocaine abstinence measures at
9 1-year follow-up.
10 So we basically didn't find any gradation,
11 much of a gradation here. From this sample, it
12 looked like the drug use is episodic for these
13 cocaine users. There were relatively few
14 intermittent users, mostly continuous users for
15 abstainers. Some people seemed to functional
16 relatively well despite drug use, and we really
17 couldn't summarize outcome as one successful index
18 in these data. A lot of limitations, a limited
19 number of outcome measures.
20 We really relied on the ASI plus urine
21 and/or self-report. There was a group of complete
22 abstainers, so there was a somewhat restricted

Page 204

1 range of outcomes, and patients with psychiatric
2 comorbidities requiring psychotropic medications
3 were excluded.
4 Just a few comments on this Iceland study
5 with naltrexone. If anybody's never been to
6 Iceland, I would really recommend it as a place to
7 visit. It's a very, very interesting place. And
8 we wanted to see if we could see not excessively
9 replication I guess, but a signal that naltrexone
10 worked for amphetamine users because at the time we
11 did this, amphetamine use was a big problem up
12 there.
13 The study that we based on was something
14 that was published from Sweden in the American
15 Journal of Psychiatry. And there they found
16 that -- and this was oral naltrexone with or
17 without -- everybody in drug counseling, with or
18 without oral naltrexone, and there you found a
19 significant less positive urines in the naltrexone
20 group.
21 This study -- and we're working on a paper
22 writing this Iceland study up. You really

<p style="text-align: right;">Page 205</p> <p>1 can't -- we sort of thought of this, well, it's the 2 same group. It's a Scandinavian group. They're 3 genetically similar. But the patients in this 4 population were real -- there's a different sample. 5 These patients were very carefully selected, 6 people who were only amphetamine dependent. They 7 rejected three-quarters of the people that they 8 screened. They had no alcohol dependence. No 9 dependence on any other drug except nicotine, and 10 they had to demonstrate two weeks worth of negative 11 urines before being randomized into this study. So 12 they really focused down on pure amphetamine 13 dependence. 14 In Iceland, our population was very 15 different, as you'll see in a minute. Also, from 16 what I've seen, they've got the best treatment 17 programs that I've ever seen. They have 18 centralized addiction treatment. Everybody gets 19 hospitalized before starting treatment. Good 20 access treatment's free. This is a hospital. The 21 population endorses the disease concept. They feel 22 that addiction is a health problem, not a legal</p>	<p style="text-align: right;">Page 207</p> <p>1 Three-quarters are alcohol dependent, cannabis 2 dependence, cocaine. There was a lot of other drug 3 use among this group. This was a heavy drug-using 4 group. Very little opioid dependence. That was an 5 exclusion criteria, but there's very little of that 6 in Iceland. 7 This was retention in the study treatments, 8 as you see, and that is getting the Vivitrol 9 injections. And here, we've got urines. We've 10 gotten a total of 2400 urines on this entire 11 sample. We got a little over 1200, a little bit 12 more than half. And look. Of the 1247 urines, 13 only 53 were positive for anything. A statistician 14 looked at that. Kevin Lynch didn't believe they 15 were amphetamines addicts because that's a very low 16 rate. But then, if you impute missing urines as 17 positive, that's what you get there. 18 So it looked like about half the patients 19 were doing pretty well, and those were primarily 20 the ones that stayed in treatment. And this is the 21 percent of drug-negative urines, amphetamines. 22 Benzos were the most common, but it was very low</p>
<p style="text-align: right;">Page 206</p> <p>1 problem. The staff, to be certified as a 2 counselor, you have to pass a national exam after 3 two years of training. And they really use 4 evidence-based practice. 5 That's just a summary. Detox first, 7 to 6 10 days in the hospital. And then they either go 7 to residential or directly to IOP with follow-up 8 outpatient. 9 We randomized 100 people primarily seeking 10 problems for amphetamine dependence, randomized to 11 Vivitrol or Vivitrol placebo. Alkerme's provided 12 the medication free of charge, and we're very happy 13 about that, stratified by gender and IV status. 14 And they were randomized before they went to the 15 outpatient treatment because remember, some went to 16 residential and then outpatient, and others went 17 directly from Vogur to outpatient. 18 The population is really different than the 19 population in the Swedish study. They were all 20 dependent on amphetamines, and they were averaging 21 using a little over 18 days a month, a little bit 22 more than the Swedish group. But look at that.</p>	<p style="text-align: right;">Page 208</p> <p>1 across the board. 2 So really, we didn't see anything. We 3 didn't see a signal of a naltrexone effect. There 4 could very -- if we looked at a more restrictive 5 sample, perhaps, like the Swedish did maybe, we 6 would have seen it. We have not analyzed the data 7 as per -- McCann and Li will be doing that. 8 That's just a little overview. We're going 9 to have trouble analyzing the data according to Li 10 because we are missing a lot of follow-up data on 11 people that dropped out of treatment. A 12 contributor to that is that the Icelandic IRB would 13 not approve patient payments to come back for 14 treatment. They said, look, they're getting 15 treatment free. It's a national policy. Because 16 we wanted to put patient payments in to get them to 17 come back, but it couldn't get through their IRB if 18 we put that in there. 19 We do have some follow-up data from 20 telephones and self-report and all that kind of 21 stuff, but we're going to have issues with that. 22 But that's something we're going to be working on.</p>

Page 209

1 So that's what I have to present. Thanks.
2 DR. McCANN: Just a couple of questions
3 (inaudible - off mic.) I can start it off. For
4 the Vivitrol study in Iceland, I actually saw those
5 data presented a year and a half ago. I got to
6 apologize for my memory. So I need to ask, did you
7 look for any correlation between amount of
8 amphetamine use in these subjects and some other
9 endpoint to look --
10 DR. WOODY: Yes. We will be looking at
11 that. Craving went down. What I have is craving
12 went down, again, in the people that stayed in
13 treatment. We haven't drilled down on that. One
14 of the things that's been a delay is that we have
15 all the data, but they were originally entered into
16 the database in Iceland, and there were issues
17 getting it correctly moved over to us. So we're a
18 little slow in that.
19 DR. McCANN: Let me encourage others, if you
20 have any questions about the first part of the
21 presentation on the cocaine data and looking for
22 evidence of a meaningful benefit to reduce use,

Page 210

1 this is an opportunity. I thought it would be good
2 to go through some of the presentations, even if we
3 didn't have clear findings to support a clinical
4 benefit to something other than abstinence, so that
5 we could ask exactly what was looked at. I
6 encourage you to suggest other ways of looking at
7 the data that we might consider.
8 DR. MOELLER: I have a question over here.
9 Gerry Moeller. Did you look at potential ER
10 visits? We were talking about this earlier. This
11 is an aging population for the cocaine use. I see
12 a lot of patients on the inside of the hospital
13 who've had cardiovascular complications with
14 cocaine use. And each episode of use is
15 potentially a risk factor for those complications.
16 So did you look at that?
17 DR. WOODY: We looked at other treatments
18 received. Some patients did receive treatment
19 outside the study. ER visits are probably in
20 there, but I'd have to double-check. I don't
21 remember. I doubt if there are too many ER visits.
22 There were readmissions, and the readmissions would

Page 211

1 come to Vogur Hospital.
2 We have that. But again, we're sort of slow
3 in getting this out because of some issues with the
4 translation of the databases, not just from
5 Icelandic to the U.S., but the guy that did it in
6 Iceland was like a self-taught data entry guy. And
7 he got it all in there, but it was a little hard
8 for us to make sure it was in our format.
9 Yes?
10 MALE SPEAKER: For the first two trials, it
11 looked like you had a treatment effect. Did you
12 compare the sensitivity of all the different
13 outcomes among -- like effect size for all the
14 different outcomes to see if they had different
15 effect sizes, basically.
16 DR. WOODY: I'm not sure. It looked
17 like -- with the cocaine psychotherapy study, it
18 went -- everybody got better. Everybody went down.
19 You did have that significant difference
20 between -- and the others.
21 MALE SPEAKER: On that outcome, you had the
22 Y-axis -- I forget what the outcome is. Maybe it

Page 212

1 was percent negative urines. I forget what the
2 outcome -- the Y-axis. But you could reproduce
3 that same graph with a bunch of different outcome
4 measures and see if it kind of replicate -- well,
5 maybe not that same graph, but you could see if the
6 treatment effects were similar if you used
7 different outcomes. It could be a way to sort of
8 just test the sensitivity of different outcomes.
9 DR. WOODY: Yes. Okay. Thanks.
10 DR. STRAIN: Thank you.
11 (Applause.)
12 DR. McCANN: Our next speaker, Brian Kiluk,
13 did some work with Kathleen Carroll, and we're
14 really excited to see what the results of some of
15 the analyses were related to the cocaine use.
16 Presentation - Brian Kiluk
17 DR. KILUK: Hello, everybody. We'll be
18 talking about the work that I've done with Kathy as
19 a result -- the NIDA supplement that we received.
20 Kathy set up some of this in her talk, at least
21 discussing the indicators that we decided to look
22 at, as well as the challenges with defining each of

<p style="text-align: right;">Page 213</p> <p>1 those indicators. So I'm not going to go over 2 those. 3 Basically, what we did was we evaluated 4 these 15 candidate cocaine-use treatment outcome 5 measures after pooling the data across five 6 completed randomized trials for cocaine dependence. 7 We evaluated them according to criteria in terms of 8 sensitivity to medication effects, sensitivity to 9 the behavioral therapy effects, correlations or 10 relationships with post-treatment cocaine use, so 11 during the follow-up period, as well as to measures 12 of general functioning, which Kathy kind of talked 13 about, our straw man measure of general 14 functioning. And this was published last year. 15 The first portion of this, the data that I'm going 16 to go over here was published in drug and alcohol 17 dependence. 18 These are just a list of the five trials 19 that were included, that were all completed, 20 studies that have been published on. The last one 21 is currently under review, but studies that have 22 been conducted over the last 15-plus years.</p>	<p style="text-align: right;">Page 215</p> <p>1 self-reported at least, was the Substance Use 2 Calendar, which is essentially the timeline 3 follow-back, a calendar-based method. For that, we 4 can get a day-by-day frequency of cocaine use 5 during the entire study. I think some of the 6 earlier studies, we tried to gather information on 7 the quantity of cocaine use, but by and large, we 8 didn't have that across all. So we're really just 9 looking at the frequency of cocaine use. 10 As Kathy mentioned, there was some 11 discrepancy with urines, although that was pretty 12 low. On average, I think it came out to around 13 13 percent, although largely, that number was 14 driven by some of the earlier studies where we used 15 a laboratory for testing urine. So rather than 16 getting the instant result, which decreased the 17 rate of discrepancy, some of the earlier studies 18 had a bigger discrepancy. But overall, a fairly 19 low rate of discrepancy between self-reported 20 cocaine use and urine results. So that would be a 21 positive urine with a denial of self-reported 22 cocaine use in the three days prior to that urine.</p>
<p style="text-align: right;">Page 214</p> <p>1 The nice thing about all these trials is, 2 since it's within the same research group, we have 3 common assessment batteries and all and a common 4 assessment approach. Almost all of them, 4 out of 5 the 5, included a 12-week treatment phase. One of 6 the trials was only an 8-week study. That was the 7 computerized CBT trial. 8 Virtually, all looked at some sort of 9 behavioral therapies. The behavioral therapies 10 were manual guided with independent fidelity 11 ratings, medications, were placebo controlled. 12 Urine testing ranged from 1 time a week to 3 times 13 a week, depending on the study and the setting. 14 All of the trials included a follow-up 15 period that assessed substance use as well as other 16 measures up to 1 year. So 4 out of the 5 trials 17 included a 12-month follow-up period, where the one 18 trial that was only an 8-week study only included a 19 6-month follow-up. But we essentially have data 20 for most -- up to 15 months from the time of 21 randomization. 22 Our primary measure for substance use,</p>	<p style="text-align: right;">Page 216</p> <p>1 We have good rates of follow-up, greater 2 than 80 percent on the intention-to-treat sample 3 across the studies. One of the common assessments 4 that we used across all the studies was the ASI, so 5 we had some nice data there on the ASI. 6 In terms of during the follow-up period, we 7 were able to calculate mean days of cocaine use at 8 each of the follow-up time points, using a 9 substance-use calendar. One of the additional 10 measures we chose to look at was complete 11 abstinence through the entire follow-up period. So 12 again, this would be based on self-report as well 13 as at least a clean urine at the moment of the 14 assessment. 15 Then we also wanted to look at some measure 16 of global functioning or good functioning, what we 17 termed initially -- there are a couple of different 18 labels for it, but it ended up being called our 19 good outcome or good enough outcome. So this was 20 based on looking at the ASI. And rather than 21 evaluating the composite scores from the ASI, we 22 chose to use a bit more of a patient-reported, I</p>

Page 217

1 guess, outcome, just looking at the days of
2 problems across each of the domains on the ASI.
3 So we selected the ones that we thought
4 might be most salient, which would be days of
5 employment problems, days of legal problems, and
6 days of psychiatric problems. So if everybody had
7 reported zero days across all of those, as well as
8 had zero days of cocaine use, if they met that
9 criteria, we considered that a good outcome or good
10 enough outcome.
11 I'm going to breeze through some of these
12 next few slides. This is just to give an overview
13 of what the studies included in the data set look
14 like. Study 1 was a 3 x 2, included clinical
15 management, 12-step facilitation and CBT, as well
16 as either disulfiram or no med, with 121 cocaine-
17 and alcohol-dependent patients.
18 Study 2 was CBT versus interpersonal
19 therapy, and included again, disulfiram versus
20 placebo with 121 cocaine-only dependent patients.
21 So these didn't also have comorbid alcohol. So
22 this was again, a 12-week trial.

Page 218

1 Study 3 was another 12-week trial. This one
2 evaluated treatment as usual versus treatment as
3 usual plus 12-step facilitation, again, with either
4 a disulfiram or placebo. It was 112 cocaine
5 dependent. And these were patients on methadone
6 maintenance, so this sample is a little bit
7 different than some of the rest, but still,
8 cocaine-dependent and actively-using participants.
9 Study 4 was our pilot trial of the
10 computerized CBT. This was just a two-group study
11 looking at treatment as usual versus treatment as
12 usual plus the computerized CBT. This trial was at
13 an outpatient substance-use facility and took sort
14 of all-comers, any kind of drug use. And for the
15 current analyses, we only included those that were
16 primary cocaine users. So it's 38 out of the 78
17 participants that are included in this pooled data.
18 The last study was a CBT versus CBT-plus
19 contingency management, again, with a disulfiram
20 placebo platform on that. That's included in 99.
21 Just a general overview of the trials in
22 terms of what the sample looked like. Down here,

Page 219

1 we kind of have the total, so we ended up with 434
2 participants across the trials that had some data
3 during the 12-month follow-up period. About a
4 third were female. Roughly half, ethnic
5 minorities. Mean days of cocaine use at the time
6 of baseline -- so the month prior to starting the
7 study -- was 13 days out of the last 28. About
8 half of them were not working, and 16 percent were
9 referred by the criminal justice system, although
10 there is some variability across the studies here.
11 In terms of just general outcomes across the
12 trials, just so everybody gets a sense of what the
13 outcomes look like in this data, we see the rates
14 of percent of cocaine-free urines across the study.
15 They're generally pretty consistent, although the
16 12-step disulfiram study, which was in the
17 methadone maintain sample, which seems to be a bit
18 of an outlier here -- but the rest are fairly
19 consistent, percent days absent and during
20 treatment range was in the 70's to 80's, although
21 except for that third study.
22 Percent completely abstinent during

Page 220

1 treatment, we see it's not zero. So there are a
2 small proportion of people that were completely
3 abstinent during the treatment period. And then
4 here's data on our 6-month follow-up, so the
5 percentage of people that achieved that
6 good-outcome criteria. Initially, when we came up
7 with the variable, we weren't sure if anybody would
8 actually meet that criteria. So it was kind of
9 surprising that we did have some people that
10 actually achieved that. So they were not using
11 cocaine, and they reported no problems in legal
12 employment or psychiatric areas.
13 So what we did is we took these 15 candidate
14 indicators, and then evaluated them to whether they
15 were able to detect medication effects. Since the
16 disulfiram was the main medication used across the
17 trials, we were able to see whether they were
18 sensitive to detect effects across these
19 indicators.
20 I realize there's a lot of data on here, so
21 I've just tried to highlight the things or direct
22 your attention to those things that are

<p style="text-align: right;">Page 221</p> <p>1 highlighted. The indicators that seemed to come 2 out here, at least be able to detect the effect of 3 disulfiram in this case, we have days retained in 4 the treatment protocol, maximum consecutive days of 5 abstinence, so several of the continuous indicators 6 that have been discussed already, percent days 7 abstinent. 8 Some of our included dichotomous outcomes 9 that weren't detecting effects, people that 10 achieved at least a certain number of weeks of 11 abstinence during the course of the study, and we 12 have some reduction measures here, too, achieving 13 at least a 50 percent reduction versus a 75 percent 14 reduction. 15 I would state that our reduction measure is 16 fairly crude because, again, we didn't really have 17 quantity, so essentially we were looking at the 18 days of use. So we're comparing the days of use 19 prior to starting the study to the days of use in 20 the last month of the study. And that achieved at 21 least a 50 percent reduction of a 75 percent 22 reduction.</p>	<p style="text-align: right;">Page 223</p> <p>1 Relationships with whether individuals were 2 completely abstinent during the follow-up period, 3 and then the relationship with whether people 4 achieved a good outcome at each of the follow-up 5 points. 6 The shadings represent significance, so 7 anything that's not shaded was a non-significant 8 correlation. The lighter gray was considered a 9 lower -- it's significant but a magnitude of 10 correlation less than .3, and then the darker grays 11 were magnitudes greater than .3, so just to give a 12 highlight of some of the stronger relationships. 13 You can see the darker areas here. Again, the 14 continuous variables seem to come out at least 15 predicting or related to follow-up drug use, 16 cocaine use during the follow-up period. 17 Our indicator of 3-plus weeks of abstinence 18 seems to show that as well. Interestingly, the 19 ones that weren't showing up very much was the days 20 retained in the treatment protocol wasn't related 21 to much post-treatment cocaine use or good 22 functioning, as well as some of our reduction</p>
<p style="text-align: right;">Page 222</p> <p>1 So we have some indicators that can detect 2 medication effects. Here it is looking detection 3 of effects of behavioral therapies, again, some of 4 the same indicators come up here, the continuous 5 indicators, percent days of abstinent, proportion 6 of cocaine negative urine samples here. And then 7 some of our dichotomous indicators, particularly 8 the 3-plus weeks of abstinence, so achieving at 9 least 3 weeks of abstinence, I was able to detect 10 effects of the behavioral therapies. 11 Our good outcome here actually was kind of 12 lit up on this one as well, so people at the end of 13 the trial achieved that criteria for good outcome. 14 That differentiated across the behavioral 15 therapies, too. 16 Another slide with a ton of data on it, and 17 I'll just try to summarize this. This is an 18 important one, which is where we -- again, the 19 15 outcome indicators here, evaluating them 20 according to their relationship with post-treatment 21 cocaine use. So the days of use at each of the 22 follow-up points, 1, 3, 6, and 12 months.</p>	<p style="text-align: right;">Page 224</p> <p>1 measures. And again, our reduction measures were 2 pretty crude, so we kind of had a -- they were kind 3 of behind the curve, behind the ball on that one. 4 This just summarizes what we've found in 5 these evaluations. So again, thinking about our 6 criteria of sensitivity to disulfiram effects, or a 7 medication effect. Sensitivity to the behavioral 8 therapies; relationship with post-treatment cocaine 9 use; and then relationship to general functioning 10 during the post-treatment period. An X indicates 11 that that criteria was met. 12 I've highlight the ones which I think are 13 important, and red indicates ones that just didn't 14 perform very well in our analyses, in our data set. 15 So days retained in the treatment protocol, 16 achieving at least one week of abstinence during 17 the treatment period; or again, as Kathy mentioned 18 in her talk, being completely abstinent during the 19 treatment period was, again, sort of a surprising 20 one that wasn't associated or didn't detect any of 21 these effects, as well as the 50 percent reduction. 22 Ones that seemed pretty strong was the</p>

<p style="text-align: right;">Page 225</p> <p>1 abstinence in the last two weeks of treatment. 2 Again, that was one that we evaluated, which was of 3 interest, and this dichotomous outcome of achieving 4 at least three or more weeks of abstinence. And 5 that three weeks is at any time during the 6 treatment period, not just at the end. 7 As a follow-up to this, one thing that we 8 decided to look at was thinking about the 9 relationship between within-treatment cocaine use 10 and follow-up, functional outcomes. So as opposed 11 to just looking at this dichotomous of zero days of 12 problems across several areas on the ASI, we wanted 13 to be able to look at a more continuous way of 14 looking at those by using some latent growth curve 15 models to see if within-treatment cocaine use had a 16 relationship with the change in these problems over 17 time during the follow-up period. And this came 18 out last year in JCCP, for those who are 19 interested. 20 Just to describe it, our global problems 21 construct, again, we created this latent measure of 22 global problems, again, using the item from the</p>	<p style="text-align: right;">Page 227</p> <p>1 might come in with more problems in the employment. 2 So these latent constructs are accounting 3 for that. And that's taken it into account rather 4 than looking at each one individually, where you 5 might have people that don't have any employment 6 problems, this accounts for that. 7 Our within-treatment cocaine use measure 8 here, we actually looked at this two different 9 ways, one of which was a latent construct, which 10 was indicated by three continuous measures: the 11 percentage of days abstinent, the maximum 12 consecutive days abstinent, and the percentage 13 of -- this was positive cocaine urines. 14 Just to highlight, this was our 15 within-treatment cocaine use indicator. What we 16 found is that was related to post-treatment cocaine 17 use, which was significant, which is great, which 18 is what we kind of saw in some of the earlier 19 stuff. The post-treatment cocaine use, so the 20 cocaine use during the follow-up period was related 21 to the overall average problems during the 12-month 22 follow-up period. So same period of time here.</p>
<p style="text-align: right;">Page 226</p> <p>1 ASI, which was the patient reported days of 2 problems across each of the domains on the ASI, 3 except for cocaine or alcohol use, so the non-drug 4 using domains. Several steps we utilized here to 5 confirm the construct as well as evaluate using 6 conditional latent growth curve to examine the 7 association between within-treatment cocaine use 8 and to follow-up global problems over time. 9 This is our spider-web looking model, which 10 I realize probably isn't very useful to anyone 11 outside of this room or to some people who are in 12 this room, but I'll walk you through it because I 13 think it is important. 14 Across the top here is our latent measure of 15 global problems at each of the follow-up time 16 points. Again, these are indicated by the six 17 domains on the ASI days of problems. I think the 18 important thing to note about this is that rather 19 than just evaluating each of these domains 20 separately, this is accounting for some of the 21 variability. So some people might come in with 22 more problems in the legal aspect versus some that</p>	<p style="text-align: right;">Page 228</p> <p>1 Cocaine use is associated with more problems. 2 But interestingly, then, the 3 within-treatment cocaine use was actually also 4 related to this average level of global problems 5 during the follow-up period, so greater abstinence 6 was associated with fewer problems, and that was 7 significant. And this is also controlling for the 8 baseline level of problems, so it's not just that 9 people have the same problems coming in. 10 This was actually replicated with the 11 dichotomous outcome of just 21, 3-plus weeks of 12 abstinence, so we looked at that, the same 13 essential pattern here, similar coefficients, 14 similar pattern of significance, suggesting that 15 abstinence during the treatment period was 16 associated with fewer global problems. 17 Now it wasn't related to the slope, and this 18 is likely because there was very little change in 19 the number of problems or the days of reported 20 problems over the course of the 12-period. It was 21 more so kind of a stable aspect. So we may have 22 seen more changes during the treatment period that</p>

Page 229

1 were just sort of maintained during the follow-up,
2 but which is the reason why we're thinking it
3 wasn't related to the slope, which wouldn't account
4 for the change in problems. It was pretty stable.
5 To summarize so far, what we found from our
6 data was that the existing widely used continuous
7 measures seemed to be consistent predictors of
8 cocaine use and general functioning during the
9 follow-up period. Again, the positive ones were
10 percent days abstinence, the maximum days of
11 continuous abstinence during the course of the
12 study, percent positive urines. We've also looked
13 at it as percent negative, which is what we're
14 using more recently. And then days of abstinence
15 in the last 2 weeks also seem to be pretty positive
16 as well.
17 There was good performance of the urine
18 measures and abstinence at the end of treatment.
19 But again, it has to be taken into account with the
20 availability of data and all the issues that Kathy
21 described earlier with what do you do with missing
22 urines or when people drop out, and you're looking

Page 230

1 at an end-of-treatment measure. How do you
2 calculate that and how do you determine that? So
3 there's lots of issues with that.
4 Measures that seemed to perform a bit poorer
5 or at least in our data, again, were those
6 reduction measures, which I mentioned. We don't
7 really have a great way of looking at production,
8 at least in our data. And that's something that
9 we're still trying to figure out and work through
10 now to see if we can come up with a better way to
11 look at reduction over the course of time, rather
12 than just looking at the frequency of days of use.
13 But it's problematic.
14 Complete abstinence during treatment; this
15 is another one that we're still trying to chase
16 down to understand. Kathy gave the explanation
17 earlier that maybe there is some benefit to having
18 a use or a slip during the course of treatment that
19 people learn from. We found that the people that
20 were abstinent during the entire treatment period,
21 that wasn't associated with their abstinence during
22 follow-up.

Page 231

1 We looked at this, whether this was related
2 to people who were coming into treatment who were
3 referred by the legal system, so maybe they had
4 some external pressure to be abstinent during
5 treatment. But once that legal requirement was
6 resolved, maybe they returned. That didn't come up
7 so well. That was a good thought, but that didn't
8 prove correct. So we're still trying to chase down
9 that complete abstinence, but we do think there is
10 some potential benefit to having a use during
11 treatment that people learn from.
12 The end-of-treatment abstinence and the
13 3-plus weeks of abstinence seemed to be pretty
14 consistent predictor. This might be a direction to
15 kind of move in, and it's one thing that we're
16 looking at more of to see if we can evaluate this
17 in some other trials and other data sets to see if
18 we're finding the same results because this could
19 be a direction to go in. And then again, the
20 higher levels of cocaine abstinence during
21 treatment were associated with fewer problems.
22 So this is something -- we also wanted

Page 232

1 to -- a path we want to go down so that way we're
2 meeting the requirement or the notion that there is
3 some clinical benefit associated with these
4 measures of abstinence. It's not just reduced use
5 without any functional benefits. That's it.
6 (Applause.)
7 DR. McCANN: As the moderator, my threshold
8 for falling behind is one complete presentation.
9 So we're now 15 minutes behind. I think we can
10 hold questions now and ask them during the time
11 we've set aside for that for everyone. And I'm not
12 going to bother taking the time to walk up there.
13 Dr. Shengan Lai, to go along with the
14 previous Monty Python analogy, now for something
15 completely different. This is not reevaluation of
16 data from a treatment trial, but really a truly
17 novel way to look at consequences of cocaine use.
18 Presentation - Shengan Lai
19 DR. LAI: Good afternoon. I'm new here. I
20 don't know anything about the drug treatment. I
21 got really scared. But I tell you, everything I
22 did right now I owe Dr. Skolnick a lot because when

Page 233

1 I learned my data, I thought I got it trashed.
2 Although the paper published, I didn't get anything
3 out. But he said that this is a treasure. I
4 report to you.
5 I could be wrong [indiscernible - mic
6 interference] -- everybody knows. NIDA, the
7 founding study -- the FDA has not approved any
8 medications for treating cocaine addiction in
9 humans. And FDA accepted the self-reported data
10 for the heavy drinking days, but they don't accept
11 the concept, the days of heavy cocaine use.
12 Basically, the bar is much higher. They need a
13 period of abstinence that last through the end of
14 the trial.
15 FDA believes that cocaine use, behavior is
16 only a surrogate indicator for risk of health and
17 the behavior problems. That's why we need to
18 target health risks associated -- potential disease
19 markers. With NIDA to support it, we have enrolled
20 and followed up 1500 African Americans in Baltimore
21 for 14 years with a very low follow-up. The
22 dropout rate is less than 3.5 percent per year.

Page 234

1 Everybody had the CTE. There's a contract
2 in-house, the CT angiography, and we know every
3 detail for the heart condition, the arteries.
4 Part of the study participants had an MRI to
5 measure the left -- region of dysfunction. We have
6 lab data. We have lots and lots of lab data. For
7 example, recently we did an analysis, a
8 [indiscernible] analysis. The [indiscernible] size
9 is 1429. After adjustment for tool 13C,
10 ECCEHA [ph], the cardiovascular risk, cocaine use
11 was significantly associated with subclinical heart
12 disease, but actually it was not. I would get
13 these two papers out as soon as possible.
14 The objective of this study, the current
15 study, we have three objectives. Number one,
16 whether cocaine abstinence leads to less
17 endothelial damage. Second is we explored whether
18 cocaine abstinence retards coronary plaque
19 progression. Probably the FDA likes that. And
20 third, whether reduction in cocaine use leads to
21 less endothelial damage in African Americans.
22 Crack cocaine users with contract -- enhanced CT

Page 235

1 angiography confirmed less than 50 percent coronary
2 stenosis. What do we want to see -- this is
3 progression. Less than 50 percent stenosis is
4 minor. When they cross the line above 50 percent,
5 they call this significant stenosis. The
6 cardiologist has to take over.
7 In March and April last year, we recruited
8 38 cocaine users. It took one year it
9 took -- CCRC [ph] approved this study. This is
10 criteria. We recruit everybody for ongoing study,
11 and they have to confirm they are cocaine users.
12 They have a urine test to confirm they did use
13 cocaine. As clinical criteria, we don't want
14 anybody with clinical heart disease. We don't want
15 pregnant women in this study. We want people with
16 good kidney function, to be approved of course.
17 We did an interview. I know time is running
18 out. We did an interview, and like everybody, we
19 have markers. We want the people to stop using
20 cocaine. We pay them. We pay them to stop using
21 cocaine. That's why CCRC will not say, look,
22 you're going to create huge trouble for university.

Page 236

1 It took a year or two to get approved. It's worth
2 it. We did the urine test using the Dip Card, and
3 we did the CT angiography.
4 I show you the results. Right now, we have
5 74 people enrolled. The first two months, among 38
6 people, 22 people finished the study over a 6-month
7 period, baseline to 6 months. We have data. We
8 have data for the median of [indiscernible], and we
9 have all other data, and I tell you what happened.
10 This is baseline characteristics of 22
11 African American chronic cocaine users. This is
12 the data. This is baseline. Total abstinence from
13 cocaine and reduction in cocaine use. Among 22
14 participants, 11 were abstinent from cocaine for
15 6 months, while 11 continued use. Part of the
16 people reduced use. Only 2 people consistently
17 used for cocaine for 6 months; only 2.
18 I show you the figure. Baseline, everybody
19 had to use cocaine. Over time, the first month,
20 second month, six months, the amount of cocaine is
21 reduced because we pay. Then total abstinence from
22 cocaine, and the reduction in Endothelin 1.

Page 237

1 Endothelin 1 is released from the injured
2 endothelin cells. With other injury, endothelin
3 would not come out that much.
4 So basically, because we have a follow-up
5 study, we did the GEE analysis. I show you the
6 table. Here's the table. [Inaudible - off
7 microphone.]
8 It was very significant. When people quit
9 from using cocaine, the marker dropped. This is
10 follow-up study. And then we looked at the
11 reduction in cocaine use; not complete quit but
12 reduced use. You see the table. Again, you see
13 the reduction [indiscernible]. The lower of
14 cocaine use, the higher -- the higher reduction in
15 cocaine use, the lower the marker.
16 Then we looked at the incidence of coronary
17 plaque progression. That means from less than
18 50 percent to above 50 percent. Among those 22
19 people, 11 quit. Among those 11, [indiscernible]
20 of them significant stenosis within 6 months. But
21 among those 11, they still use cocaine, although
22 some reduced significant stenosis.

Page 238

1 I sent this paper to a journal. One
2 reviewer did not believe this. And I said, I will
3 send you a picture. I will show you the table.
4 Basically, this is two groups. One is they
5 completely quit; no one used cocaine in 6 months,
6 and none of them developed significant stenosis.
7 Among those 11, 2 developed significant stenosis.
8 This is a picture. This is the first
9 patient. [Inaudible - off mic.] This is at
10 baseline. There's almost no stenosis. This is 6
11 months later, almost 70 percent of stenosis. As to
12 where we got it, it's the same person.
13 (Laughter.)
14 DR. LAI: This is a problem. This is first
15 patient, and then we go to second patient. This is
16 the second patient. This patient had a
17 calcification here. However, to deposit all
18 [indiscernible] of artery -- will block any blood
19 flow. But here, 6 months later, got 65 percent of
20 the [indiscernible]. We refer this patient to the
21 cardiologist. I think he's doing the
22 [indiscernible] now.

Page 239

1 This image analyzes the [indiscernible], the
2 doctor, Elliot Fishman. He's the chief
3 cardiologist. Then I sent the data to Dr. Bluemke.
4 He's the chief of radiology at the NIH clinical
5 center. I said, "I want to use different approach
6 to analyze the data." He's using new data.
7 [Indiscernible]. Here is the LAD here. There's
8 almost no stenosis here. It's gone. This is hard
9 plaque; this is soft plaque. This is one patient.
10 He didn't want to do a second one because he said
11 it's too time consuming.
12 So the conclusions, I know it's limitations,
13 but this study provides evidence that ET-1 could be
14 used as a marker for cocaine abstinence or
15 reduction in cocaine use. The findings of the
16 study may also provide amazing new avenues of
17 research in the fight against cocaine-induced
18 premature coronary atherosclerosis.
19 When the people finished the 12-month study,
20 I gave them a certificate. Some people cried.
21 They said, "The study's over? Next week, where
22 should we go?" I wonder whether or not this study

Page 240

1 can continue, I can continue producing these
2 certificates. I want to give the certificate to
3 those who completely quit.
4 This is a study. Everybody made some
5 contribution. I have a special thanks to Dr.
6 Skolnick because he told me this is good stuff. I
7 did not know before. This study is supported by
8 NIDA. Thank you so much.
9 (Applause.)
10 DR. McCANN: If you could stay there for
11 just a couple questions. What you've presented is
12 so new to the field. I want to give folks a chance
13 to ask a couple questions, unless of course you
14 were so clear that no one has any questions.
15 DR. STRAIN: How easy it to measure this
16 biomarker?
17 DR. LAI: It's very easy.
18 DR. STRAIN: It's a simple test?
19 DR. LAI: Very simple blood test. Also, I
20 have another marker. We are working on it. I have
21 another marker, not the data yet. The hard part, I
22 have to pay extra money to analyze the plaque

Page 241

1 volume because when the plaque grows, it's three
2 dimensions then. It's not just cross-sectional.
3 And also, I have to work with Dr. Bluemke. He
4 analyzed the whole volume for the entire -- the
5 artery trees.
6 DR. STRAIN: Do you have any sense of
7 how -- I guess I'm struck by the fact that you're
8 seeing -- if I followed you, I think you've got two
9 subjects who you did with a 6-month interval and
10 showed the plaque formation over that 6-month
11 period. Is that right?
12 DR. LAI: Yes.
13 DR. STRAIN: But they've been using cocaine
14 regularly for some time. Is that right?
15 DR. LAI: Yes.
16 DR. STRAIN: So it seems peculiar that at
17 baseline, they had very little plaque accumulation.
18 Did you just look at the LAD alone?
19 DR. LAI: No. Everybody had a little
20 stenosis. We looked a -- you know, at the tree.
21 DR. STRAIN: Yes.
22 DR. LAI: The main thing is LAD.

Page 242

1 DR. STRAIN: LAD.
2 DR. LAI: Yes.
3 DR. STRAIN: It's very interesting.
4 DR. McCANN: One question, just to clarify a
5 point. When you presented a group that you said
6 had reduced cocaine use, how did you define that?
7 How much of a reduction, what kind of a change?
8 DR. LAI: Thank you. This is a very
9 important question. Basically, when the
10 participant came in, we have to do urine test. If
11 they're negative, we don't want them. We want
12 urine positive. People would pay 10 bucks. So we
13 said okay. One week later, they come over and have
14 another test. If they are negative again, we pay
15 20. If next week they come back again, we pay 25.
16 Each time you are negative, we pay you more
17 and more and more until you reach 80 bucks.
18 However, if ever you show up with a positive urine
19 test, the payment goes all the way back to
20 10 bucks.
21 So basically, the study participants, most
22 of them are mathematicians. They know how to

Page 243

1 calculate and how to save money. This is crazy
2 [indiscernible], all reduced. If the patient no
3 show, we assume they are positive.
4 DR. McCANN: Reduced would be giving any
5 negative urines?
6 DR. LAI: No. Here is the thing. We have
7 6 months, 120 days. Say we have 20 tests. We
8 divide -- if we have one positive test, it's going
9 to be 19 over 20. Every time you are positive,
10 it's 20 over 20.
11 DR. McCANN: Okay. So were looking at a
12 change over time.
13 DR. LAI: Yes.
14 DR. McCANN: You had a baseline period you
15 captures, and you were just looking for a
16 change --
17 DR. LAI: Yes, sir.
18 DR. McCANN: Okay.
19 MALE SPEAKER: Did you make any efforts to
20 try to look for other potential causal variables of
21 the outcome besides cocaine reduction, like diet?
22 Could there have been other things that were going

Page 244

1 on in the subjects that might account for that
2 outcome besides cocaine reduction?
3 DR. LAI: It's a very important question,
4 but unfortunately we did not do it. We are
5 extremely careful, just make sure we can do this
6 study right because it's very sensitive. It
7 involves money. You've got 80, right? The next
8 time if you're positive, you're all the way -- you
9 wouldn't get 80. You always would come back to get
10 trained. Some time we have -- we just pay
11 attention to the validity of a urine test. We will
12 do later on if we have money.
13 DR. McCANN: Thank you very much. We've
14 reached my 15-minute behind threshold, so now I'll
15 introduce Ivan Montoya.
16 Presentation - Ivan Montoya
17 DR. MONTOYA: In the spirit of NIDA's
18 interest, looking at the reductions of drug use
19 associated with functional outcomes, we have some
20 data sets that we wanted to start mining. So my
21 presentation is just dissecting a little bit of
22 data sets. I'm not going to present any final

<p style="text-align: right;">Page 245</p> <p>1 conclusions. It's just some thoughts about 2 potential analyses and maybe ideas, to get some 3 ideas from you, always to analyze this data and 4 also maybe for you, too, that you use this data for 5 future analysis. 6 The three questions that we have, one is, 7 are quantitative urine cocaine results associated 8 with psychosocial measures independent of 9 treatment? Are changes in quantitative urine 10 cocaine results associated with psychosocial 11 changes, in this case, during treatment? And the 12 third question, is a percent reduction of 13 quantitative cocaine urine associated with 14 psychosocial changes? 15 I'm going to go question by question, and 16 this is what we have. This is the data that we 17 have. We have data from 7 phase 2, double-blind, 18 randomized clinical trials of different 19 pharmacotherapies for cocaine dependence. They 20 were conducted by NIDA through our contract program 21 and ranked. And they all have quantitative urine 22 toxicology analysis that were collected 3 times a</p>	<p style="text-align: right;">Page 247</p> <p>1 regression. So it's a pretty straightforward 2 analysis. 3 Those are the results of the ASI. For the 4 ASI, those are the different domains of the ASI. 5 Basically, you can see this is the line that you 6 need to look; this one. That is the linear 7 regression with the confidence intervals. And as 8 you can see, for most of the ASI domains, there 9 were no significant difference. The only one that 10 shows some trend was for the drug severity domain 11 of the ASI. 12 The same thing for the Clinical Global 13 Impression for the observed and self-rated. In 14 this case, for the severity, there was observed a 15 linear association between the quantitative urine 16 drug use. I have to say that the quantitative 17 urine drug, as was mentioned this morning, has a 18 huge variability. And because of that, we have to 19 convert it to a logarithmic 10, so all the data is 20 logarithmic, not absolute values. 21 This is the Clinical Global Impression 22 Severity. This is for the observed rate and the</p>
<p style="text-align: right;">Page 246</p> <p>1 week. 2 So those are the studies. The studies, some 3 of them were for 8 weeks, and some of them were for 4 12 weeks. Those are the medications that were 5 tested, and those are the sample sizes for each one 6 of those studies. The studies are already 7 published, and all of those studies were negative. 8 This is the total sample size. It's about 1,353 9 subjects, and they also received manual-based, 10 weekly, individual cognitive behavioral therapy. 11 For outcome variables, we have the ASI. We 12 have all the domains of the ASI, and we also have 13 the Clinical Global Impression, the observer, 14 self-rated, severity an improvement, and the Brief 15 Substance Craving Scale. 16 The first question, the idea was to look and 17 see if we could see any signal by just doing an 18 analysis, comparing the quantitative urine results 19 and the different psychosocial measures. The idea 20 was to see if lower cocaine use was associated with 21 better psychosocial function independent of 22 treatment. And for that, we used linear</p>	<p style="text-align: right;">Page 248</p> <p>1 self-rated. For both, there was an increase in 2 association between the urine test and the Clinical 3 Global Impression. For the change, which is the 4 other part of the CGI, there were no significant 5 differences. 6 The other measure that we used was the Brief 7 Substance Craving Scale, and for that one also, 8 there was a trend. You can see with a greater 9 amount of cocaine use or the greater the 10 concentration of cocaine in urine, the worse the 11 outcome, more craving. 12 With this, we went for the second question. 13 The second question was, are there changes in 14 quantitative urine cocaine results associated with 15 psychosocial changes during treatment? That means, 16 so those are the different trajectories of 17 treatment that we can have in patients. We have 18 treatment weeks here. We have cocaine use. 19 Patients can decrease, they can be stable, or they 20 can increase their drug use. The same is for the 21 psychosocial measures. They can decrease, they can 22 remain the same, or they can increase.</p>

<p style="text-align: right;">Page 249</p> <p>1 In this case, for this analysis, what we did 2 was for each participant during treatment, we 3 calculated the slope of the log-10 benzoylegonine, 4 and we compared that with the slope of the ASI 5 domains, the CGIS course, the self-reported cocaine 6 use, and treatment of retention. And for that, we 7 calculated a regression coefficient and a p-value. 8 Here is what we have. What we have is the 9 slope for, in this case, the log BE in each one of 10 the ASI domains. You can see here for the ASI, for 11 most of the domains, there's nothing except for the 12 severity. We can see there are not [indiscernible] 13 associations. This means that during time, during 14 treatment, the patients who decreased drug use 15 during treatment, their also ASI drug score 16 decreases, but not the scores of the ASI. 17 For Clinical Global Impression, the same 18 analogy. We have for both the slopes observed and 19 the self-rated severity, not for the changes but 20 only just the severity, there was a significant 21 association. So the higher the 22 concentration -- sorry. The higher the slope, the</p>	<p style="text-align: right;">Page 251</p> <p>1 50/50 presents chance of getting the right answer 2 from the patient. So clinically may not be too 3 terribly meaningful, but it statistically is very 4 significant. 5 The other analysis that we wanted to look at 6 the data was retention. We discussed during the 7 day the retention is very important, and we wanted 8 to see if the changes in the retention, if any of 9 the changes were associated with survival and 10 treatment. So here we have days of randomization. 11 We have a year survival. 12 The data was divided in 4 groups by 13 quartiles. The first group, the black group, is 14 this group that had a very fast reduction in drug 15 use. The blue group is a group that had an 16 increase in drug use. And then the red group was a 17 group that had sort of like a decrease in drug use, 18 and the green group was the group that had changes 19 increase and decrease in drug use. 20 The retention was shorter for those who 21 decreased use more rapidly -- that's the first 22 quartile -- and those who increased the use.</p>
<p style="text-align: right;">Page 250</p> <p>1 more changes in the treatment. And the reduction 2 in log BE or concentration of drug use, the better 3 the outcome based on the Clinical Global 4 Impression. 5 This is for the Brief Substance Cravings 6 Scale. It was marginally significant. This is the 7 analysis looking at the urine quantitative 8 benzoylegonine versus self-reported cocaine use. 9 As you can see, there was a very good correlation 10 between those two measures and prompted us to ask 11 the question, what is the kappa coefficient, to the 12 agreement coefficient, between the urine BE and 13 self-reported drug use? 14 So this is the data looking at the kappa. 15 The kappa, as you can see here, is .5. Between .4 16 and .75 is a good correlation. So I think there's 17 a very similar agreement and what Kathy found in 18 her study. Also, the result here looking at the 19 self-report versus quantitative, new or used, those 20 are the agreements, in general, pretty decent 21 agreements. I know that clinically for me, an 22 agreement of 50 percent in the patient means that</p>	<p style="text-align: right;">Page 252</p> <p>1 That's the fourth quartile. That for me clinically 2 is pretty interesting because those are the 3 subjects that -- one group is the group that comes 4 to treatment, do very well, and then they leave 5 treatment. The other group is the group that do 6 very bad, and they just leave treatment because 7 they don't feel like they want to stay. That I 8 thought was interesting to mention. 9 The third question is -- well, that question 10 has been lingering around for a long time; what is 11 the percent of reduction in drug use associated 12 with psychosocial improvement? In this case, we 13 look at the quantitative urine results, and we 14 classify subjects as success, those subjects who 15 reduced their drug use by 50 percent or more in the 16 urine BE between baseline and the end of treatment. 17 And failure, those that reduction was less than 18 50 percent. 19 Why 50 percent? Fifty percent was 20 arbitrary. We did analysis looking at 25 percent, 21 75 percent, but 50 percent was the one that showed 22 the best results. So we did a separate analysis</p>

<p style="text-align: right;">Page 253</p> <p>1 for 8 weeks of treatment or 12 weeks of treatment 2 because there were significant differences at 3 baseline at the end of treatment in between those 4 two treatment groups. 5 We looked at the end of treatment analysis, 6 comparing weeks of treatment -- comparing the 7 beginning of the treatment versus the end of the 8 treatment. So we just compared the two points 9 during the treatment. And subjects with missing 10 data were excluded from the analysis because that 11 was an exploratory analysis with multiple subjects, 12 and we didn't include those that had missing data. 13 And we did a step-down Bonferroni correction 14 because of the multiple analysis. 15 The first one is the differences in mean ASI 16 scores between treatment failure and success in 17 that group that received 8 weeks of treatment. So 18 I'm going to start with the 8 weeks of treatment. 19 This is the ASI alcohol score and the ASI drug 20 score. There was good news, there were reductions 21 in the ASI scores. When we compare success and 22 failure, there were no significant differences.</p>	<p style="text-align: right;">Page 255</p> <p>1 treatment, in the ASI, we didn't find anything. 2 The CGI, there may be some association. For the 3 second question, any changes during treatment, for 4 the ASI, not very much; for the CGI Severity, 5 there's possibly a [indiscernible] association. 6 Self-reported cocaine use, definitely. And for 7 retention, there's also a nice [indiscernible] 8 association. 9 Finally, for the percent reduction in 10 cocaine, quantitative success versus failure, for 11 the 8 weeks and the 12 weeks, what we found mostly 12 was the differences in craving and the CGI. So in 13 conclusion, the ASI may not be a sensitive measure 14 to treatment change, at least that's measured by 15 urine quantitative BE. The CGI appears sensitive, 16 measures that may be associated with treatment 17 success. Self-reported reviews is somewhat 18 reliable, as I said. And cocaine use affects 19 retention and treatment, the slope of the cocaine 20 use. The 50 percent in cocaine in urine 21 quantitative with treatment success is associated 22 with improvement in the CGI and craving scales in</p>
<p style="text-align: right;">Page 254</p> <p>1 This is for the rest of the domains in the ASI. 2 There were no significant differences. 3 Now, for the Brief Substance Cravings Scale, 4 when we compared the failure versus the success, we 5 can see here that there is a significant 6 difference. The delta, the reduction in urine BE 7 and the delta here is significantly different. The 8 same thing was for the CGIs. The CGI for both the 9 observed rate and the self-rated there was a 10 significant difference for the 8 weeks of 11 treatment. 12 Now moving to the 12 weeks of treatment, 13 this is the ASI. The only significant difference 14 was for the drug score, which is the only 15 significant difference that we found in the ASI. I 16 don't consider that very meaningful. But for the 17 other scores, the craving scale and the CGI, they 18 all were significant. There were very significant 19 differences between success and failure, as I said, 20 defined by 50 percent reduction in drug use. 21 In summary, what we have is the question 22 about quantitative urine results independent of</p>	<p style="text-align: right;">Page 256</p> <p>1 8- and 12-weeks treatment regimens. 2 I just want to finish with an advertisement 3 to advertise two funding opportunity announcements 4 that we have open right now. One is for 5 competitive revisions, what used to be called 6 competitive supplements. And I know that some 7 people in the audience have already submitted 8 applications to this funding opportunity 9 announcement. The second, which was recently 10 published, is a program announcement for the R21 or 11 33, looking at reductions in illicit drug use and 12 functional outcomes. Thank you. 13 (Applause.) 14 DR. McCANN: I'll take the liberty of 15 starting with the first question. And I know 16 better than to ask you what else have you done, 17 have you done this or that. I know you've 18 presented what you and Shou-Hua have pulled 19 together. What I have in mind might be an idea for 20 something additional we could look at. 21 Where you see the improvement in CGI and 22 craving scales, in people have reduced by</p>

Page 257

1 50 percent or more, certainly a group of the people
2 who've reduced by 15 percent or more will have
3 quit. So I'm wondering how much of that would have
4 been driven by people within the people who reduced
5 15 percent or more who actually quit and how much
6 would still be apparent in people who reduced but
7 didn't quit.
8 In a number of the slides that Dan and Raye
9 showed, they'd show people with heavy drinking,
10 with moderate drinking, versus abstinent. I guess
11 one of the reasons I'm asking is as challenging it
12 may be to achieve abstinence, it's a heck of a lot
13 easier to work with in some of our trials and
14 really capturing percent reduction in use.
15 DR. MONTOYA: Yes. I think the number of
16 urine samples that are negative are pretty small,
17 but still I think it's worth doing that analysis.
18 It's probably good to have a third group with
19 abstinence. As I said at the beginning of the
20 presentation, the data is so rich that there might
21 be many opportunities for doing many types of
22 analyses, including not only abstinence but also

Page 258

1 looking -- like Kathy and Brian presented, like the
2 last 3 weeks of treatment, if that supports the
3 same results. There are many other types of
4 analyses, looking at different percentages.
5 FEMALE SPEAKER: I have a quick question.
6 I'm trying to understand the 50 percent reduction.
7 So the baseline was a urine sample taken at study
8 entry, and then there was a subsequent urine
9 sample. My question, there would be like a lot of
10 sources of variation, how recently they last used,
11 how pure the cocaine was, and so on and so forth.
12 How comfortable are you that a 50 percent
13 reduction of quantitative benzoylegonine between
14 sample A and sample B is actually a 50 percent
15 reduction in their overall cocaine use?
16 DR. MONTOYA: I am not comfortable at all.
17 It is just to measure -- there may be many clinical
18 factors associated, the quality of the drug use.
19 The variability, as I said, is huge. There are
20 lots of limitations. I think the data is this, and
21 it needs to be further mined.
22 FEMALE SPEAKER: Did you have some other

Page 259

1 measures of reduction based on the timeline
2 follow-back or other kinds of things that you
3 explored?
4 DR. MONTOYA: Yes. We have self-reported
5 drug use collected by timeline follow-back. And
6 that's how the self-reported drug-use data was
7 presented. And as I said, correlated -- or at
8 least in agreement with the BE was acceptable. It
9 wasn't too bad.
10 MALE SPEAKER: You had a graph with the
11 survival curves. There are four groups. And I
12 think you were making some -- I didn't quit catch a
13 conclusion. There's something about this is an
14 implication for what happens when people drop out.
15 Are they dropping out because they are getting
16 better as opposed to getting worse? Did you say
17 something to that?
18 DR. MONTOYA: The conclusion of this slide
19 is that people are dropping out for two reasons:
20 because they get better or they get really bad.
21 MALE SPEAKER: Could you tell like the
22 relative prevalence of each of those reasons of the

Page 260

1 groups? I don't know. In alcohol, we kind of
2 assume when people drop out, they kind of are
3 getting back. I don't know if it's different here.
4 DR. MONTOYA: I'm sure they have the
5 numbers, but I don't remember.
6 MALE SPEAKER: Each one is a quartile,
7 right?
8 DR. MONTOYA: But the quartile is a quartile
9 of the division of the data by log B -- by the
10 slopes. And this the quartile of number of
11 subjects, the quartile of the reduction, or the
12 changes.
13 MALE SPEAKER: Oh, okay.
14 MALE SPEAKER: So there could be very few
15 people --
16 DR. MONTOYA: It's the slope.
17 MALE SPEAKER: So there could be very few
18 people in the people that drop out because they're
19 getting better.
20 DR. MONTOYA: I think the sample size is big
21 enough -- Shou-Hua, do you remember?
22 DR. LI: Eleven hundred.

Page 261

1 DR. MONTOYA: Yes, I know. But the sample
2 size in each one of the quartiles --
3 DR. LI: I think each quartile is
4 one-quarter.
5 DR. MONTOYA: We have the data. I can look
6 at the data.
7 FEMALE SPEAKER: We always see a lag in
8 terms of improvement in social functioning. It
9 takes a while I guess to get your job back in line
10 and getting along better with your family and so
11 forth. It doesn't happen right --
12 DR. MONTOYA: Yes. I think that's a very
13 good point. Perhaps 8 or 12 weeks of treatment is
14 not enough to see changes in the ASI, specifically
15 for legal, some of those changes. In fact, some
16 changes in the ASI are desirable. I was talking
17 with Phil the other day, and in one of the cases,
18 there was an increase in the medical domain, which
19 means that the subjects are now more aware -- the
20 patients are more aware of their medical problems
21 and they are seeking treatment.
22 That's why I'm so cautious about this data

Page 262

1 and the interpretation of this data, just
2 presenting the results. But the interpretation can
3 go in many different directions.
4 DR. STRAIN: Should we move to the
5 discussant?
6 DR. McCANN: We'll introduce Phil Skolnick
7 here to give us a discussant rant. I saw Lewis
8 Black recently, so you have a lot to live up to,
9 Phil.
10 Discussant - Phil Skolnick
11 DR. SKOLNICK: I didn't bring any slides,
12 but I have a couple of remarks. It would be hard
13 for me not to make remarks at this meeting.
14 We're here to think about the clinical
15 benefit of -- how to evaluate clinical benefit in
16 stimulant trials. I think the operant, the word
17 that's missing, is a clinically meaningful benefit.
18 The tendency in the past has been to focus on
19 psychosocial outcomes, and that's valid, and you
20 could have a clinically meaningful benefit from
21 that.
22 The issue, though, I think from Ashley

Page 263

1 Slagle's talk, is to try to move towards more
2 proximal measures that can be associated with
3 abstinence or reductions in use. And I think
4 Dr. Lai's talk, it's really impressive that you can
5 relate something over time with a change
6 potentially in atherosclerosis, something which has
7 a medical benefit. You can tell a patient, if you
8 take this drug, and you in fact over time reduce
9 your cocaine use or you eliminate your cocaine use
10 and have a reduction in the risk of
11 atherosclerosis. I mean, that's a really
12 significant outcome. So we're still in early days.
13 One of the issues I think that Dr. Lai's
14 data brings out is the term of our clinical trials.
15 Currently, most of the trials are 12 weeks or
16 16 weeks, and that really may be too short of time
17 to capture some of the changes that we want to see,
18 either in a medical outcome or by a psychosocial
19 outcome. And I think the more distal we get, the
20 more difficult it is to really evaluate that in a
21 time frame of a 12-week trial or 16-week trial.
22 There are ways to modify the trials to make

Page 264

1 them longer, but then you have the issues of if
2 patients are actually responding to the treatment,
3 they may really want to get a life and a job and
4 not show up twice a week to give urine samples and
5 things like that.
6 There's one other thing I wanted to say;
7 well, there are a couple more things. But one of
8 the things I wanted to say was we talked a little
9 bit about stratification. One of the things that's
10 interesting, when I listen to some of the data, was
11 that you have data from trials that are
12 non-medication trials. And you have some
13 interesting data that Kathy presented and Brian
14 presented, which are a mix of therapy trials and
15 pharmacotherapy trials. And even though we have
16 some behavioral interventions in our
17 pharmacotherapy trials, you wonder if in fact the
18 outcomes are identical, if some of the data from
19 the therapy trials alone would really obtain for a
20 pharmacotherapy trial. We don't know that, and we
21 really have to think about that.
22 The other thing I wanted to say just in

Page 265

1 concluding -- two things. Sorry. The first one is
2 Ivan mentioned that we have an FOA out for outcome
3 measures, basically reduced use. And I would
4 encourage those of you in the audience that do that
5 kind of research to think about applying for that
6 grant. It's a very high priority for us at NIDA.
7 The final thing, it's more of an
8 aspirational statement, is that part of the issue
9 that was brought up earlier today is that we don't
10 have any medications that are effective, or don't
11 appear to be effective, for cocaine or
12 methamphetamine use disorder. But one thing that
13 has really sort of been ignored over the years is
14 stratification based on compliance, meaning
15 medication compliance during the trial.
16 From what we've seen in the trials where
17 we've actually tried to measure compliance or a
18 snapshot of compliance, in the substance-use
19 disorder trials, it's such a low level of
20 compliance and so little agreement with traditional
21 measures, which is pill counts or self-report, that
22 we may have had successful medications and that

Page 266

1 signal was masked because people took the drug and
2 threw it in the toilet instead of taking it.
3 So one of the things we can do, especially
4 in phase 2, where it's not a pivotal trial, is just
5 stratify based on adherence in both the placebo
6 group and the medication group, and see in fact if
7 there's a signal. And that might down the road
8 help us enrich our populations perhaps, or at least
9 it's a starting point to talk to the regulators
10 about how to best work these medications through.
11 That's it. Really a good session. It's
12 been a great meeting. Thank you.
13 DR. STRAIN: Thank you.
14 I wonder if we might take -- we're close to
15 a break time, I know, but maybe take five minutes
16 for questions for any of the presenters, including
17 the discussant, because I think there has been a
18 lot of really good material here.
19 DR. McCANN: And especially for Brian
20 because I did cut him off without allowing any
21 questions when he got done speaking.
22 DR. STRAIN: Feeling guilty about that,

Page 267

1 David?
2 DR. McCANN: Yes, I am.
3 (Laughter.)
4 Q&A - Group Discussion
5 DR. STRAIN: So questions for any of the
6 speakers, including Brian.
7 MALE SPEAKER: I guess I had a question for
8 Brian. It was a great presentation, and I liked
9 how you compared all the different outcomes to
10 determine which ones might be more sensitive. I
11 guess the issue of how to handle missing data is
12 such an important one, especially when you're
13 comparing across dichotomous versus continuous
14 outcomes. And if there's differential dropout in
15 the treatment arms, that can really impact the
16 effect of the imputation that's done.
17 For instance, if each missing day -- each
18 time you're missing an outcome in repeated
19 measures, that can really -- if you're looking at a
20 continuous outcome measure, if there's differential
21 dropout, it can really punish one arm, versus like
22 a dichotomous outcome, it's not as bad if you have

Page 268

1 missing data, assuming this really conservative
2 imputation scheme of missing equal failure. That's
3 what we find in our alcohol trials.
4 I guess my question is, did you guys try to
5 handle missing data in any way in yours yet? I
6 know there's many different ways to skinning a cat,
7 but --
8 DR. KILUK: The paper that came out on drug
9 and alcohol dependence, we operationalized each of
10 the indicators and said how we were handling
11 missing data. As Kathy talked, there were multiple
12 ways. So we didn't look at it every different way
13 that you could have calculated it, although we did
14 come up with these reasons for why we chose the way
15 we did or for handling other missing data, where if
16 we're looking at end of treatment, is it the last 4
17 weeks they were in the treatment period or is it
18 the last 4 weeks of when the treatment period is
19 supposed to be, whether they were there or not.
20 In lots of ours, we just looked at when the
21 people were actually in the treatment and tried not
22 to sort of negatively impact those that dropped out

Page 269

1 if there was differential dropout because that is a
2 big factor as well. I don't know if that answered
3 your question. I mean, there are multiple ways to
4 look at missing data. We operationalized it one
5 specific way, and that's how that came out in ours.
6 MALE SPEAKER: I guess the first question
7 would be to figure out is there differential
8 dropout. If yes, then you really have to be real
9 careful and try to apply -- I don't know.
10 Sensitivity analyses are -- because there's no good
11 way to handle missing data. There's no magic
12 bullet for it, so you have to run the analyses
13 using different imputations and see if the
14 treatment effect size matters.
15 DR. CARROLL: And that's essentially what we
16 do. And I think it was only really in that one
17 trial where we got differential attrition by
18 treatment condition. So that helps, and
19 then -- this crazy thing that we do is chase people
20 down and try to get them, whether or not they
21 dropped out. We have sizeable numbers of those
22 randomized, non-starters and dropouts.

Page 270

1 And it is. It's really interesting. I'm
2 not sure that -- in most cases when people leave,
3 they're not doing well, but not always. It's sort
4 of a range that happens when people drop out, and
5 it makes a lot of difference about whether you
6 include the data post-dropout or not. It really
7 does. And it's not always in the ways you would
8 expect.
9 We obsess about it, and all you can do is
10 really try to minimize it, and then really just
11 chase those folks down. And it does hurt some more
12 than others. In jumping into this, it would be
13 best if we were doing it all roughly the same way,
14 or at least having a consistent -- making the
15 assumptions transparent I think is really the only
16 way to do it.
17 That's why I think I'm so passionate about
18 just come up with something that we all calculate
19 the same way because right now it really is apples
20 and oranges, behavioral trials and pharma trials.
21 We often can't compare outcome. One of the things
22 I'd like to come out of this meeting is that we

Page 271

1 just agree to start somewhere; that we all do it
2 more the same than we have been in the past.
3 DR. STRAIN: Perhaps on that optimistic
4 note, we could take our break.
5 Valorie, are we next-door? Why don't we
6 plan to reconvene here at 3:15 as scheduled, and
7 we'll be doing our last session. Thanks to all the
8 presenters.
9 (Applause.)
10 (Whereupon, a recess was taken.)
11 DR. STRAIN: Why don't we go ahead. Rachel
12 Skeet's going to now talk to us. And I don't have
13 your title in front of me for your talk, but I'll
14 let you introduce it. Thanks.
15 Presentation - Rachel Skeete
16 DR. SKEETE: There's the title. Good
17 afternoon, everyone. Thank you for this
18 opportunity to be a part of this meeting and share
19 some lessons learned for trials in other addiction
20 areas. I was the clinical reviewer for the new
21 drug application for probuphine, and this is for
22 maintenance treatment of opioid addiction.

Page 272

1 Today, I'll be discussing key lessons that
2 our review team learned as we reviewed this
3 application. I'd like to stress that this will not
4 be a discussion of probuphine. Instead, I'll be
5 discussing the lessons we learned during our review
6 that may have implications for stimulant trials.
7 And I'll be referring to the probuphine program
8 only to illustrate these lessons. For this talk,
9 I'll be using publicly available information only.
10 And before proceeding, I'll make a disclaimer that
11 these are my views and not necessarily those of the
12 FDA.
13 This is an overview of the key points that
14 I'll discuss. The lessons learned are listed here
15 as discreet concepts, but you'll see that there's
16 some overlap between the treatment design elements
17 that I discuss. As I mentioned, I'm using
18 probuphine as a case study. I'll be using the
19 probuphine example to illustrate four main points
20 that were challenges for us during our review of
21 this application. As I mentioned, I'm using
22 probuphine as a case study.

<p style="text-align: right;">Page 273</p> <p>1 For the four main points, the first has to 2 do with the choice of treatment responder and 3 failure definitions. In the case of the probuphine 4 trials, the protocol-specified treatment failure 5 definition was based on rescue medication needs. 6 Drug use behavior was not considered in definition. 7 But at the same time, a measure of drug-use 8 behavior but not a measure of rescue medication 9 needs was used as a protocol-specified criteria for 10 evaluating treatment response or efficacy. 11 The second point is that trial design can 12 make the placebo failure almost certain, and in so 13 doing, it can bias a trial towards a positive 14 result. The way this happened with probuphine is 15 that both trial groups were allowed rescue 16 medication based on withdrawal and craving 17 symptoms, but the placebo group is almost certain 18 to have higher rescue probuphine needs. 19 As I mentioned earlier, treatment failure 20 was based on rescue medication needs, and so the 21 placebo patients often met the thresholds for the 22 treatment failure definition, and then they were</p>	<p style="text-align: right;">Page 275</p> <p>1 This was actually described earlier -- thank you to 2 the people from NIAAA -- when they showed you their 3 curves of cumulative proportions of responders. 4 What we learned from the response profile is that 5 showing a difference in the curves alone is not 6 enough. We still need to understand the 7 relationship between drug-use patterns and clinical 8 benefit. 9 Finally, we learned that the way in which 10 you display the results can really influence how 11 the results are perceived, so the choice of how to 12 display the findings bears considerable attention. 13 I'm not going to expand on each of the four 14 lessons learned using the probuphine case study. 15 I'm first going to give you a brief background on 16 probuphine and the trials. Again, this is not a 17 discussion of probuphine. I'm only providing this 18 background information to give you some context for 19 the discussion. 20 Probuphine is an implantable formulation of 21 buprenorphine. It provides sustained release of 22 buprenorphine for up to 6 months. I'll be</p>
<p style="text-align: right;">Page 274</p> <p>1 discontinued from the study. So once a patient was 2 discontinued, their urine samples from that point 3 on were considered as positive. And you'll see 4 that this was much more common in the placebo 5 group. 6 Thirdly, treatment retention or a longer 7 time in treatment on study does not always mean 8 that patients are improving. Here you see that 9 patients remain in a trial and presented for urine 10 collection visits 3 times a week for 6 months, but 11 they were still continuing to use illicit opioids. 12 The other point with time and treatment on 13 study has to do with grace periods. We allow 14 sponsors to include grace periods in trials where 15 we ignore data for the first few months. This is 16 because we think that patients may need some time 17 early on in treatment to engage in treatment. 18 However, we learned -- and you'll see -- that it's 19 not guaranteed that patients will improve over 20 time. 21 The final points or lessons that we learned 22 have to do with the response profile approach.</p>	<p style="text-align: right;">Page 276</p> <p>1 referring to the individual implant units you see 2 here as rods, and each of these rods contains 3 80 milligrams of buprenorphine. So treatment with 4 probuphine involves initial treatment -- in other 5 words, induction -- with a sublingual or 6 transmucosal form of buprenorphine, and that's to 7 reach a target dose of 12 to 16 milligrams per day 8 for at least 3 days. Then 4 rods are inserted into 9 the upper arm. And then based on supplemental 10 buprenorphine or rescue needs, an additional 5th 11 rod can be inserted. The rods are taken out in 12 6 months, and treatment can be continued by 13 implanting into the opposite arm for another 14 6 months. 15 There were 2 probuphine efficacy and safety 16 trials, which I'm describing for context only to 17 illustrate the lessons learned. Remember, this is 18 not a discussion of probuphine. PRO-805 and 19 PRO-806, which I'll sometimes call study 5 and 6 20 for short, were 24-week, phase 3, randomized, 21 double-blind, placebo-controlled trials in 22 opioid-dependent patients. Study 6 had an</p>

Page 277

1 open-label sublingual arm, however, I'm limiting
2 the discussion of the trials to the probuphine and
3 placebo arms and to a discussion of efficacy only.
4 Like the proposed dosing procedures I just
5 described, in these trials, subjects were initially
6 treated with sublingual buprenorphine to reach a
7 target dose of 12 to 16 milligrams per day.
8 Probuphine or placebo rods were then inserted for
9 24 weeks. An additional rod was added if
10 protocol-specified, supplemental sublingual
11 buprenorphine needs were met.
12 Patients could receive supplemental or
13 rescue buprenorphine for withdrawal symptoms when
14 subjects scored more than 12 on the Clinical Opioid
15 Withdrawal Scale or if they had what the study
16 called cravings and endorsed more than
17 20 millimeters on the Craving Visual Analog Scale,
18 or if they requested buprenorphine, and the request
19 was seen as appropriate by the investigator. Now,
20 in study 5, only one criterion needed to be met,
21 but for study 6, all three needed to be met.
22 Rescue buprenorphine was obtained at the

Page 279

1 by investigator decision.
2 The primary endpoint was a cumulative
3 distribution function, or CDF, which is consistent
4 with what we consider a response profile. It was a
5 cumulative distribution function of the percentage
6 of opioid-negative urines over the 24 weeks of
7 treatment. For a urine sample to be considered
8 opioid negative, both the urine sample and
9 self-report around the time a particular urine
10 sample was collected had to be negative. Missed
11 samples were considered positive.
12 This slide shows how the cumulative
13 distribution function works. I won't spend too
14 much time on it because it was discussed earlier;
15 thanks again. The CDF looks at opioid-negative
16 results cumulatively. For example, in this
17 histogram illustration, it's showing patients at
18 each of these categories of opioid-negative urines
19 in a treatment arm.
20 Where you see the 8 percent of patients who
21 had 95 percent of their urine samples negative for
22 opioids, when this is looked at in a CDF, these

Page 278

1 clinic or pharmacy, and patients were required to
2 get a dose increase or insertion of a 5th rod if
3 they received supplemental buprenorphine on 3 or
4 more days for 2 consecutive weeks or 8 or more days
5 over 4 consecutive weeks.
6 During the trials, urine samples were
7 collected 3 times a week and investigators were
8 blinded to the urine toxicology results. Patients
9 also provided self-report of illicit opioid use
10 approximately every 2 weeks. Patients were
11 discontinued early for treatment failure and non-
12 compliance as well as other reasons.
13 We considered treatment failure and
14 non-compliance as two of the key reasons that
15 relate to efficacy. So subjects were considered
16 treatment failures if after they got a dose
17 increase of a 5th rod, they still met the same
18 protocol-specified criteria, that I mentioned
19 earlier for supplemental buprenorphine, that
20 required them to get that 5th rod. They were
21 considered non-compliant if they missed 9 urine
22 visits in a row, 6 counseling sessions in a row, or

Page 280

1 patients making up that 8 percent would be counted
2 in the category of patients with 95 percent urines
3 negative or more. And they would also be counted
4 in the at least 85 percent category, at least
5 75 percent category, and so on, because if they
6 have at least 95 percent of their samples negative,
7 they also would have satisfied all the other lesser
8 categories.
9 This slide provides an overview of the
10 primary efficacy results that I'll be using to
11 illustrate each of the lessons learned, from opioid
12 addiction trials and this case study. The primary
13 efficacy measure, again, was a CDF. It was the
14 primary endpoint that we agreed upon. This type of
15 analysis has advantages and involving clinical
16 trial design areas, like the are of opioid
17 addiction, where it's difficult to establish a
18 definitive responder definition.
19 We were unable to come to an agreement about
20 an appropriate responder definition in this case,
21 so we saw the response profile as one way that we
22 could avoid excluding those patterns of use that

<p style="text-align: right;">Page 281</p> <p>1 could represent a clinically meaningful change in 2 drug-taking behavior, but may not be part of a 3 fixed definition of response.</p> <p>4 When we consider the use of a response 5 profile for the analysis, though, we hoped and we 6 envisioned that the curves would separate at those 7 points along the X-axis that represent abstinence 8 or near abstinence. We're talking about this area 9 right here. And that's particularly if we were 10 allowing a grace period. However, as you'll see, 11 the findings in the probuphine case were different 12 than what we had expected.</p> <p>13 These graphs, as well as additional analyses 14 that I'll be showing you later on, were generated 15 by David Petullo. He was the statistical reviewer 16 for the probuphine application. On the left side 17 of this slide is a graphical representation of the 18 findings for each trial, and this is showing the 19 CDF curves. On the right is a tabular summary.</p> <p>20 Let's first look at the graphs. On the 21 X-axis is a proportion of opioid-negative urine, 22 and then on the Y-axis is the proportion of</p>	<p style="text-align: right;">Page 283</p> <p>1 lower compared to study 5, and this probably 2 represents a higher dropout rate with a stricter 3 criteria for receiving rescue medication.</p> <p>4 Now on to a discussion of the specific 5 lessons learned using these findings for 6 illustration. The first lesson, again, deals with 7 the treatment response and treatment failure 8 definitions. This slide shows subject level urine 9 toxicology data for day 5 -- for study 5. Each 10 subject is represented as a point along the Y-axis. 11 So when you follow a line across, you see all of 12 the patients urine toxicology results over that 13 24-week period. A blue dot is a negative urine 14 sample, red is positive, and a plus sign is 15 missing.</p> <p>16 As an example, the placebo patient, the 17 first one on the very bottom that you see 18 here -- and you might have to take my word for 19 it -- had 1 opioid-negative urine sample, then 2 20 positive samples, and then was discontinued. From 21 that point on, all the rest of the urine samples 22 are considered positive. Ideally, on these graphs,</p>
<p style="text-align: right;">Page 282</p> <p>1 patients. The solid curve is a probuphine arm, 2 while the dash curve is placebo. If you look at 3 the 0.3 mark on the X-axis, this refers to 4 30 percent or more urine samples negative for 5 opioids.</p> <p>6 Looking at the proportion of subjects 7 meeting this threshold, between about 40 and 50 8 percent of probuphine patients had 30 percent or 9 more opioid-negative samples, while a little under 10 30 percent of placebo patients had 30 percent or 11 more. Again, we had hoped to see a separation of 12 curves on the right-hand side of the curve for both 13 trials and higher proportions of patients achieving 14 abstinence or near abstinence. However, what we 15 saw instead was separation towards the left and 16 middle of the X-axis, where these changes in drug- 17 use behavior are less conclusive, particularly for 18 study 5.</p> <p>19 The tabular summary on the right shows the 20 same findings. There were no abstinent patients 21 and few near abstinent patients. You can see also 22 that the placebo rates in study 6 are markedly</p>	<p style="text-align: right;">Page 284</p> <p>1 you would see a lot of blue overall, especially on 2 the probuphine side, but instead you see a lot of 3 red for opioid positive urines.</p> <p>4 Drug-use behavior, again, based on urine 5 toxicology and self-report data, was used to 6 evaluate efficacy, and that's what you're seeing 7 here. But it was not considered in the 8 protocol-specified treatment failure definition. 9 We find it difficult to interpret these results 10 because there a considerable number of patients who 11 continued to use throughout the entire treatment 12 period, even though they didn't meet 13 protocol-specified treatment failure definitions.</p> <p>14 We found the subject level urine toxicology 15 to be similar for study 6. And here in the 16 probuphine arm compared with study 5, there's 17 arguably more evidence of opioid use. So when we 18 reviewed the results of these trials, we were left 19 with a number of uncertainties. We wondered how 20 the investigators would have assessed treatment 21 response if they had been aware of the urine 22 toxicology results. Also, there were observer</p>

Page 285

1 rated clinical global measures that were assessed
2 as secondary outcomes, but the urine toxicology
3 findings again weren't available to the
4 investigators. So we questioned the utility of a
5 global assessment measure in this context.
6 Finally, when you look at the number of
7 patients who continue to use illicit opioids during
8 this study, these are those patients with red dots
9 most of the way if not all the way through. We
10 wondered how the results might have differed if
11 drug-use behavior was part of the treatment-failure
12 definition.
13 Another lesson we learned relates again to
14 the potential for a trial to almost guarantee
15 placebo failure, and when this happens, the trial
16 can be biased toward a positive result. To
17 illustrate this plan, I'm using subject level
18 analyses of rescue buprenorphine use during the
19 trials.
20 This analysis is pretty similar to the ones
21 you just saw for the urine toxicology results.
22 Here, though, subjects are aligned in the order of

Page 286

1 when they discontinued from the trial. X's
2 represent the point where a patient discontinued.
3 Red dots are for days when a patient use rescue
4 buprenorphine, and dashes are for days with not
5 use. When you look at the placebo patients, you
6 can see that many discontinue early, and you can
7 also see a lot of red prior to the early -- the
8 continuations here singling that there was a lot of
9 rescue buprenorphine use up to that point.
10 Remember that patients were discontinued
11 when they met the protocol-specified treatment
12 failure definition, and treatment failure was based
13 on use of rescue buprenorphine, but it wasn't based
14 on drug-use behavior.
15 Once these patients discontinued from the
16 trial, they weren't providing additional urine
17 samples, so those samples from then on were counted
18 as missing. Missing urines were considered as
19 positive, so this means that these patients were
20 judged to have opioid-positive urines from the time
21 they discontinued all the way to the end of the
22 168-day or 24-week window.

Page 287

1 We found this imbalance in placebo failure
2 and dropout difficult to interpret. This was
3 because it appeared to us that the imbalance
4 stemmed from opioid withdrawals symptoms for those
5 on placebo and also from the treatment failure
6 definitions. It seemed that it had less to do with
7 an effect of drug-use behavior, although drug-use
8 behavior was used to evaluate efficacy.
9 The reason we thought this is because, as I
10 mentioned earlier, patients had to reach a target
11 dose of 12 to 16 milligrams per day of sublingual
12 buprenorphine for 3 days before they received
13 probuphine or placebo rods. After the placebo
14 subjects reached its target dose and then were
15 abruptly discontinued, you can see how they could
16 need a lot of rescue early on. But they ended up
17 meeting the protocol-specified treatment failure
18 definition by virtue of these rescue needs only.
19 On the probuphine side, patients stayed in
20 the study much longer, but we saw before that many
21 continued to use opioids throughout the entire
22 treatment period. Our understanding here was that

Page 288

1 they were receiving buprenorphine and didn't need
2 as much rescue, so they did not meet the
3 protocol-specified treatment failure definition.
4 On the other hand, based on evidence of illicit
5 opioid use that we saw earlier, many of the
6 probuphine patients didn't appear to be treatment
7 responders to us.
8 In study 6, there appear to be even more
9 placebo dropouts than there were for study 5 and
10 less concentration of rescue buprenorphine use
11 among the early discontinuations relative to study
12 5. We think this may be the case because of the
13 more restrictive rescue buprenorphine criteria in
14 study 6. Again, all three criteria were needed for
15 study 6, and one criterion was needed for study 5.
16 The next lesson we learned during our review
17 was that treatment retention does not always equal
18 improvement. This is the subject disposition
19 summary for each of the trials. It summarizes the
20 reasons for early withdrawal that we consider to be
21 related to efficacy. In both studies, twice as
22 many subjects in the placebo arm withdrew early

Page 289

1 compared to the probuphine arm. Treatment failure
2 seems to be an important driver here with
3 non-compliance also contributing to early
4 withdrawals.
5 Neither the protocol-specified definition
6 for treatment failure nor for compliance considered
7 drug use. From the last set of graphs, we saw that
8 patients continued to use opioids throughout the
9 entire treatment period and were not considered
10 treatment failures. Therefore, even though
11 patients in the probuphine arm had longer time on
12 study, they still didn't necessarily improve over
13 time.
14 Another view of ours related to time on
15 study --
16 MALE SPEAKER: Quick question.
17 DR. SKEETE: Yes?
18 MALE SPEAKER: What do you mean by
19 non-compliance? We usually think about not taking
20 your meds is non-compliant.
21 DR. SKEETE: Right. I should say
22 protocol-specified definition of non-compliance.

Page 290

1 So again, that was -- so if they missed 9
2 consecutive urine visits or they missed 6
3 consecutive counseling sessions.
4 MALE SPEAKER: Thanks.
5 DR. SKEETE: This now talks about looking at
6 grace period. Another thing that we look at with
7 time on study is that patients may need some time
8 to engage in treatment. We believe that if we
9 allowed for a grace period where we ignored the
10 first few months in the analyses, it would help to
11 show a treatment effect. However, I review of the
12 probuphine application taught us that patients are
13 not guaranteed to improve over time.
14 The two graphs on this slide show you
15 cumulative distribution function of the percent of
16 opioid-negative urines when all the data are
17 included -- that's the top graph -- and when we
18 allowed for a 4-month grace period. That's the
19 bottom set of curves. For study 5, whether or not
20 we allow for a grace period, the overall efficacy
21 findings are similar.
22 For study 6, we also see that a similar

Page 291

1 pattern of drug-taking behavior is evident,
2 regardless of whether the grace period is allowed.
3 So we saw that it's not inevitable that patients
4 will improve substantially over the course of the
5 treatment period, and the grace period won't
6 necessarily help in demonstrating a treatment
7 effect.
8 The last set of lessons we learned have to
9 do with the response profile approach. Remember
10 that the response profile is essentially a way to
11 look at an entire continuum of treatment responses
12 over a range of responses. We're interested in
13 individual treatment responses in these addiction
14 trials, so the response profile can be advantageous
15 in showing individual responses while not limiting
16 treatment response to a single responder
17 definition. It allows some flexibility in defining
18 clinically meaningful changes in drug-taking
19 behavior when a specific responder definition is
20 difficult to establish.
21 These are the main set of curves for the
22 primary endpoint. These results differ from what

Page 292

1 we had anticipated when we agreed upon this
2 approach. We expected to see more compelling
3 results and separation of the curves at the
4 right-hand side of the X-axis among a larger number
5 of patients. For both of these studies, there was
6 a statistically significant difference in favor of
7 probuphine. The difference was in the more minor
8 changes in drug-taking behavior for study 5.
9 We didn't consider these overall changes in
10 drug-taking behavior to automatically translate
11 into clinical benefit, so we learned that when
12 using the response profile approach, demonstrating
13 a difference in the curves is not enough. We still
14 need to understand the relationship between the
15 changes in drug-taking behavior, which is a
16 surrogate endpoint and clinical benefit.
17 This is the last graph I'll be showing you
18 today. I'd like you to take a quick look at this
19 graph and see what you gather from the display. So
20 what's your interpretation at first glance? When
21 you take a quick look, you may think that there
22 were a number of patients achieving abstinence or

Page 293

1 near abstinence, especially when you look at the
2 Y-axis, and you see the higher percentages of
3 patients, for example, those 90 percent or above.
4 And you see that plotted against the higher
5 proportion of opioid-negative urine samples along
6 the X-axis.

7 It may even look as though the placebo arm,
8 which is in pink, is doing a little better,
9 especially if I told you there was a statistically
10 significant difference between the two curves.
11 However, this graph is just another representation
12 of all the information that you've seen so far, so
13 why does this one tell a different story from the
14 others?

15 This is the original graph that was used to
16 demonstrate the sponsor's results. This display
17 resulted from graphing the proportion of subjects
18 who submitted a certain level of negative urine
19 samples or fewer. All the other curves you've seen
20 have graphed their proportion of subjects who
21 submitted a certain level of negative urine samples
22 or greater.

Page 294

1 On this graph, approximately 50 percent of
2 subjects in the probuphine arm had no more than
3 30 percent urine samples negative, while
4 approximately 70 percent of placebo patients had no
5 more than 30 percent urine samples negative. This
6 shows you just how much the choice we make in
7 presenting the graphs impacts our understanding of
8 the results.

9 In summary, the key lessons we learned were
10 that treatment failure and responder definitions
11 are difficult to interpret when they don't take
12 into account all the available information in the
13 study that is considered important. For placebo
14 failure, trials can be designed in such a way that
15 they all but guarantee placebo failure, and that
16 could bias the trial toward a positive result.

17 It's difficult to interpret a treatment
18 effect in this context, particularly if the
19 treatment effect is also equivocal in the treatment
20 arm. For treatment retention, we learned that
21 remaining in a study or staying on treatment longer
22 does not automatically amount to clinical benefit

Page 295

1 or improvement. At the same time, it doesn't
2 appear that patients will necessarily improve over
3 time, so allowing a grace period for patients to
4 engage in treatment will not necessarily help to
5 demonstrate a treatment effect.

6 Finally, with the response profile approach,
7 from examining the curves, we've learned that any
8 difference does not equal a clinically important
9 one. We need to understand the relationship of the
10 findings to clinical benefit. We also saw that
11 because of the impact the display of the results
12 has on your perception of results, the choice of
13 parameters used for the graphical display bears
14 close attention.

15 This ends my presentation, and I'd like to
16 thank you for your attention, especially at the end
17 of the day. And I'd also like to acknowledge those
18 in DAAAP who provided leadership and guidance both
19 for the review and for this talk, and also for the
20 many reviews both in CDER and CDRH, that's the drug
21 center and the devices center who participated in
22 this drug device review, and our statistical

Page 296

1 reviewer. And if there's time, I'll open for
2 questions.

3 (Applause.)

4 Q&A - Group Discussion

5 DR. STRAIN: Thank you, Dr. Skeete.

6 This is open for questions, this talk.

7 George?

8 DR. WOODY: George Woody. One of the real
9 advantages for alcohol, you know how much alcohol
10 they're taking. But when they're using heroin, you
11 don't know how much heroin they're taking. You
12 could ask them how many times a day they're using
13 or how many days they're using, but more typical,
14 how many days of use I think is the most common
15 thing.

16 Within that, theoretically at least, you
17 could show use, but there could be a reduction in
18 the amount of use because the urine test will
19 register. Sometimes I think that with -- like
20 naltrexone -- or certainly with methadone, you see
21 a lot of continued use in methadone. But it's
22 almost like you take an alcoholic and turn him into

Page 297

1 a social drinker with some of the things. But when
2 you're evaluating the opioid studies, it's a little
3 hard to get that because you don't know how much,
4 just as a comment. I don't know how to get around
5 that.
6 DR. SKEETE: Right. If you have
7 suggestions, we're always open to hear. That's one
8 of the difficulties in looking at specifically
9 opioid use.
10 DR. STRAIN: Kyle?
11 DR. KAMPMAN: You said that just because
12 there was a difference in the use, that there
13 wasn't necessarily a clinical benefit. But I kind
14 of remember from that trial, weren't there a whole
15 bunch of secondary outcomes that favored
16 probuphine?
17 DR. SKEETE: The primary outcome -- I have
18 to, again, remember this is publicly available
19 information only, so I'm trying to remember all
20 that was said --
21 DR. KAMPMAN: Maybe I shut my mouth.
22 DR. SKEETE: -- all the other things. There

Page 298

1 were other secondary outcomes that were evaluated
2 and that did show some potential. But the way that
3 the study was designed it was to look at that CDF,
4 and it was powered to look at that.
5 Some of the secondary outcomes, including
6 the one that I did mention, was also the observer
7 rated clinical global impression. And that was
8 hard to interpret because the investigators, when
9 they were making those conclusions, weren't aware
10 of any of the urine toxicology results. So we're
11 still not sure how that would have been impacted or
12 not had they been able to have that information in
13 front of them.
14 Treatment retention was actually a secondary
15 endpoint. So, yes, that was a positive outcome,
16 but you can see the nuances of that is that they
17 still were continuing to use over the time.
18 MALE SPEAKER: My understanding of the
19 cumulative responder curves, there was a big
20 treatment effect at certain levels of reduction,
21 but you're saying that that's because there's
22 differential dropout in the way of imputing the

Page 299

1 missing data in the placebo group really
2 punishes -- the placebo group makes them look a lot
3 worse.
4 What was the reason why we think that there
5 is more differential dropout with placebo group?
6 Do you have any suspicions?
7 DR. SKEETE: There are a couple of things.
8 One is the way that the -- when they started
9 treatment -- so both groups start on sublingual
10 buprenorphine, and they have to reach a target dose
11 because they need something before they get the
12 implant put in. They have to reach a target dose
13 of 12 to 16 milligrams. So they are stabilized on
14 that dose or "stabilized" reaching that target dose
15 between 10 to 16 days.
16 Once they get that target dose, and they're
17 doing okay on that dose, they then get switched to
18 the placebo or the probuphine rod. Now, the
19 placebo group is essentially abruptly discontinued
20 from treatment, and then the only thing that they
21 get is the rescue buprenorphine, whereas the other
22 group has a low level of buprenorphine that can

Page 300

1 manage withdrawal. So now there is sort of
2 differences in that, and that's what we think is
3 some of the issue there.
4 MALE SPEAKER: But there's been a way to do
5 it -- I know -- a way to do it better?
6 DR. SKEETE: Well, if you have some
7 suggestions -- that's one of the things we wanted
8 to bring out is we wanted to be able to
9 compare -- we wanted to be able to see if there was
10 some way to look at it compared to placebo. And
11 the rescue medication was actually put it there
12 because it would have been considered unethical to
13 just put people on -- get them up to a probably
14 16 dose, and then just abruptly discontinue, and
15 then give them nothing.
16 We're open to hearing if there are thoughts
17 on ways that you could see a way of looking at
18 placebo or treatment effect while you can still now
19 have this differential placebo dropout that we saw.
20 DR. STRAIN: David?
21 DR. McCANN: For the rescue medication, were
22 they allowed to take that home at all, or did they

Page 301

1 have to take it on site?
2 DR. SKEETE: They had to take it on site.
3 DR. SKOLNICK: Phil Skolnick. Could you
4 comment -- if you're allowed to -- on the
5 difference between the phase 2 design and the
6 phase 3 design? The sponsor must have been
7 incited to go to phase 3 based on the end of
8 phase 2 meeting. And I'm just wondering --
9 DR. SKEETE: How that happened?
10 DR. SKOLNICK: Yes.
11 DR. SKEETE: Some of that stuff I think is
12 not publicly available.
13 DR. SKOLNICK: Well, if you can't, you
14 can't.
15 DR. SKEETE: Yes. Actually -- yes. I'm not
16 sure I can mention that one.
17 DR. STRAIN: Kenzie?
18 DR. PRESTON: For that particular trial,
19 could they have chose retention in treatment as a
20 primary outcome measure? Because really what, it
21 seems to me, that you're comparing is a
22 detoxification versus maintenance. And there's

Page 302

1 already literature to say that people do better
2 with longer term treatment maintenance than detox.
3 DR. SKEETE: In other words -- so instead of
4 using the response profile based on urine
5 toxicology --
6 DR. PRESTON: Drug use.
7 DR. SKEETE: -- drug use, because they have
8 used treatment retention instead. The only thing,
9 though, is that we still have the concerns about
10 what the treatment retention was saying. When we
11 looked at the treatment retention results, we saw
12 that they were staying in -- the people on the
13 probuphine arm were staying in a trial twice as
14 long as the other -- twice as often as the placebo
15 group. But at the same time, they were using
16 illicit opioids.
17 So it was hard for us to say that the
18 treatment and retention alone was enough because
19 even if they're staying in the treatment, they're
20 still using illicit opioids. I guess it
21 would -- you would need to demonstrate that
22 treatment retention alone actually will translate

Page 303

1 to the clinical benefit. Because what we're seeing
2 is that the use behavior is being used as a
3 surrogate that we sort of understand to translate
4 to clinical benefit. But the treatment retention
5 alone, I guess we would have to see that it
6 demonstrates that it's clinical benefit.
7 FEMALE SPEAKER: I guess I would like to put
8 into the conversation the point of the lesson,
9 which is the study design sounded good initially,
10 but in seeing the results, we learned about the
11 challenge. It wasn't so much a differential
12 dropout rate. We had differential drop out due to
13 the placebo and active treatments in a number of
14 different therapeutic areas. In pain, for
15 instance, it's classic. You see more dropouts in
16 placebo due to lack of efficacy, adverse events and
17 active treatment groups, really has an impact on
18 how you impute.
19 Here, it was a protocol defined
20 discontinuation and attention to whatever actual
21 treatment assignment related dropping out may have
22 occurred. And that's where it became challenging

Page 304

1 because unsuccessful treatment was defined based on
2 the use of rescue, but not on the ongoing or
3 continuous use of illicit drug. And it created an
4 opportunity to differentiate the two treatment
5 groups when neither was particularly successful.
6 So I think the point here is -- the lesson
7 is when you define a treatment failure, A, what do
8 you do with that person? Do you continue them in
9 the study and collect information; and B, do you
10 take all the proper endpoints into consideration in
11 defining your treatment failure?
12 So I think that those are sort of -- the
13 point being, we have to use this as an opportunity
14 to understand the impact of choices. You don't
15 want to create a study that fails to distinguish
16 treatment effect if, for instance, there's a large
17 amount of rescue. Right? Because that can mask a
18 treatment effect. On the other hand, you don't
19 want to exaggerate an effect by failing to take
20 into account what might, in retrospect now, be
21 useful to consider as part of your treatment
22 failure definition.

Page 305

1 So if you're going to penalize, in a sense,
2 the placebo group for needing rescue -- now
3 granted, you would technically penalize both groups
4 if they need a rescue. You should probably
5 also -- I don't mean penalize, but I mean take into
6 account. You should probably also take into
7 account other things such as a certain amount of
8 illicit drug use.

9 Those are the sorts of things that may be
10 useful in thinking about design of the stimulant
11 trials once there is a product. And the other
12 issues that have been discussed in terms of entry
13 criteria and everything else, if the paradigm
14 chosen is to, for instance, use a treatment failure
15 design, not to fall prey to a similar situation.

16 DR. STRAIN: Other thoughts?
17 (No response.)

18 DR. STRAIN: It's complicated. This is
19 the -- my thought is it's easier to figure out how
20 to not design a study -- and this isn't unique to
21 this than it is to how to design a study. And
22 that's what I struggle with, with this.

Page 306

1 Were you going to respond or say something
2 further? Because I was going to go off to another
3 question. It sort of gets back to this.

4 In part, this is an example of the design of
5 the trial, but we're also focused upon the outcome
6 measures. And I wonder for stimulant trials if
7 there are specific lessons from this trial
8 regarding outcome measures that could help inform
9 us for stimulant trials, not just in terms of study
10 design but in study measures.

11 DR. SKEETE: I think -- well, the study
12 design will impact the measures. But one of the
13 things is if you -- you might -- we've been talking
14 today about whether abstinence is the only way we
15 can go or are there other use patterns that might
16 make a difference.

17 One thing that you may be able to take away
18 is thinking about this response profile approach.
19 If you were to go and look at stimulant trial and
20 sent that way, what could you take from here, from
21 the opioid addiction trial setting to say how you
22 would apply that to a stimulant trial might be one.

Page 307

1 Another one, someone mentioned whether you
2 could use treatment retention, but again, it still
3 will go back to the study design, but again, to
4 think about is treatment retention; how would that
5 apply in a stimulant trial, for example, and what
6 do you need to think about in terms of the trial
7 design to be able to do that.

8 DR. STRAIN: I'm not sure if I can
9 articulate this, but it strikes me that -- what
10 we're trying to show is clinical benefit. So often
11 what we're basing that upon is drug use, and what
12 we're basing drug use upon is urine results. I
13 guess from this study the difficulties are the
14 compounds of supplement probuphine use, early
15 dropout, and illicit drug use.

16 I think those are the three sort of things
17 that are potentially impacting the interpretation
18 of drug use, which is what we're saying is the
19 measure of clinical benefit. Have I got that
20 sequence right?

21 DR. SKEETE: Yes.

22 DR. STRAIN: One of the things I guess I'm

Page 308

1 getting my head wrapped around is are there other
2 measures of clinical benefit that may be of value
3 beyond drug use, endothelial damage or something,
4 potentially.

5 Ken, please.

6 DR. SILVERMAN: This is Ken Silverman. I
7 don't have an answer to that question. This study
8 is confusing. I'm not sure what -- except one
9 thing it does have in common with other studies
10 that have been talked about today is that missing
11 data is a big problem. And in fact, I think it's
12 probably the biggest threat to the quality and
13 validity of the outcomes than anything, maybe more
14 than what measure you happen to pick.

15 Extended-release naltrexone, the Depotrex
16 trial that showed that extended-release naltrexone
17 increased retention. And when you impute missing
18 samples as positive, it also looked like it reduced
19 opioid use. But of course when you impute missing
20 samples as positive, it also reduced
21 benzodiazepine, amphetamine, marijuana, cocaine,
22 and everything else that they tested for. And that

Page 309

1 publication was pretty thoughtful that they
2 included different types of missing data, and only
3 the missing positive showed these effects between
4 the two groups.
5 In fact, I think the same problem exists for
6 the extended-release Vivitrol study that was used
7 to approve Vivitrol for opioid dependence.
8 Vivitrol also increased retention substantially,
9 and it looks about the same amount that it improved
10 urinalysis results, which I think were also based
11 on missing samples positive.
12 MALE SPEAKER: Thought in that particular
13 study -- I worked on the Vivitrol program -- I
14 don't think that there was any forced criteria
15 where patients were ejected from the study on one
16 criteria.
17 MALE SPEAKER: No, no. I didn't mean to
18 suggest that. I'm not even talking about the FDA
19 specifically. But if you looked at the urinalysis
20 results, there's a big difference. Vivitrol
21 extended retention. People who got Vivitrol were
22 in treatment longer than people who got placebo.

Page 310

1 And then when you look at your analysis, when you
2 compare the two groups on your analysis results, if
3 you impute missing samples as positive --
4 MALE SPEAKER: What we did in that
5 particular -- one difference I think also with
6 antagonist treatment, as opposed to agonist, you
7 can't really use and get high while you're on an
8 antagonist. So there is maybe a difference between
9 being assured that you're on a blocker.
10 MALE SPEAKER: I've got --
11 MALE SPEAKER: Just to say, for the criteria
12 that we use for that particular study was that in
13 order to be successful you had to show up at the
14 clinic. You had to give a urine, and the urine had
15 to be negative. In any other situation, you are
16 considered positive. So there was no kind of --
17 MALE SPEAKER: Well, still -- we shouldn't
18 argue about this specific study, although I still
19 think that that study imputed missing samples as
20 positive.
21 FEMALE SPEAKER: I think this is a very
22 important point, and perhaps you all are familiar

Page 311

1 with the National Academy of Sciences' report, from
2 a few years ago, that looked at the issue of -- it
3 started off as what's the right way to impute
4 missing data in a long-term study? And the answer
5 was, minimize missing data because all methods of
6 imputation suffer from some type of problem.
7 MALE SPEAKER: That's right.
8 FEMALE SPEAKER: And there is additional
9 layers there. So when imputation is necessary
10 rather than a single imputation, for instance, last
11 observation, baseline observation, positive, what
12 is another approach? There's something called the
13 multiple imputation method, and I refuse to tell
14 you how I understand that because it's the
15 kindergarten version. But that's one approach.
16 But more importantly is the way it's been
17 stressed to minimize missing data, even if someone
18 goes off treatment, to keep them in the study and
19 collecting data from them. Now, I grant that this
20 population in contrast to a pain population may be
21 harder to do that with. But the idea of different
22 incentives to bring them in, that's I guess the

Page 312

1 challenge for this therapeutic area, is how do you
2 get these people in even if there's going to be a
3 positive urine that they're trying to hide?
4 Those are the kinds of things, if people
5 have ways where there have been better successes
6 there, that would be a best practice.
7 MALE SPEAKER: Yes, that's my point. The
8 reason that I mentioned this is mostly to say that
9 probably the most important thing that we an agree
10 upon is that you have to -- you can't accept
11 studies that have differential retention, and you
12 have to have comparable and high rates of
13 collection, and you have to find methods to do it.
14 I think if you looked at the results that
15 Kathy Carroll and Brian presented, they have like
16 these long-term follow-ups, 1, 3, 6, whatever. I
17 think you've got over 80 percent of those urine
18 samples for those. The problem is you can get
19 samples like that -- and we do as well, for like
20 monthly samples -- but when you try and do it for
21 Monday, Wednesday, Friday urine samples, you cannot
22 do it.

Page 313

1 So developing methods and criteria that
2 says, okay, this is an acceptable trial if you get
3 comparable retention, high rates of collection --
4 MALE SPEAKER: One other interesting thing
5 that occurred in that --
6 DR. STRAIN: Hold on one second. Hold one
7 second because I want to thank Dr. Skeete. I think
8 we're moving into a more general discussion, so you
9 can sit down if you'd like.
10 MALE SPEAKER: I just wanted to make just
11 one other follow-up, which I think was a really
12 interesting lesson learn that we had from the
13 Vivitrol opioid program. We did specify for that
14 trial a response profile. And at the end of the
15 day, though, if you looked at the subset of
16 patients who stayed in for the entire study and
17 were completely abstinent on Vivitrol, there was a
18 significant difference from placebo.
19 I think my interpretation was that was
20 something that was important to the FDA reviewers.
21 So although maybe we came at the trial from a
22 different -- we were looking at response profile,

Page 314

1 and I think there was a preference on the FDA to
2 look at that subset that were completely abstinent.
3 There was a situation where I think we agreed to
4 agree. So that may also have applicability when
5 thinking about trials and stimulant.
6 DR. STRAIN: Thanks. Kathy, you had a
7 comment. And you need to get near a microphone,
8 and then Dan.
9 DR. CARROLL: I think we can think about
10 these things a little bit differently because the
11 mind-set really is, they're gone, they're gone, and
12 it doesn't have to be that way. You can collect
13 data -- you have to train the staff and you have to
14 train the patients, too, that participation in
15 treatment doesn't have to be linked to
16 participation in the trial. And you can have them
17 go to the labs. They don't have to come in to the
18 nasty clinic and get yelled at by the staff to do
19 it. You can interview them in different places.
20 You can do the labs.
21 There are ways you can do this, and I'm not
22 clear why we invest so much in these trials, and

Page 315

1 then don't go that little bit more to get the data,
2 which just kills it. I think we have to not use
3 trials that get differential or get less than
4 80 percent of the samples because you just don't
5 know it.
6 DR. STRAIN: Dan and then David.
7 DR. FALK: I guess my question was -- I
8 don't know if Rachel -- if the FDA has a position
9 on this. But with responder profiles, that's a
10 very kind of post hoc way -- you can't
11 declare -- can someone declare up front for a
12 phase 3 trial, like we're going to look at
13 abstinence or we're going to look at all the other
14 possible cut point and kind of decide.
15 So the general question is, how would the
16 FDA -- could the FDA ever prove something for a
17 medication based on a cut point that wasn't defined
18 as a primary just from looking at the responder
19 profiles? Or maybe even a more general question,
20 how does the FDA use responder profiles?
21 FEMALE SPEAKER: So I'm going to speak not
22 as the FDA. I'm going to discuss responder

Page 316

1 definitions, continuous responder functions, and
2 the analysis. There are statistical methods that
3 can be applied to evaluate the separation of the
4 curves. So there is not a specification of a cut
5 point, there is just an analysis of the separation
6 of the curves.
7 I can't describe the details, I just know
8 they exist because they are proposed in other
9 therapeutic areas. The question, though, or the
10 relevant point from the probuphine example is that
11 that type of analysis, the separation of curves,
12 may not actually be the right outcome for all
13 clinical situations. If the value to the patient
14 is dependent on the far right of the curve, then
15 the analysis needs to reflect that. If any
16 separation along the curve that meets the
17 statistical endpoint is sufficient to confirm
18 clinical meaningfulness for the endpoint reflected
19 in that curve, then that is also appropriate, but
20 it's going to change by clinical setting.
21 So responder definitions and responder data
22 can be analyzed using this continuous function. It

Page 317

1 can be changed into a dichotomous outcome. If
2 there's a particular point, for instance in
3 epilepsy looking at 30 or 50 percent reduction in
4 seizure frequency, is often part of their endpoint
5 structure.
6 So the answer is, there are a lot of
7 possibilities, but it has to fit the clinical
8 setting.
9 DR. FALK: So the right side would be total
10 abstinence of the cumulative responder curves, and
11 that might have been proposed as an a priori
12 primary outcome, and they didn't hit it. Now, if
13 you see the rest of the curves, yes, they're kind
14 of bias because of the differential drop out and
15 everything. So what looks like to be kind of a
16 whopper of a treatment effect somewhere in the
17 middle range -- are you saying that it would be up
18 to them to validate that 50 percent reduction is
19 really clinically meaningful?
20 FEMALE SPEAKER: So for instance, if you see
21 a large difference in treatment arms in the number
22 of people who have a 30 percent reduction in

Page 318

1 seizures, who are enrolled with intractable
2 epilepsy, or a 30 percent reduction in pain, or a
3 30 percent reduction in positive urines, what does
4 that mean?
5 The epilepsy people are happy. In some
6 clinical settings, the pain people are happy. It
7 doesn't sound like addiction people will be very
8 happy with that outcome based on the conversation
9 we're having unless we decide or you decide that
10 that cut represents a clinical benefit.
11 So what is the benefit for that population?
12 More people with a 30 percent reduction of the
13 measure, or should it be a 50 percent reduction, or
14 a 90 percent reduction of that measure, what
15 correlates with clinical benefit in that setting?
16 DR. FALK: Can that be done after?
17 FEMALE SPEAKER: No.
18 DR. FALK: That has to be done a priori --
19 FEMALE SPEAKER: It can be done any time
20 during exploratory work, but --
21 DR. FALK: Yes, in the phase 2 trial.
22 FEMALE SPEAKER: -- when you are planning a

Page 319

1 phase 3 study, I believe the general standard, not
2 just an FDA standard -- but if you want a
3 statistical analysis to be -- well, you folks tell
4 me. How much post hoc analysis do you believe, and
5 when do you call it quits? There's a regulatory
6 reason why we don't like too much post hoc stuff.
7 DR. FALK: That's what we said. I think we
8 said that in our paper, that maybe this could
9 be -- CPR, the cumulative proportion could be good
10 for phase 2 trials to inform what a good cut point
11 might be for a phase 3.
12 FEMALE SPEAKER: I'm going to comment that
13 one of the biggest things we learn from these
14 trials is that the cumulative responder analysis
15 sounds like a really great idea. We thought it was
16 going to obviate the need to explore relationships
17 about one particular responder definition. And
18 it's so vulnerable to missing data because there
19 are so many different pieces of data that are
20 collected.
21 It's so vulnerable to missing data. It's so
22 vulnerable to patients not completing the trial,

Page 320

1 whether for protocol-specified discontinuation
2 criteria or because for whatever other reason they
3 didn't. And because there are so many unanswered
4 questions about how various places on the curve
5 really predict clinical benefit, that as great an
6 idea as it sounded, it didn't really turn out the
7 way we hoped.
8 I think we got lucky with the Vivitrol
9 trial. The complete abstinent responder definition
10 also worked, so we did not have to negotiate
11 whether what worked was really a good thing to
12 work. So maybe I would say that we could -- it's
13 easy to adjudicate missing patients if you have one
14 single responder definition. I know people don't
15 like that idea, but it is much less vulnerable to
16 missing data if you can find them and they can tell
17 you that they are using right now. Then you could
18 call them a treatment failure. It seems like it
19 could be less costly to collect that information.
20 This is sort of sexy when you think about it, but
21 then it just didn't work the way we hoped it would.
22 That's my big lesson.

Page 321

1 DR. STRAIN: Dave, you've been very
2 patiently waiting.
3 DR. McCANN: I just wanted to comment on the
4 issue of differential dropout, and if you get that,
5 you just have to ignore results of the study. I
6 think sometimes the FDA can be very intelligent and
7 make good decisions, and to acknowledge that
8 remaining in treatment is a benefit compared to
9 dropping out. I think it's one of the best things
10 that they've acknowledged in treatment.
11 As we do our cocaine trials, we define
12 success very much the way you described for
13 Vivitrol and opiates. To be a success you have to
14 be there in treatment, giving urine, and being
15 clean, and you have to self-report no use. So if
16 you're there and you're giving a dirty urine, or
17 you're saying that you're using, or if you're no
18 longer there and you've disappeared, you're a
19 failure. That can give you an effect by virtue of
20 differential dropout.
21 I went back and looked at data for a lot of
22 our meth and cocaine trials. I don't do SAS

Page 322

1 programming, but I asked our statistician, can you
2 print me the last 3 weeks of urine for everybody
3 who dropped out of urine early. I want to see if
4 anybody was clean. I heard it suggested that, oh,
5 sometimes you get people, they're better, they go
6 get a job, and they drop out because they're doing
7 well. I did not see that in the data at all. I
8 didn't see clean people leaving early. It just
9 wasn't there.
10 So I think that supports the idea of people
11 who've dropped out being treated as failures and
12 requiring people to be there showing clean urines
13 and reporting no use at the end as success. If I
14 had to bet, for Vivitrol and opiate addiction,
15 which way differential dropout would go, I would
16 have expected the people getting that antagonist to
17 say, "Screw this, I'm out of here," and the
18 placebos to stay in.
19 The fact that you saw it in the other
20 direction to me was really surprising, and it
21 suggested there was something meaningful there, the
22 decreased craving that was shown in those studies,

Page 323

1 that seemed to be very important.
2 DR. STRAIN: Ken?
3 DR. SILVERMAN: This is Ken Silverman again.
4 I agree about retention. Retention is good. And
5 as a measure itself, it's fine and may be an
6 important measure. But I actually don't agree
7 about the fact that you could assume that someone
8 who has left treatment or has not provided urine
9 samples is doing badly, having positive -- your
10 urinalysis results are your outcome measure if
11 you're assuming that they're positive. I just
12 don't think that's necessarily right. It could be
13 right, but it's not necessarily right.
14 That's all. That's why I was
15 advocating -- and I agree with what Kathy said
16 about just the need to have trials. And if there
17 were these requirements to have not lack of
18 differential retention and high rates of
19 collection, people would find ways to get it done,
20 and it's actually pretty easy. Just like that guy;
21 just pay them. And if you pay them enough --
22 MALE SPEAKER: The more we pay them, the

Page 324

1 more likely we're going to get professional
2 subjects who really don't want to quit, but want
3 money to buy drugs.
4 DR. SILVERMAN: I don't think that's true.
5 MALE SPEAKER: I do.
6 DR. STRAIN: George?
7 DR. WOODY: In the Russian studies, we have
8 followed up people who dropped out, especially
9 looking at HIV risk. And there's a big difference
10 between HIV risk in those that relapsed and those
11 that didn't. There's a lot of data showing such
12 high relapse rates with opiate dependence when they
13 finish detoxification. So I think that in the case
14 of opiates, you can really be pretty sure that
15 maybe not everybody, but a great majority of the
16 dropouts would have relapsed. Now that may not
17 equally apply to cocaine or amphetamines that tend
18 to be less -- you have more episodic use. But with
19 opiate dependence, it tends to have a somewhat
20 different pattern.
21 DR. STRAIN: Other comments or questions?
22 Connie?

Page 325

1 DR. WEISNER: I kind of hesitate to say
2 this, but I think a lot of this does have to do
3 with who are in these studies, the whole issue of
4 advertisements. Those people are really different
5 from people who are having to come to treatment
6 because they're in trouble with their job or their
7 family, and maybe you get some of those kind of
8 people. Like I was saying to David, everybody in
9 those Kaiser samples has to take that drug test to
10 somebody, even if it's their wife.
11 We have really good follow-up rates in our
12 studies because they're there anyway, and they have
13 to be there, or there, for one reason or another,
14 choosing to be there.
15 In the past, health plans -- I'll talk a
16 little bit about this tomorrow. Health plans
17 haven't really wanted to participate in this kind
18 of research, but it's really different now with the
19 high profile of pain medication, opiates, and
20 marijuana issues that they're dealing with. And
21 they would like medications. So there are
22 different maybe ways, different patient populations

Page 326

1 that would really help solve some of this. So that
2 speaks for developing relationships with health
3 systems or whatever.
4 MALE SPEAKER: I think what you're saying is
5 really interesting, and it highlights there are
6 different objectives. There's a component of
7 getting a drug approved demonstrating some sort of
8 benefit. It may sound trite, but it really is the
9 case that that really is just the beginning. I
10 know that colleagues at, for example, the
11 University of Pennsylvania, are doing a lot of work
12 and other places on opiate treatment and the
13 criminal justice system.
14 So to your point, really getting a drug
15 approved just means, yes, there is some evidence of
16 benefit, but then there's this whole other question
17 about who do you actually use it in to get that
18 benefit and what kind of settings.
19 Wrap Up – Eric Strain
20 DR. STRAIN: Not to prolong the conversation
21 unduly, but I want to go back to -- because I think
22 we're evolving into -- or part of our discussion is

Page 327

1 evolving into a focus upon urine results as an
2 outcome measure that demonstrates abstinence. We
3 could have probably a really quick meeting if we
4 decided that because, all right, we're done. It's
5 here in results you've got to show abstinence.
6 There we go.
7 But I think part of our charge as well is to
8 think broader in this particular area of stimulant
9 use. We don't necessarily have to discuss it
10 today. It could be something to ponder and to
11 return to tomorrow. But we can think of other
12 things beyond urine results abstinence as the goal,
13 or at least something that we think should be
14 investigated as a potential -- I believe where I'm
15 at now -- so long as we can show that there's a
16 clinical benefit to that.
17 I don't know what that is, but I think
18 that -- in some ways I think we may be held
19 prisoner by the opioid research stuff, where so
20 much of the opioid research with buprenorphine was
21 people were coming everyday, and we could get urine
22 so frequently, and it was so easy to measure those

Page 328

1 results. I think we should think broader in this
2 category and be open to the idea that there could
3 be other outcomes beyond urine results that could
4 be identified a research or considered.
5 I want to put that out there. I think where
6 I'm at is, how do we show clinical benefit? What's
7 the analog to the drink when the drink was used for
8 HDD? Yes, Steve?
9 DR. SPARENBORG: This is Steve Sparenborg at
10 NIDA. Some people in the room are aware of this,
11 but one small part of NIDA is sponsoring -- through
12 a contract, we're developing a patient-reported
13 outcome for cocaine use. The purpose of this is to
14 come up with a typical kind of questionnaire that
15 is based on, first, expert opinion. Experts have
16 been questioned by professional interviewers from
17 Northwestern University and gotten the lay of the
18 land for what patients are like. And the next step
19 is for interviewers to talk to cocaine users,
20 addicts. And then based on that, go through the
21 typical psychometric process.
22 We're having the FDA oversee this process.

1 We've just barely started communicating with them.
2 But it will be done through the drug development
3 tool process. And our hope is that although the
4 data shown today don't show a lot of -- it's not
5 really likely that we're going to find a lot based
6 on the lack of concordance with psychosocial
7 outcomes and reduced drug use. But maybe there's
8 something that a cocaine patient could express to
9 the interviewers that would lead us to helping to
10 identify what those issues are and helping the
11 patient to identify with something in the treatment
12 program that they feel more respected, more hope,
13 more something. They feel something differently
14 that we haven't seen yet, and that that could
15 eventually become a lead to something we can study
16 in a trial.
17 Otherwise, I think it's just leave no stone
18 unturned. Even though the current evidence isn't
19 super promising, we really have to go through this
20 official process, I believe, to say that, all
21 right, we went down this path and this is what we
22 got. It might not be useful, but it just might.

1 I think their feet in the water here on this. And
2 clearly, they're very interested in continuing this
3 from the program announcements and FOAs that
4 they've mentioned.
5 DR. STRAIN: So I want to thank all the
6 speakers today, and I want to thank all of you for
7 your attention, and I hope to see many of you at
8 dinner tonight. Thanks.
9 (Whereupon, the meeting was adjourned.)

1 Adjournment
2 DR. STRAIN: Thank you.
3 If there are no other comments or questions,
4 I want to thank everybody for a real intellectually
5 stimulating day. I think we've sort of gone from
6 soup -- I guess we haven't gone from soup to nuts
7 because that would imply we don't have more to do
8 tomorrow. But we're on the home stretch, and I
9 really do appreciate it.
10 Just to remind you, we've heard from the
11 perspective of the FDA on this process of outcome
12 measures and their development, and a great talk
13 this morning. Then we've heard from Kyle about the
14 development of a particular measure, some of the
15 psychometrics he worked with. Then we had some
16 great talks from NIAAA about heavy drinking days,
17 and those have really helped me to crystallize in
18 my mind a process that NIAAA has gone through that
19 could be very informative for what's being done
20 here. And then this afternoon we've heard some
21 innovative approaches that have been used by NIDA
22 as they've started putting not just their toes but

	237:19,19,21;238:7	15-minute (1) 244:14	135:13	57:5;182:6
\$	112 (2) 38:15;218:4	15-plus (1) 213:22	2011 (2) 153:13;196:14	30-day (1) 75:3
\$600 (1) 53:21	11-item (1) 39:5	16 (9) 162:7;219:8;263:16; 276:7;277:7;287:11; 299:13,15;300:14	2014 (1) 138:18	30-item (1) 39:5
[12 (26) 52:7;103:7;104:1,13; 108:5;113:2;145:19; 161:13;167:9;168:6,10; 169:11;199:20;203:3; 222:22;246:4;253:1; 254:12;255:11;261:13; 263:15;276:7;277:7,14; 287:11;299:13	168-day (1) 286:22	20's (1) 50:20	30's (1) 50:20
[inaudible (4) 174:17;190:15;237:6; 238:9	12.5 (1) 128:5	16-week (1) 263:21	21 (5) 51:10;62:5;100:7; 148:13;228:11	33 (1) 256:11
[indiscernible (1) 233:5	120 (1) 243:7	17 (3) 111:14;113:20;134:15	22 (5) 69:10;236:6,10,13; 237:18	34 (1) 43:10
[indiscernible] (14) 234:8,8;236:8;237:13, 19;238:18,20,22;239:1, 7;243:2;249:12;255:5,7	1200 (1) 207:11	177 (1) 57:5	23 (2) 53:22;69:10	3-4 (1) 170:2
[ph] (4) 190:17;192:14; 234:10;235:9	121 (2) 217:16,20	18 (5) 38:7;44:15;57:17; 82:20;206:21	24 (5) 49:11,11;199:11; 277:9;279:6	35 (2) 8:2;38:18
[sic] (1) 6:2	1247 (1) 207:12	18,000 (1) 122:2	2400 (1) 207:10	36 (1) 100:3
0	12-month (7) 201:6,21;202:11; 214:17;219:3;227:21; 239:19	18-item (1) 82:22	24-week (3) 276:20;283:13;286:22	37 (2) 50:18;100:17
0.3 (1) 282:3	12-period (1) 228:20	19 (1) 243:9	25 (3) 38:17;242:15;252:20	38 (5) 8:2;117:3;218:16; 235:8;236:5
07 (2) 110:21;150:8	12-step (4) 199:12;217:15;218:3; 219:16	1973 (1) 39:4	27 (1) 54:1	3-month (1) 112:6
1	12-week (5) 165:14;214:5;217:22; 218:1;263:21	198 (1) 112:7	28 (2) 55:18;219:7	3-plus (4) 222:8;223:17;228:11; 231:13
1 (24) 49:20,20;92:19;116:2, 11;117:5,18,21;121:2,7; 124:2;137:18,18;139:8; 140:19,20;214:12,16; 217:14;222:22;236:22; 237:1;283:19;312:16	12-weeks (1) 256:1	1980s (1) 40:13	3	3's (1) 151:20
1,353 (1) 246:8	13 (5) 53:20;111:12;113:3; 215:13;219:7	1992 (1) 61:14	3 (58) 30:3;51:5,7;52:14,21, 21;54:3;79:19;100:7; 110:8,22;111:14;115:6; 116:12;117:2;123:4,22; 130:22;133:18,19; 139:8;141:22;145:17; 149:15;151:7;164:14, 15;166:2,3,11,12;167:8; 168:9;170:9;173:7; 200:19;214:12;217:14; 218:1;222:9,22;223:10, 11;245:22;258:2; 274:10;276:8,20;278:3, 7;287:12;301:6,7; 312:16;315:12;319:1, 11;322:2	4
1.5 (1) 141:21	137 (1) 101:12	1-year (3) 99:21;203:5,9	3,000 (1) 168:6	4 (23) 30:8;51:5;53:8;99:3; 110:20;114:6;128:5,7; 140:18,18;145:17; 188:5;191:22;192:21; 214:4,16;218:9;250:15; 251:12;268:16,18; 276:8;278:5
1:25 (1) 194:17	1383 (1) 100:1	2 (41) 29:17;52:14;93:6; 101:7,15;111:3,15; 113:3,22;115:6;116:2, 11;117:4,5,5,7;124:2; 139:8;141:4,16,17,19, 21;142:2;202:6;217:14, 18;229:15;236:16,17; 238:7;245:17;266:4; 276:15;278:4,10; 283:19;301:5,8;318:21; 319:10	3,5 (3) 121:12,14;233:22	4.4 (4) 121:1,10,11,13
1:30 (2) 194:18,18	13C (1) 234:9	2.4 (1) 102:22	3:00 (1) 196:5	40 (3) 74:9;154:20;282:7
1:35 (1) 194:19	14 (5) 27:4;41:16;48:12; 161:9;233:21	2.5 (1) 101:11	3:15 (1) 271:6	40,000 (1) 106:7
10 (19) 43:12;52:13;96:1; 115:6;116:12;117:8,9, 12;118:4,8;139:3,8; 168:11;169:21;206:6; 242:12,20;247:19; 299:15	140/90 (1) 138:15	20 (15) 37:17;52:1;55:7; 116:12;117:9;142:9; 160:15;175:21;187:5; 242:15;243:7,9,10,10; 277:17	30 (23) 7:22;47:14;49:9,14; 50:7;74:8;75:8,9;76:3; 103:21;117:3;154:20; 282:4,8,10,10;294:3,5; 317:3,22;318:2,3,12	400 (1) 187:5
100 (2) 133:4;206:9	1429 (1) 234:9	2006 (1) 150:7	300 (2)	402 (1) 53:17
100,000 (2) 122:1,22	15 (14) 43:16;119:8;127:11; 162:7;173:16;179:6,7; 213:4;214:20;220:13; 222:19;232:9;257:2,5	2009 (1)		43 (4) 133:12,19;134:5,15
11 (10) 41:16;48:12;148:13; 160:12;236:14,15;	15,000 (1) 122:2			434 (2) 161:10;219:1

99:21;290:18	110:7;214:19;220:4; 236:6;241:9,10	90 (5) 116:14;133:4,13; 293:3;318:14	4;189:4;191:20;194:4; 196:16,19,20,22;197:2, 5,10,16;198:2,22; 200:20;202:6,8;203:3,6, 8;210:4;216:11;221:5, 11;222:8,9;223:17; 224:16;225:1,4;228:5, 12,15;229:10,11,14,18; 230:14,21;231:9,12,13, 20;232:4;233:13; 234:16,18;236:12,21; 239:14;257:12,19,22; 263:3;281:7,8;282:14, 14;292:22;293:1; 306:14;315:13;317:10; 327:2,5,12	account (9) 146:3;227:3;229:3,19; 244:1;294:12;304:20; 305:6,7 accounting (2) 226:20;227:2 accounts (1) 227:6 accumulation (1) 241:17 accurate (1) 164:4 accurately (1) 20:3 achievable (1) 171:2 achieve (1) 257:12 achieved (9) 130:14,17;140:17; 220:5,10;221:10,20; 222:13;223:4 achieving (8) 142:12;200:19; 221:12;222:8;224:16; 225:3;282:13;292:22 acknowledge (3) 71:10;295:17;321:7 acknowledged (1) 321:10 acronym (3) 97:10,14;100:13 acronyms (2) 9:1;97:12 across (30) 31:16;32:22;62:3; 71:5;149:12;155:14; 158:1;160:10;162:17; 168:5;180:6;208:1; 213:5;215:8;216:3,4; 217:2,7;219:2,10,11,14; 220:16,18;222:14; 225:12;226:2,14; 267:13;283:11 action (1) 95:5 activated (1) 6:3 active (6) 58:20;97:9;131:18; 182:15;303:13,17 actively-using (1) 218:8 activities (1) 63:21 activity (4) 14:2;64:9;159:18; 161:1 ACTION (7) 6:8;8:17,18;9:1,11; 10:7;153:8 actual (7) 14:1;84:19;135:3;
5	7	941 (1) 123:6 95 (3) 279:21;280:2,6 99 (1) 218:20 995 (1) 103:15	abstinence-based (1) 185:10 abstinent (56) 41:15;48:2,3,9,15; 66:15;74:17;98:15; 103:4,19;104:10,11,15, 17,22;105:2,6,10;107:4, 7,10;109:6;112:14; 113:11,16;132:13; 143:7;155:8;160:15; 161:12,22;162:2; 165:20;167:4;168:4; 169:8,16;173:10; 193:10;219:22;220:3; 221:7;222:5;223:2; 224:18;227:11,12; 230:20;231:4;236:14; 257:10;282:20,21; 313:17;314:2;320:9 abuse (2) 106:3;154:5 academic (4) 33:3;69:22;97:22;98:4 academicians (1) 9:4 Academy (1) 311:1 accelerated (2) 16:21;28:15 accept (5) 87:17;141:14;188:3; 233:10;312:10 acceptability (2) 162:15;173:22 acceptable (7) 46:12;94:16;159:3; 184:6;197:16;259:8; 313:2 accepted (7) 61:11;125:18;163:21; 190:4;196:21;197:3; 233:9 Access (3) 49:20,20;205:20 according (4) 199:17;208:9;213:7; 222:20	
5 (37) 30:13,18;99:4;104:4; 108:18;114:7;115:6; 130:18;134:7,9,11,12; 139:8,14;145:17; 164:14;168:9;169:21; 191:22;192:13,20,21; 214:5,16;250:15; 276:19;277:20;282:18; 283:1,9,9;284:16;288:9, 12,15;290:19;292:8 5.4 (2) 121:2,9 50 (38) 53:3,15;133:3,14,18; 142:7,9;153:19;165:17, 22;168:21;171:11,20; 176:4;221:13,21; 224:21;235:1,3,4; 237:18,18;250:22; 252:15,18,19,21;254:20; 255:20;257:1;258:6,12, 14;282:7;294:1;317:3, 18;318:13 50/50 (2) 200:1;251:1 500 (1) 199:18 53 (1) 207:13 5th (4) 276:10;278:2,17,20 5-year (1) 105:3	7 (8) 38:8;52:6,7;121:5; 139:3;155:10;206:5; 245:17 70 (4) 133:3;188:9;238:11; 294:4 70's (1) 219:20 74 (1) 236:5 75 (8) 133:14,17;171:10; 221:13,21;250:16; 252:21;280:5 76 (1) 51:6 78 (1) 218:16	A AAA-CTTION (1) 8:17 abandoned (2) 151:15;180:13 abbreviate (1) 98:19 abbreviated (1) 191:3 ability (5) 21:3;30:10;48:20; 59:15,17 able (29) 16:20;26:22;31:21; 66:21;71:15;82:4;84:3; 95:9;114:7;128:11; 130:13;149:16;154:13; 155:13;157:10;164:2; 181:18;184:1;216:7; 220:15,17;221:2;222:9; 225:13;298:12;300:8,9; 306:17;307:7 above (6) 49:11;57:17;62:5; 235:4;237:18;293:3 abruptly (3) 287:15;299:19;300:14 absent (2) 109:12;219:19 absolute (2) 193:9;247:20 absolutely (1) 154:9 abstainers (3) 102:15;203:15,22 abstinence (117) 51:8;52:22;53:2;57:8; 62:14;66:22;73:19; 83:18;99:6;100:7; 101:21;102:2,21; 106:22;109:19;110:16, 17;111:19,22;112:3,8, 11;114:10,18;124:7; 126:1;130:17;132:10; 133:5,11;134:3,5;143:7; 154:21;155:2;156:15; 157:1;159:14;161:6; 162:4;166:15;169:20; 170:1,10;171:2;173:7,8, 8;178:17;187:20;188:1,	8 8 (17) 117:20;134:8;161:13; 166:2;167:9;168:6,10; 246:3;253:1,17,18; 254:10;255:11;261:13; 278:4;279:20;280:1 8- (1) 256:1 8.2 (1) 103:2 8.5 (1) 128:7 80 (8) 167:17;216:2;242:17; 244:7,9;276:3;312:17; 315:4 80-90 (1) 63:9 80s (1) 192:14 80's (1) 219:20 85 (1) 280:4 85-90 (1) 200:6 87 (1) 49:8 8-week (3) 74:10;214:6,18	
6	9	AAA-CTTION (1) 8:17 abandoned (2) 151:15;180:13 abbreviate (1) 98:19 abbreviated (1) 191:3 ability (5) 21:3;30:10;48:20; 59:15,17 able (29) 16:20;26:22;31:21; 66:21;71:15;82:4;84:3; 95:9;114:7;128:11; 130:13;149:16;154:13; 155:13;157:10;164:2; 181:18;184:1;216:7; 220:15,17;221:2;222:9; 225:13;298:12;300:8,9; 306:17;307:7 above (6) 49:11;57:17;62:5; 235:4;237:18;293:3 abruptly (3) 287:15;299:19;300:14 absent (2) 109:12;219:19 absolute (2) 193:9;247:20 absolutely (1) 154:9 abstainers (3) 102:15;203:15,22 abstinence (117) 51:8;52:22;53:2;57:8; 62:14;66:22;73:19; 83:18;99:6;100:7; 101:21;102:2,21; 106:22;109:19;110:16, 17;111:19,22;112:3,8, 11;114:10,18;124:7; 126:1;130:17;132:10; 133:5,11;134:3,5;143:7; 154:21;155:2;156:15; 157:1;159:14;161:6; 162:4;166:15;169:20; 170:1,10;171:2;173:7,8, 8;178:17;187:20;188:1,	9 (6) 101:17;103:6;134:8; 155:10;278:21;290:1	
6 (31) 103:17,21;104:1,12; 149:16;192:13;222:22; 236:7,15,17;237:20; 238:5,10,19;243:7; 274:10;275:22;276:12, 14,19,22;277:21;278:22; 282:22;284:15;288:8,14, 15;290:2,22;312:16 60 (2) 151:3;171:21 60-patient (1) 55:6 60s (1) 192:12 65 (3) 139:10;141:5;238:19 692 (1) 122:21 6-minute (1) 15:18 6-month (6)	9 9 (6) 101:17;103:6;134:8; 155:10;278:21;290:1			

140:17;170:19;178:9; 303:20 actually (95) 5:11;6:11;8:17;15:8, 11;16:2;34:5;36:3,7,18; 42:16,21;43:6,7;44:16; 45:8;53:12,14;55:20,22; 56:7,8,17,19;57:1,22; 58:5,8;60:8;73:4;76:3; 80:14;85:5,7;87:8; 88:10,11;93:6;100:20; 101:7;104:7;105:15,16; 106:14;108:6;111:5; 113:3;114:1;115:16; 122:16;127:12,17; 133:3;135:19;142:11; 150:3,5,11;156:9; 160:21;161:14;167:17; 174:18;177:4;178:1,15; 180:2;188:7,12;192:18; 200:16;201:12;203:3; 209:4;220:8,10;222:11; 227:8;228:3,10;234:12; 257:5;258:14;264:2; 265:17;268:21;275:1; 298:14;300:11;301:15; 302:22;316:12;323:6, 20;326:17 acute (4) 137:7,13,14;192:2 acutely (1) 183:9 add (5) 34:19;77:13;88:3; 117:5;193:3 added (4) 98:17;105:21;132:16; 277:9 Adderall (1) 76:5 addicted (1) 65:9 Addiction (27) 8:19;47:7;64:7;65:15; 73:13;84:11;91:15,17, 20;92:12;98:11,17; 115:19;175:8;182:20; 183:7;205:18,22;233:8; 271:19,22;280:12,17; 291:13;306:21;318:7; 322:14 addictions (5) 9:8;34:14;38:21;68:2; 88:3 addictive (1) 42:12 addicts (4) 47:21;85:1;207:15; 328:20 adding (2) 158:14;200:12 addition (3) 17:20;28:8,16	additional (11) 27:8;80:10;193:17; 199:13;216:9;256:20; 276:10;277:9;281:13; 286:16;311:8 addressed (1) 174:3 adequate (7) 19:10,21;24:12,19; 31:2;170:5;179:18 adherence (1) 266:5 adjourned (1) 331:9 Adjournment (1) 330:1 adjudicate (2) 176:18;320:13 adjustment (1) 234:9 adjustments (1) 30:17 administer (1) 44:15 administered (4) 42:18;43:1,9;44:22 ado (1) 96:10 adulterants (1) 172:15 advantage (2) 74:3;125:2 advantageous (1) 291:14 advantages (5) 51:13;166:16;188:7; 280:15;296:9 adverse (4) 18:11;65:8,14;303:16 advertise (1) 256:3 advertisement (1) 256:2 advertisements (1) 325:4 advice (3) 25:2;32:5;143:16 advocating (2) 92:1;323:15 affairs (2) 10:3;97:19 affecting (1) 88:22 affects (2) 139:12;255:18 aficionado (1) 153:22 African (5) 53:18;200:2;233:20; 234:21;236:11 afternoon (5) 124:6;156:8;232:19; 271:17;330:20	afterward (1) 8:8 afterwards (1) 8:14 Again (91) 10:13;16:10;32:12; 49:12;50:19;51:9,10; 54:22;55:15,16;59:19; 67:16;99:2;101:4;102:4, 7,20;103:20;104:9,11; 107:20;109:8;111:9,10, 18;113:2,15;114:9,12; 116:12;117:19;134:4; 135:22;152:16,22; 157:5;161:21;162:10; 163:15;165:9;166:16; 170:13;171:19;172:19; 178:2;180:1;184:19; 185:4;186:18;194:21; 200:21;209:12;211:2; 216:12;217:19,22;218:3, 19;221:16;222:3,18; 223:13;224:1,5,17,19; 225:2,21,22;226:16; 229:9,19;230:5;231:19; 237:12;242:14,15; 275:16;279:15;280:13; 282:11;283:6;284:4; 285:3,13;288:14;290:1; 297:18;307:2,3;323:3 against (12) 22:17;36:17;66:3; 105:8;131:3;136:14; 138:10,16;139:10; 189:13;239:17;293:4 age (2) 53:14,14 agencies (1) 124:19 agenda (5) 7:15;8:6;10:4;76:22; 95:10 aggression (1) 171:4 aging (2) 53:16;210:11 ago (8) 53:13;89:22;100:14; 170:11;193:17;198:16; 209:5;311:2 agonist (1) 310:6 agree (8) 75:13;88:1;271:1; 312:9;314:4;323:4,6,15 agreed (3) 280:14;292:1;314:3 agreeing (1) 84:20 agreement (6) 250:12,17,22;259:8; 265:20;280:19 agreements (2)	250:20,21 agrees (1) 33:15 ahead (5) 43:5;52:2;91:4; 177:15;271:11 aim (1) 135:1 airport (1) 6:20 al (1) 135:13 alcohol (63) 39:3;52:8;65:17,17, 20;66:4;74:2;77:10; 84:18;96:10,17;98:10; 105:15;106:2,11,11; 108:5,18;112:7;115:18; 118:15;120:8,19; 121:21;122:3,22; 123:15;128:14;129:3; 133:3;136:18;140:6; 141:14;142:3;144:19; 146:5,11,18,19,21; 155:8;165:6;173:5; 177:14;178:5,19; 182:10;185:8;187:19; 189:2,16;200:3;205:8; 207:1;213:16;217:21; 226:3;253:19;260:1; 268:3,9;296:9,9 alcohol-dependent (6) 48:3,5;52:8;57:4; 123:1;217:17 alcoholic (1) 296:22 alcoholics (3) 39:18,20;177:22 alcohol-related (6) 100:12;107:15;120:4; 126:12,16;131:4 alcohol's (1) 139:11 alert (1) 24:9 algorithm (1) 181:15 aligned (1) 285:22 Alkerme's (1) 206:11 all-comers (1) 218:14 allow (8) 51:20;115:8,9;116:11; 117:6,12;274:13;290:20 allowed (9) 5:14;116:10;122:16; 273:15;290:9,18;291:2; 300:22;301:4 allowing (7) 59:21;117:9,9,14; 266:20;281:10;295:3	allows (1) 291:17 alluded (1) 81:14 alluding (1) 135:12 almost (16) 45:9;78:12;81:7; 157:1;158:4,5;196:10; 199:18;214:4;238:10, 11;239:8;273:12,17; 285:14;296:22 alone (10) 22:12;198:19;200:17, 18;241:18;264:19; 275:5;302:18,22;303:5 along (7) 197:19;232:13; 261:10;281:7;283:10; 293:5;316:16 aloud (1) 90:22 Alterman (3) 45:18,19;51:15 alternate (1) 131:21 alternative (3) 129:20;132:4;171:1 although (18) 45:4;57:19;65:14; 69:20;82:16;85:16; 215:11,13;219:9,15,20; 233:2;237:21;268:13; 287:7;310:18;313:21; 329:3 altogether (1) 65:18 always (30) 35:3,22;75:10;90:20; 107:20;108:11;121:4; 130:15;145:4;156:14; 157:1;159:19;160:2; 161:21;169:13;170:15; 175:5;178:11;183:17; 184:4,20;194:8;244:9; 245:3;261:7;270:3,7; 274:7;288:17;297:7 amantadine (4) 54:16;55:2,10;72:1 amazing (1) 239:16 American (4) 53:19;200:2;204:14; 236:11 Americans (2) 233:20;234:21 among (16) 43:14;53:15;56:7; 66:4;78:15;147:2;207:3; 211:13;236:5,13;237:18, 19,21;238:7;288:11; 292:4 amount (22)
---	--	--	--	--

22:15,16;23:4;119:7; 120:8,13,19;121:21; 139:6;141:14;143:4; 145:22;146:20;174:13; 209:7;236:20;248:9; 294:22;296:18;304:17; 305:7;309:9	234:2;235:1;236:3 ankle (1) 146:8 announcement (2) 256:9,10 announcements (3) 146:12;256:3;331:3 answered (1) 269:2 antagonist (3) 310:6,8;322:16 anticipated (1) 292:1 anti-depressant (1) 156:17 anti-tumor (1) 28:12 anxiety (1) 38:11 anymore (1) 49:20 apart (2) 87:5;103:3 apologize (2) 65:5;209:6 apparent (1) 257:6 apparently (1) 35:6 appear (4) 265:11;288:6,8;295:2 appeared (3) 112:1;181:18;287:3 appears (4) 114:12,17,20;255:15 appetite (3) 38:9;40:22;47:2 Applause (12) 33:22;60:3;129:13; 143:19;153:2;174:15; 212:11;232:6;240:9; 256:13;271:9;296:3 apples (1) 270:19 applicability (1) 314:4 application (5) 271:21;272:3,21; 281:16;290:12 applications (1) 256:8 applied (1) 316:3 apply (6) 20:12;25:16;269:9; 306:22;307:5;324:17 applying (1) 265:5 appreciate (7) 11:12;82:12;87:10; 89:14;175:4,12;330:9 appreciated (5) 67:18;68:7;70:9;	71:12;175:5 approach (17) 11:4,15;20:14;156:11; 168:3;178:10,22;214:4; 239:5;274:22;291:9; 292:2,12;295:6;306:18; 311:12,15 approached (1) 156:7 approaches (5) 63:9;129:5;155:21; 193:10;330:21 approaching (3) 155:22;162:6;167:6 appropriate (17) 12:19;13:15,18,22; 19:20;20:12;25:10;27:2; 30:17;31:13;80:20; 153:16;157:6;187:15; 277:19;280:20;316:19 appropriately (1) 82:6 approval (11) 12:9;16:15,20,21; 17:9;23:1,26;13;27:20; 28:15,15;122:11 approve (3) 194:3;208:13;309:7 approved (7) 88:14;233:7;235:9,16; 236:1;326:7,15 approximate (1) 15:21 approximately (3) 278:10;294:1,4 April (1) 235:7 arbitrarily (1) 52:21 arbitrary (1) 252:20 Archives (1) 71:16 area (6) 9:6,8;88:15;281:8; 312:1;327:8 areas (10) 33:14;72:16;118:16; 220:12;223:13;225:12; 271:20;280:16;303:14; 316:9 arguably (1) 284:17 argue (1) 310:18 argument (1) 89:3 arm (14) 267:21;276:9,13; 277:1;279:19;282:1; 284:16;288:22;289:1, 11;293:7;294:2,20; 302:13	arms (3) 267:15;277:3;317:21 around (31) 44:19;69:9,10;100:4; 107:19;110:21;111:12; 113:20;115:14;117:8; 122:18;124:5;128:5,7; 145:11;146:8;152:4; 160:11;163:7,10; 165:15;167:1;170:9; 191:22;192:13;193:7; 215:12;252:10;279:9; 297:4;308:1 arrested (1) 66:1 arrests (2) 63:21;64:2 arriving (1) 8:3 arrows (1) 133:13 arteries (1) 234:3 artery (2) 238:18;241:5 arthritis (2) 90:9,12 Arthur (4) 45:18,18;46:1;51:15 articulate (1) 307:9 articulating (1) 175:15 A's (1) 8:18 ascertainment (1) 177:7 Ashley (12) 11:3,6,10;66:10; 67:20;79:16;85:22; 92:13;120:10;127:7; 137:21;262:22 Ashley's (3) 67:12;74:20;83:21 ASI (47) 47:10,12,14,15;52:13, 18;53:4,21;63:22;64:15; 75:7;86:6;199:19; 203:20;216:4,5,20,21; 217:2;225:12;226:1,2, 17;246:11,12;247:3,4,4, 8,11;249:4,10,10,15,16; 253:15,19,19,21;254:1, 13,15;255:1,4,13; 261:14,16 aside (4) 46:8;51:14;58:15; 232:11 aspect (4) 66:7;191:14;226:22; 228:21 aspects (5) 12:13;17:14;19:1;	68:12;139:13 aspirational (1) 265:8 ASSA (2) 39:9;69:13 assess (3) 18:11;69:7;199:22 assessed (5) 13:20;199:18;214:15; 284:20;285:1 assessing (3) 64:6;73:10;148:17 assessment (35) 13:15,18,22;15:13; 19:13,19;20:4,13,20; 21:18;22:11;23:5,14; 24:20;25:11,14;26:6,8, 16;28:5,6,18,22;29:3; 32:6,20;33:5;37:5;39:2; 85:12;145:8;214:3,4; 216:14;285:5 assessments (31) 12:10,17;13:2,3,8,9; 14:11;19:17;22:4;24:7; 25:1,5;26:4,7;27:2,6,11, 13;30:21;31:1,2,12,14; 32:21;33:8,11;68:8; 69:3;80:5;163:1;216:3 assignment (1) 303:21 assist (2) 31:11;89:10 assistance (1) 169:2 associated (33) 44:7;57:7;64:9,10; 65:21;71:22;72:6; 151:17;201:20;203:2,5, 8;224:20;228:1,6,16; 230:21;231:21;232:3; 233:18;234:11;244:19; 245:7,10,13;246:20; 248:14;251:9;252:11; 255:16,21;258:18;263:2 association (7) 226:7;247:15;248:2; 249:21;255:2,5,8 associations (1) 249:13 assume (4) 177:3;243:3;260:2; 323:7 assuming (3) 164:18;268:1;323:11 assumption (2) 165:11;167:20 assumptions (4) 164:19;166:10;168:2; 270:15 assured (1) 310:9 atherosclerosis (3) 239:18;263:6,11
--	--	--	---	--

attend (1) 98:2	188:1,18;189:13;192:10, 14;194:19;196:10,13; 208:13,17;242:15,19; 244:9;260:3;261:9; 306:3;307:3;321:21; 326:21	121:19;128:22;133:10; 135:14;138:22;140:12; 189:16;190:22;201:4, 22;202:9,12,17;203:10; 211:15;213:3;233:12; 237:4;238:4;242:9,21; 247:5;265:3	beneficial (6) 36:15,19;80:22;91:21; 197:3,3	308:3;327:12;328:3
attention (12) 14:5;24:13,19;27:2; 172:8;220:22;244:11; 275:12;295:14,16; 303:20;331:7	backed (1) 69:17	basing (2) 307:11,12	benefit (76) 12:2,14,15,18;14:18, 18,20;15:1,7,8,10,11,14; 16:5,10,14,18,19;17:2; 19:10,18;20:5;21:22; 22:17;24:15;25:8,15; 28:3,17;31:22;35:19; 65:18;80:7,16;91:17; 118:5;122:16;125:8; 177:2,4;180:13;196:7; 197:10;198:1;209:22; 210:4;230:17;231:10; 232:3;262:15,15,17,20; 263:7;275:8;292:11,16; 294:22;295:10;297:13; 303:1,4,6;307:10,19; 308:2;318:10,11,15; 320:5;321:8;326:8,16, 18;327:16;328:6	bias (3) 273:13;294:16;317:14
attentive (1) 35:2	backfill (1) 165:8	basis (3) 26:16;27:3,12	benefits (10) 12:6,12;13:1;22:19; 23:1,6;69:2;123:17; 150:4;232:5	biased (1) 285:16
attribute (1) 75:10	background (7) 5:8;11:13;92:19; 94:20;95:7;275:15,18	basket (1) 65:14	benzodiazepine (1) 308:21	big (18) 21:16;40:13;101:16, 18;106:6;142:6;153:12, 12;163:19;184:5; 204:11;260:20;269:2; 298:19;308:11;309:20; 320:22;324:9
attrition (4) 162:16;164:18;200:4; 269:17	backing (1) 129:18	Bathrooms (2) 10:21,21	Benzos (1) 207:22	bigger (3) 30:8;109:14;215:18
audience (2) 256:7;265:4	bad (11) 50:2,2,3;64:10;66:5; 69:22;168:14;252:6; 259:9,20;267:22	batteries (2) 65:20;214:3	benzoylcegonine (3) 55:20,21;56:4	biggest (6) 61:16;101:8;111:16, 17;308:12;319:13
author (1) 115:4	badly (1) 323:9	battery (1) 66:2	benzoylegonine (3) 249:3;250:8;258:13	biggies (1) 43:2
automatically (2) 292:10;294:22	bait (1) 89:16	bears (2) 275:12;295:13	besides (2) 243:21;244:2	Bill (3) 41:10;100:14;126:18
availability (2) 162:16;229:20	balance (1) 78:1	beautiful (1) 52:12	best (18) 17:5;22:7;35:5;54:10; 58:16;62:16;77:18; 161:14;176:6;200:15; 201:1;203:4;205:16; 252:22;266:10;270:13; 312:6;321:9	bingers (1) 172:5
available (16) 8:12;11:9;29:10;31:1; 33:5;82:3;89:11;93:1; 95:3;187:13;196:14; 272:9;285:3;294:12; 297:18;301:12	ball (1) 224:3	became (3) 44:9;48:9;303:22	bet (1) 322:14	binges (1) 179:2
avenues (1) 239:16	Baltimore (1) 233:20	become (7) 19:15;66:14;67:4; 111:15;153:22;181:1; 329:15	beta (1) 82:13	biologic (1) 36:14
average (13) 38:16;53:14;54:1; 101:12;108:16;109:10; 122:18;128:3,4,6; 215:12;227:21;228:4	Bankole (2) 56:22;136:5	becomes (3) 17:22;18:17;82:6	betray (1) 189:14	biological (1) 158:9
averaged (2) 103:2;128:5	bar (1) 233:12	begin (8) 32:9;39:11;125:9; 157:10,13;159:8; 177:12;191:7	better (36) 26:21;31:9;40:4; 42:22;43:22;50:1;54:14; 56:9;57:12;59:5;61:15; 71:22;77:21;87:3;93:22; 94:8;111:4;130:13; 155:10;180:9;189:1; 200:16;211:18;230:10; 246:21;250:2;256:16; 259:16,20;260:19; 261:10;293:8;300:5; 302:1;312:5;322:5	biomarker (2) 17:1;240:16
averaging (1) 206:20	barely (1) 329:1	beginning (14) 7:21;23:19;24:15; 41:14;43:4;54:16;74:7; 159:21;161:6,13; 173:13;253:7;257:19; 326:9	block (1) 238:18	
avoid (3) 5:19;25:3;280:22	base (1) 93:11	behave (1) 48:17	blocker (1)	
avoiding (1) 73:16	based (35) 150:20,21;151:14; 165:19,21,22;173:5; 186:15;191:6;193:8; 196:7;204:13;216:12, 20;250:3;259:1;265:14; 266:5;273:5,16,20; 276:9;284:4;286:12,13; 288:4;301:7;302:4; 304:1;309:10;315:17; 318:8;328:15,20;329:5	behavior (21) 13:19;64:9;65:17; 135:3;233:15,17;273:6, 8;281:2;282:17;284:4; 285:11;286:14;287:7,8; 291:1,19;292:8,10,15; 303:2		
aware (7) 6:9;194:12;261:19,20; 284:21;298:9;328:10	baseline (28) 48:13;53:22;54:13; 55:17;57:9;75:3,8;94:5, 9,12;132:9;158:10; 171:15;174:5;176:5; 219:6;228:8;236:7,10, 12,18;238:10;241:17; 243:14;252:16;253:3; 258:7;311:11	behind (6) 149:14;224:3,3;232:8, 9;244:14		
away (3) 78:17;165:2;306:17	basic (3) 37:22;49:3;81:17	believes (1) 233:15		
B	basically (35) 39:6,11;41:12;61:13; 98:12,21,22;100:11,17; 105:22;106:9;107:13;	below (2) 49:12;62:5		
back (57) 6:15;7:1;11:21;34:5; 54:20;55:8;57:9;60:15; 61:13;67:20;68:6;71:21; 76:5;78:4;80:5;83:4,21; 87:10;88:20;89:21; 92:13;103:21;104:14; 107:20;109:1,16; 111:13;117:2;127:8; 134:10;150:8;156:1; 164:14;168:10;170:8; 175:9;184:17;187:20;				

<p>310:9 blood (18) 16:16;123:20,21; 124:2;131:5;136:1; 138:9,11,19,21;142:5; 145:22;146:11,17,19,21; 238:18;240:19 blue (9) 102:2,3;110:17; 111:10;116:18;140:14; 251:15;283:13;284:1 Bluemke (2) 239:3;241:3 blunt (1) 93:22 board (1) 208:1 Bob (7) 5:11,12,13,20;8:22; 11:8;67:4 bolts (1) 129:11 Bonferroni (1) 253:13 bookend (1) 67:11 bored (1) 163:9 boring (1) 46:7 borrowing (1) 133:6 boss (2) 194:7,9 both (25) 20:17;54:6;67:9; 68:11;69:2,3;76:18; 97:7;112:10;140:3; 175:16;199:6;248:1; 249:18;254:8;266:5; 273:15;279:8;282:12; 288:21;292:5;295:18, 20;299:9;305:3 bother (2) 135:9;232:12 bottom (4) 104:9;132:16;283:17; 290:19 bradycardia (3) 45:9;70:2,4 brain (2) 42:12;44:7 brave (1) 160:8 break (10) 95:16,20,21;124:9; 147:2;175:3;193:22; 194:17;266:15;271:4 breakfast (1) 194:19 breaks (2) 6:11;164:7 breeze (1)</p>	<p>217:11 Brian (12) 10:4;156:8;161:4; 174:6;212:12,16;258:1; 264:13;266:19;267:6,8; 312:15 Bridget (1) 106:8 brief (6) 51:9;246:14;248:6; 250:5;254:3;275:15 briefly (4) 99:15;100:10;103:11; 129:16 brilliant (1) 45:19 bring (8) 8:8;31:22;78:10; 175:1;197:8;262:11; 300:8;311:22 bringing (1) 29:6 brings (3) 136:11;142:19;263:14 broad (1) 65:14 broader (5) 11:22;19:5;67:7; 327:8;328:1 brought (5) 75:19;78:16;89:4; 190:7;265:9 bucks (3) 242:12,17,20 building (1) 59:14 bulk (1) 131:2 bullet (1) 269:12 bullets (1) 26:1 bunch (5) 8:18;51:5;171:1; 212:3;297:15 buprenorphine (24) 275:21,22;276:3,6,10; 277:6,11,13,18,22; 278:3,19;285:18;286:4, 9,13;287:12;288:1,10, 13;299:10,21,22;327:20 burden (1) 159:16 BURKE (5) 83:6,9,9;84:14;92:10 busy (1) 85:14 buy (1) 324:3 buy-in (1) 185:15 buys (1) 183:8</p>	<p style="text-align: center;">C</p> <p>calcification (1) 238:17 calculate (9) 137:2;153:20;157:17; 162:11;165:18;216:7; 230:2;243:1;270:18 calculated (3) 249:3,7;268:13 Calendar (2) 215:2;216:9 calendar-based (1) 215:3 call (7) 119:12;133:21; 134:11;235:5;276:19; 319:5;320:18 called (6) 115:13;127:11; 216:18;256:5;277:16; 311:12 came (34) 7:3;37:18,20;39:15; 40:18;41:13;48:1;54:6; 85:17,18;99:12;106:8; 123:12;125:16;127:4; 132:7;142:6;150:16,17; 152:13;153:16;157:1; 162:7;165:9;171:17; 172:9;191:12;215:12; 220:6;225:17;242:10; 268:8;269:5;313:21 can (199) 5:12;6:19,21;10:5,16; 12:17;13:13;14:12; 16:14;18:8,12;20:4; 21:18,20;22:5;23:3; 24:6,20;25:2;26:3,21; 29:20;30:6;31:19;32:19; 33:15;34:5,20;35:14; 36:13,18;51:16,17; 54:13;64:1;72:14,20; 77:22;80:8;88:9;89:10; 91:4;93:17,18;94:7; 96:22;98:7;101:9,12; 102:5;103:2;104:6; 110:13,20;111:19; 113:8;114:11;115:22; 117:18;118:7,11,18,20, 21;123:16;124:4;125:6; 127:3;128:19;131:3,11; 132:4,9,13;133:1;137:2; 143:15;144:1;153:4; 154:20;155:10;157:10, 13,17;158:3;160:20; 162:12,15;164:3;167:12, 14;169:6,15;170:6; 171:7,8,9;172:5;174:3; 176:9,18;177:1,4;178:5, 15,15,21;179:16,18,19; 180:2,22;181:1,4;182:4;</p>	<p>183:12,15;184:12,13; 186:3,17;191:15;209:3; 215:4;222:1;223:13; 230:10;231:16;232:9; 240:1,1;244:5;247:5,8; 248:8,17,19,19,20,21,21, 22;249:10,12;250:9,15; 254:5;261:5;262:2; 263:2,4,7;266:3;267:15, 19,21;270:9;273:11,13; 275:10;276:11,12; 282:21;285:16;286:6,6; 287:15;291:14;294:14; 298:16;299:22;300:18; 301:16;304:17;306:15; 307:8;312:18;313:9; 314:9,12,16,19,20,21; 315:11;316:3,22;317:1; 318:16,19;320:16,16; 321:6,19;322:1;324:14; 327:11,15;329:15 cancer (2) 120:15,19 cancers (1) 140:3 candidate (3) 173:16;213:4;220:13 candidates (1) 173:4 cannabis (1) 207:1 cap (1) 141:16 capitalize (1) 178:3 capture (1) 263:17 captures (1) 243:15 capturing (1) 257:14 Card (1) 236:2 cardiologist (3) 235:6;238:21;239:3 cardiovascular (3) 138:22;210:13;234:10 care (9) 60:13,14;130:6;154:6; 159:11,15,22;184:22; 193:18 career (1) 55:13 careful (6) 69:14;132:2;134:16; 166:4;244:5;269:9 carefully (2) 22:18;205:5 cares (1) 154:22 carried (2) 106:10;114:6 CARROLL (20)</p>	<p>62:1,10;100:14;153:5, 6,7;168:16;174:19; 175:12;178:7;179:16; 180:8;186:14,17;188:5; 190:16;212:13;269:15; 312:15;314:9 carryover (1) 181:16 case (25) 13:14;14:2;43:10; 49:10;51:7,10;55:18; 72:5;183:20;221:3; 245:11;247:14;249:1,9; 252:12;272:18,22; 273:3;275:14;280:12, 20;281:11;288:12; 324:13;326:9 cases (5) 13:22;35:13;168:8; 261:17;270:2 cat (1) 268:6 catch (2) 181:13;259:12 categories (14) 26:10;118:11,20; 123:2,15,16,19;125:19; 129:4;186:1,6,8;279:18; 280:8 category (7) 84:12;118:11;125:1; 280:2,4,5;328:2 cats (1) 142:13 causal (1) 243:20 caution (1) 69:14 cautious (1) 261:22 CBT (8) 154:19,20;214:7; 217:15,18;218:10,12,18 CBT-plus (1) 218:18 CCRC (2) 235:9,21 CDER (3) 28:21;33:12;295:20 CDF (6) 279:3,15,22;280:13; 281:19;298:3 CDRH (1) 295:20 ceasing (1) 65:17 Celia (9) 65:2;66:16;106:15; 175:1,6,7;192:18;194:2; 197:6 Celia's (1) 193:1 cell (1)</p>
--	---	---	--	---

6:2 cells (1) 237:2 Center (12) 38:20;45:20;51:13,18; 56:22;59:12,17,21; 69:22;239:5;295:21,21 centers (2) 40:17;59:11 centralized (1) 205:18 certain (9) 95:12;197:1;221:10; 273:12,17;293:18,21; 298:20;305:7 certainly (22) 61:15;65:10;67:7; 71:18;77:5;82:7;96:3; 98:9;101:18;102:9; 103:5;108:17;119:11; 120:4;126:9;162:14,18; 164:2;169:15;171:22; 257:1;296:20 certificate (2) 239:20;240:2 certificates (1) 240:2 certified (1) 206:1 CGI (9) 248:4;254:8,17;255:2, 4,12,15,22;256:21 CGIS (2) 249:5;254:8 chairing (1) 5:5 challenge (7) 124:12;136:8;139:16; 142:16;182:22;303:11; 312:1 challenges (7) 31:16;130:5;136:3; 142:19;177:5;212:22; 272:20 challenging (3) 139:17;257:11;303:22 chance (2) 240:12;251:1 change (40) 16:4;21:3,5,18,19,20; 22:10,13;23:4,4;30:11, 12;56:15;62:3,13;66:20; 68:14,15,20;94:8; 126:14;144:13;146:16, 17;150:19;156:16,22; 157:3;160:20;225:16; 228:18;229:4;242:7; 243:12,16;248:3; 255:14;263:5;281:1; 316:20 changed (1) 317:1 changes (31)	22:12;23:9;38:10,12; 40:22;41:1;42:11;44:7; 160:6;228:22;245:9,11, 14;248:13,15;249:19; 250:1;251:8,9,18;255:3; 260:12;261:14,15,16; 263:17;282:16;291:18; 292:8,9,15 changing (2) 36:17;124:1 channels (1) 89:5 characteristics (5) 31:10;155:19;163:22; 173:20;236:10 characterizes (1) 160:12 charge (3) 126:22;206:12;327:7 charged (2) 184:13,13 chase (4) 230:15;231:8;269:19; 270:11 cheaper (1) 146:13 Check (4) 6:19,21;114:18;152:3 checked (1) 58:7 checklist (1) 24:1 chief (2) 239:2,4 choice (5) 26:4;273:2;275:11; 294:6;295:12 choices (1) 304:14 choir (3) 154:4,4;194:15 cholesterol (1) 123:20 choose (5) 134:17;141:21,21,22; 161:5 choosing (1) 325:14 chose (4) 216:10,22;268:14; 301:19 chosen (1) 305:14 chronic (9) 90:8;119:6,8;120:9; 137:7,9,10,13;236:11 chronically (1) 161:17 Chuck (3) 51:15;53:4;98:4 churn (1) 138:4 cigarette (1)	62:15 CINA (1) 60:16 cirrhosis (1) 122:5 cited (1) 190:5 claims (3) 18:6;27:3,12 clarification (1) 179:12 clarify (2) 82:9;242:4 classes (1) 139:14 classic (1) 303:15 classified (1) 103:18 classify (1) 252:14 clean (13) 40:8;42:1;55:3;77:12; 165:20;166:21,22; 196:20;216:13;321:15; 322:4,8,12 clear (8) 20:5;92:1;152:2; 170:7,12;210:3;240:14; 314:22 clearly (5) 42:6;64:10;158:15; 187:6;331:2 clinic (5) 14:2;85:14;278:1; 310:14;314:18 clinical (160) 7:10,17;8:20;9:3;12:1, 7,14,20;13:3,8,16;14:7, 11;15:11;16:10,13,18, 19;17:2,5;18:5;19:4,11, 19;20:13;22:5;23:16,19; 25:20,21;27:5,15;28:3, 18,22;29:2,15;31:2,8,11, 14;32:7;33:8;34:12,16; 37:12;38:4;41:4,42:10; 44:4,6;50:10;51:18; 52:6;54:11;58:2;60:13, 14,16;65:12,18;66:9; 69:4;71:6;72:1,6;74:7; 77:2;80:9;84:1;89:1; 91:2;94:22;96:16,20,22; 97:2;99:13;103:9;108:5, 18;118:4,15,18;119:11, 13;122:12,15;123:19; 124:14;125:8;129:3; 132:12;137:1;139:19; 140:15,18;141:1;143:9, 15;148:15;154:15; 155:3,15;156:4,11; 162:10;163:4,6;168:7; 177:2,4,5;178:15; 183:19;196:6;210:3;	217:14;232:3;235:13, 14;239:4;245:18; 246:13;247:12,21; 248:2;249:17;250:3; 258:17;262:14,15; 263:14;271:20;275:7; 277:14;280:15;285:1; 292:11,16;294:22; 295:10;297:13;298:7; 303:1,4,6;307:10,19; 308:2;316:13,18,20; 317:7;318:6,10,15; 320:5;327:16;328:6 clinically (17) 7:13,16;45:13;83:2; 130:9;179:3;197:10; 198:1;250:21;251:2; 252:1;262:17,20;281:1; 291:18;295:8;317:19 clinician (5) 13:17;44:22;84:7; 130:12;157:18 clinicians (11) 13:6;29:20;40:14; 41:3;82:3;86:22;124:21; 150:3;154:8;159:5; 185:15 close (9) 78:2;102:6,9,13; 107:10;114:5;160:14; 266:14;295:14 closely (3) 15:21;17:10;19:1 closer (1) 104:17 clue (1) 154:22 Cocaine (210) 37:4,5,10;38:7,10; 39:12,21;40:2,13;41:17, 20,22;42:5,8,9,16,18; 43:1,2,7,9,11,14,19,20, 21,22;44:5,7,10;47:1,8, 9,13,15,17,19;48:1,2,4,6, 17,18,22;51:22;52:4; 53:7,19,20,21;54:17; 58:21;62:15;63:13; 71:11,18;74:3,8;75:4,9, 17;78:12,15,22;79:3; 83:14;84:5,10,22;86:5, 16;87:2;91:13;143:4; 149:10;156:4,19;157:6; 158:21;160:20;161:14; 163:16;164:22;165:5; 167:8,16;168:9;170:4; 172:12;173:5;174:4; 178:18;179:1,6;182:1,1, 20;183:7,8;191:16; 198:14;199:6;201:1,6, 18;202:10;203:1,4,8,13; 207:2;209:21;210:11, 14;211:17;212:15; 213:6,10;215:4,7,9,20,	22;216:7;217:8;218:4, 16;219:5;220:11;222:6, 21;223:16,21;224:8; 225:9,15;226:3,7;227:7, 13,15,16,19,20;228:1,3; 229:8;231:20;232:17; 233:8,11,15;234:10,16, 18,20,22;235:8,11,13,20, 21;236:11,13,13,14,17, 19,20,22;237:9,11,14,15, 21;238:5;239:14,15; 241:13;242:6;243:21; 244:2;245:7,10,13,19; 246:20;248:9,10,14,18; 249:5;250:8;255:6,10, 18,19,20;258:11,15; 263:9,9;265:11;308:21; 321:11,22;324:17; 328:13,19;329:8 cocaine- (4) 48:2;57:4;200:3; 217:16 cocaine-dependent (12) 37:14,14;39:20;40:15; 43:10,12;52:11;53:16; 58:15;85:15;86:12; 218:8 cocaine-free (1) 219:14 cocaine-induced (1) 239:17 cocaine-injecting (1) 203:2 cocaine-only (1) 217:20 cocaine's (1) 201:15 cocaine-use (1) 213:4 cocaine-withdrawal (1) 43:18 co-chairing (1) 5:11 coefficient (3) 249:7;250:11,12 coefficients (1) 228:13 coffee (1) 6:13 cognitive (2) 198:18;246:10 cohort (8) 23:7,10 coincided (1) 47:6 collaborating (1) 76:1 Collaborative (1) 198:15 colleague (1) 129:8 colleagues (2) 80:9;326:10
--	---	---	---	--

collect (12) 137:10,12;155:2,4; 158:19,20;162:18; 168:6;176:19;304:9; 314:12;320:19	52:8;217:21 co-morbid (1) 50:16 comorbidities (2) 151:6;204:2	174:8 compliance (7) 265:14,15,17,18,20; 278:12;289:6	conclusions (3) 239:12;245:1;298:9 conclusive (1) 282:17 concordance (1) 329:6 concurrent (4) 46:6,18,20;70:13 condition (12) 12:21;17:13;19:2; 23:8,10;24:14;31:11; 66:13;81:8;90:9;234:3; 269:18 conditional (1) 226:6 conditions (3) 36:6;91:2;162:17 conducted (7) 7:9;49:1,5;100:1; 118:14;213:22;245:20 confidence (1) 247:7 confident (2) 33:15;73:11 confirm (5) 17:1;226:5;235:11,12; 316:17 confirmed (2) 138:7;235:1 confusing (3) 97:13,15;308:8 congruent (1) 87:9 connect (1) 73:15 connection (2) 73:14;87:1 Connie (9) 85:21;86:1;103:13; 104:6;119:19;152:6; 184:8;190:7;324:22 Connie's (2) 103:14;188:18 cons (1) 162:9 consecutive (8) 166:11,12;221:4; 227:12;278:4,5;290:2,3 consensus (2) 142:6,12 consequence (5) 104:3;126:12,16; 152:4;192:6 consequences (51) 65:9,14,21;66:3; 100:11,12;101:6,13; 102:7,18;104:20; 106:20;107:5,15;117:15, 22;118:2;120:4;128:19; 131:4;135:4;136:6; 137:7,8,14,19;138:11, 16;139:11,15,22;140:3; 142:18;143:12;148:11,	15,19;149:1,4,7,17,19; 152:1,12;189:17; 190:10;191:4,8;192:3,8; 232:17 conservative (4) 122:20;123:3;141:9; 268:1 consider (18) 15:17;17:6;20:22; 21:1;25:18;38:13;46:7; 68:1,22;76:13;183:1; 210:7;254:16;279:4; 281:4;288:20;292:9; 304:21 considerable (2) 275:12;284:10 consideration (3) 22:9;99:10;304:10 considerations (3) 23:12;27:18;30:21 considered (24) 14:12;18:5;20:8;35:4; 77:4;110:3;217:9;223:8; 273:6;274:3;278:13,15, 21;279:7,11;283:22; 284:7;286:18;289:6,9; 294:13;300:12;310:16; 328:4 considers (1) 35:6 consist (1) 101:21 consistency (3) 46:5,11;70:12 consistent (10) 51:11;54:4;168:13; 201:12;219:15,19; 229:7;231:14;270:14; 279:3 consistently (3) 59:8;186:21;236:16 consortia (1) 33:2 constellation (2) 40:18;71:17 construct (5) 21:2;30:6;225:21; 226:5;227:9 constructs (1) 227:2 consultant (1) 142:11 consultation (1) 33:11 consumed (3) 120:9,20;143:4 consuming (1) 239:11 consumption (5) 121:21;128:14; 136:18;140:6;142:3 contains (1) 276:2
collected (6) 170:5;245:22;259:5; 278:7;279:10;319:20	co-morbidities (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14	complicated (17) 155:5;156:19;159:19; 161:2;164:21;168:22; 169:7,10,22;170:20; 172:3,16,20;179:8; 180:1;188:16;305:18	component (1) 326:6 components (1) 28:20 composite (3) 53:4,22;216:21 compounds (1) 307:14 comprehensive (1) 25:16 compromise (1) 77:9 computation (1) 173:21 computerized (3) 214:7;218:10,12 conceivably (1) 66:4 conceive (1) 73:17 concentration (6) 181:22;182:3;248:10; 249:22;250:2;288:10 concentrations (1) 181:11 concept (9) 29:14;67:21;68:13; 110:1;113:7,7;198:21; 205:21;233:11 concepts (8) 17:7,18,20;18:4,7,17; 19:5;272:15 conceptualize (1) 28:17 conceptualizing (2) 24:14;25:8 concern (1) 73:5 concerned (2) 74:4;105:18 concerns (2) 35:2;302:9 conclude (1) 84:3 concluded (2) 135:19;202:22 concluding (1) 265:1 conclusion (4) 84:8;255:13;259:13, 18	comorbidity (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14 company (1) 125:5 comparable (2) 312:12;313:3 compare (11) 84:5;109:4,6;111:18; 114:9;155:14;211:12; 253:21;270:21;300:9; 310:2 compared (16) 43:12;56:16;57:8; 68:15;104:10;105:10; 106:20;249:4;253:8; 254:4;267:9;283:1; 284:16;289:1;300:10; 321:8 comparing (7) 140:16;221:18; 246:18;253:6,6;267:13; 301:21 comparisons (1) 155:14 compatible (1) 171:4 compelling (1) 292:2 competitive (2) 256:5,6 complaints (1) 61:16 complete (13) 49:14;156:14;161:5; 173:7;177:6;178:17; 203:21;216:10;230:14; 231:9;232:8;237:11; 320:9 completed (6) 16:22;49:9;119:16,17; 213:6,19 completely (17) 73:21;81:5;92:18; 155:8;158:5;160:14; 161:12,22;219:22; 220:2;223:2;224:18; 232:15;238:5;240:3; 313:17;314:2 completing (1) 319:22 completion (1) 50:7 complex (3) 170:14;171:13;172:11 complexity (1)
collected (6) 170:5;245:22;259:5; 278:7;279:10;319:20	comorbidity (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14	complicated (17) 155:5;156:19;159:19; 161:2;164:21;168:22; 169:7,10,22;170:20; 172:3,16,20;179:8; 180:1;188:16;305:18	component (1) 326:6 components (1) 28:20 composite (3) 53:4,22;216:21 compounds (1) 307:14 comprehensive (1) 25:16 compromise (1) 77:9 computation (1) 173:21 computerized (3) 214:7;218:10,12 conceivably (1) 66:4 conceive (1) 73:17 concentration (6) 181:22;182:3;248:10; 249:22;250:2;288:10 concentrations (1) 181:11 concept (9) 29:14;67:21;68:13; 110:1;113:7,7;198:21; 205:21;233:11 concepts (8) 17:7,18,20;18:4,7,17; 19:5;272:15 conceptualize (1) 28:17 conceptualizing (2) 24:14;25:8 concern (1) 73:5 concerned (2) 74:4;105:18 concerns (2) 35:2;302:9 conclude (1) 84:3 concluded (2) 135:19;202:22 concluding (1) 265:1 conclusion (4) 84:8;255:13;259:13, 18	comorbidity (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14 company (1) 125:5 comparable (2) 312:12;313:3 compare (11) 84:5;109:4,6;111:18; 114:9;155:14;211:12; 253:21;270:21;300:9; 310:2 compared (16) 43:12;56:16;57:8; 68:15;104:10;105:10; 106:20;249:4;253:8; 254:4;267:9;283:1; 284:16;289:1;300:10; 321:8 comparing (7) 140:16;221:18; 246:18;253:6,6;267:13; 301:21 comparisons (1) 155:14 compatible (1) 171:4 compelling (1) 292:2 competitive (2) 256:5,6 complaints (1) 61:16 complete (13) 49:14;156:14;161:5; 173:7;177:6;178:17; 203:21;216:10;230:14; 231:9;232:8;237:11; 320:9 completed (6) 16:22;49:9;119:16,17; 213:6,19 completely (17) 73:21;81:5;92:18; 155:8;158:5;160:14; 161:12,22;219:22; 220:2;223:2;224:18; 232:15;238:5;240:3; 313:17;314:2 completing (1) 319:22 completion (1) 50:7 complex (3) 170:14;171:13;172:11 complexity (1)
collected (6) 170:5;245:22;259:5; 278:7;279:10;319:20	comorbidity (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14	complicated (17) 155:5;156:19;159:19; 161:2;164:21;168:22; 169:7,10,22;170:20; 172:3,16,20;179:8; 180:1;188:16;305:18	component (1) 326:6 components (1) 28:20 composite (3) 53:4,22;216:21 compounds (1) 307:14 comprehensive (1) 25:16 compromise (1) 77:9 computation (1) 173:21 computerized (3) 214:7;218:10,12 conceivably (1) 66:4 conceive (1) 73:17 concentration (6) 181:22;182:3;248:10; 249:22;250:2;288:10 concentrations (1) 181:11 concept (9) 29:14;67:21;68:13; 110:1;113:7,7;198:21; 205:21;233:11 concepts (8) 17:7,18,20;18:4,7,17; 19:5;272:15 conceptualize (1) 28:17 conceptualizing (2) 24:14;25:8 concern (1) 73:5 concerned (2) 74:4;105:18 concerns (2) 35:2;302:9 conclude (1) 84:3 concluded (2) 135:19;202:22 concluding (1) 265:1 conclusion (4) 84:8;255:13;259:13, 18	comorbidity (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14 company (1) 125:5 comparable (2) 312:12;313:3 compare (11) 84:5;109:4,6;111:18; 114:9;155:14;211:12; 253:21;270:21;300:9; 310:2 compared (16) 43:12;56:16;57:8; 68:15;104:10;105:10; 106:20;249:4;253:8; 254:4;267:9;283:1; 284:16;289:1;300:10; 321:8 comparing (7) 140:16;221:18; 246:18;253:6,6;267:13; 301:21 comparisons (1) 155:14 compatible (1) 171:4 compelling (1) 292:2 competitive (2) 256:5,6 complaints (1) 61:16 complete (13) 49:14;156:14;161:5; 173:7;177:6;178:17; 203:21;216:10;230:14; 231:9;232:8;237:11; 320:9 completed (6) 16:22;49:9;119:16,17; 213:6,19 completely (17) 73:21;81:5;92:18; 155:8;158:5;160:14; 161:12,22;219:22; 220:2;223:2;224:18; 232:15;238:5;240:3; 313:17;314:2 completing (1) 319:22 completion (1) 50:7 complex (3) 170:14;171:13;172:11 complexity (1)
collected (6) 170:5;245:22;259:5; 278:7;279:10;319:20	comorbidity (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14	complicated (17) 155:5;156:19;159:19; 161:2;164:21;168:22; 169:7,10,22;170:20; 172:3,16,20;179:8; 180:1;188:16;305:18	component (1) 326:6 components (1) 28:20 composite (3) 53:4,22;216:21 compounds (1) 307:14 comprehensive (1) 25:16 compromise (1) 77:9 computation (1) 173:21 computerized (3) 214:7;218:10,12 conceivably (1) 66:4 conceive (1) 73:17 concentration (6) 181:22;182:3;248:10; 249:22;250:2;288:10 concentrations (1) 181:11 concept (9) 29:14;67:21;68:13; 110:1;113:7,7;198:21; 205:21;233:11 concepts (8) 17:7,18,20;18:4,7,17; 19:5;272:15 conceptualize (1) 28:17 conceptualizing (2) 24:14;25:8 concern (1) 73:5 concerned (2) 74:4;105:18 concerns (2) 35:2;302:9 conclude (1) 84:3 concluded (2) 135:19;202:22 concluding (1) 265:1 conclusion (4) 84:8;255:13;259:13, 18	comorbidity (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14 company (1) 125:5 comparable (2) 312:12;313:3 compare (11) 84:5;109:4,6;111:18; 114:9;155:14;211:12; 253:21;270:21;300:9; 310:2 compared (16) 43:12;56:16;57:8; 68:15;104:10;105:10; 106:20;249:4;253:8; 254:4;267:9;283:1; 284:16;289:1;300:10; 321:8 comparing (7) 140:16;221:18; 246:18;253:6,6;267:13; 301:21 comparisons (1) 155:14 compatible (1) 171:4 compelling (1) 292:2 competitive (2) 256:5,6 complaints (1) 61:16 complete (13) 49:14;156:14;161:5; 173:7;177:6;178:17; 203:21;216:10;230:14; 231:9;232:8;237:11; 320:9 completed (6) 16:22;49:9;119:16,17; 213:6,19 completely (17) 73:21;81:5;92:18; 155:8;158:5;160:14; 161:12,22;219:22; 220:2;223:2;224:18; 232:15;238:5;240:3; 313:17;314:2 completing (1) 319:22 completion (1) 50:7 complex (3) 170:14;171:13;172:11 complexity (1)
collected (6) 170:5;245:22;259:5; 278:7;279:10;319:20	comorbidity (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14	complicated (17) 155:5;156:19;159:19; 161:2;164:21;168:22; 169:7,10,22;170:20; 172:3,16,20;179:8; 180:1;188:16;305:18	component (1) 326:6 components (1) 28:20 composite (3) 53:4,22;216:21 compounds (1) 307:14 comprehensive (1) 25:16 compromise (1) 77:9 computation (1) 173:21 computerized (3) 214:7;218:10,12 conceivably (1) 66:4 conceive (1) 73:17 concentration (6) 181:22;182:3;248:10; 249:22;250:2;288:10 concentrations (1) 181:11 concept (9) 29:14;67:21;68:13; 110:1;113:7,7;198:21; 205:21;233:11 concepts (8) 17:7,18,20;18:4,7,17; 19:5;272:15 conceptualize (1) 28:17 conceptualizing (2) 24:14;25:8 concern (1) 73:5 concerned (2) 74:4;105:18 concerns (2) 35:2;302:9 conclude (1) 84:3 concluded (2) 135:19;202:22 concluding (1) 265:1 conclusion (4) 84:8;255:13;259:13, 18	comorbidity (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14 company (1) 125:5 comparable (2) 312:12;313:3 compare (11) 84:5;109:4,6;111:18; 114:9;155:14;211:12; 253:21;270:21;300:9; 310:2 compared (16) 43:12;56:16;57:8; 68:15;104:10;105:10; 106:20;249:4;253:8; 254:4;267:9;283:1; 284:16;289:1;300:10; 321:8 comparing (7) 140:16;221:18; 246:18;253:6,6;267:13; 301:21 comparisons (1) 155:14 compatible (1) 171:4 compelling (1) 292:2 competitive (2) 256:5,6 complaints (1) 61:16 complete (13) 49:14;156:14;161:5; 173:7;177:6;178:17; 203:21;216:10;230:14; 231:9;232:8;237:11; 320:9 completed (6) 16:22;49:9;119:16,17; 213:6,19 completely (17) 73:21;81:5;92:18; 155:8;158:5;160:14; 161:12,22;219:22; 220:2;223:2;224:18; 232:15;238:5;240:3; 313:17;314:2 completing (1) 319:22 completion (1) 50:7 complex (3) 170:14;171:13;172:11 complexity (1)
collected (6) 170:5;245:22;259:5; 278:7;279:10;319:20	comorbidity (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14	complicated (17) 155:5;156:19;159:19; 161:2;164:21;168:22; 169:7,10,22;170:20; 172:3,16,20;179:8; 180:1;188:16;305:18	component (1) 326:6 components (1) 28:20 composite (3) 53:4,22;216:21 compounds (1) 307:14 comprehensive (1) 25:16 compromise (1) 77:9 computation (1) 173:21 computerized (3) 214:7;218:10,12 conceivably (1) 66:4 conceive (1) 73:17 concentration (6) 181:22;182:3;248:10; 249:22;250:2;288:10 concentrations (1) 181:11 concept (9) 29:14;67:21;68:13; 110:1;113:7,7;198:21; 205:21;233:11 concepts (8) 17:7,18,20;18:4,7,17; 19:5;272:15 conceptualize (1) 28:17 conceptualizing (2) 24:14;25:8 concern (1) 73:5 concerned (2) 74:4;105:18 concerns (2) 35:2;302:9 conclude (1) 84:3 concluded (2) 135:19;202:22 concluding (1) 265:1 conclusion (4) 84:8;255:13;259:13, 18	comorbidity (1) 18:19 companies (8) 33:13,15;97:20,21; 124:19,22;125:4;197:14 company (1) 125:5 comparable (2) 312:12;313:3 compare (11) 84:5;109:4,6;111:18; 114:9;155:14;211:12; 253:21;270:21;300:9; 310:2 compared (16) 43:12;56:16;57:8; 68:15;104:10;105:10; 106:20;249:4;253:8; 254:4;267:9;283:1; 284:16;289:1;300:10; 321:8 comparing (7) 140:16;221:18; 246:18;253:6,6;267:13; 301:21 comparisons (1) 155:14 compatible (1) 171:4 compelling (1) 292:2 competitive (2) 256:5,6 complaints (1) 61:16 complete (13) 49:14;156:14;161:5; 173:7;177:6;178:17; 203:21;216:10;230:14; 231:9;232:8;237:11; 320:9 completed (6) 16:22;49:9;119:16,17; 213:6,19 completely (17) 73:21;81:5;92:18; 155:8;158:5;160:14; 161:12,22;219:22; 220:2;223:2;224:18; 232:15;238:5;240:3; 313:17;314:2 completing (1) 319:22 completion (1) 50:7 complex (3) 170:14;171:13;172:11 complexity (1)
collected (6) 170:5;245:22;259:5; 278:7;279:10;31				

contemplate (1) 34:9	100:19	counseling (13) 198:17,18,18,19;	created (2) 225:21;304:3	234:2,22;236:3
content (10) 20:22;21:1,6,7,17; 29:18;30:5;33:16;70:2; 71:7	controlled (3) 135:20;185:12;214:11	199:10,16;200:15,17,18, 21;204:17;278:22;290:3	creating (1) 80:2	CTE (1) 234:1
context (32) 11:22;23:20;25:11,11, 13;29:14,16;30:16,18; 31:18;32:8;34:13;35:18; 49:4;59:12;68:21;71:13; 81:11;82:13;93:15; 94:21;95:7,12,13; 162:19,21;163:6;189:2; 275:18;276:16;285:5; 294:18	controlling (1) 228:7	counselor (1) 206:2	credibility (1) 108:12	CTN (1) 198:9
contexts (3) 12:19;163:2,4	conundrum (1) 92:16	counselors (1) 199:14	cried (1) 239:20	Cumulative (11) 115:13;133:7;275:3; 279:2,5,12;290:15; 298:19;317:10;319:9,14
contingency (1) 218:19	conundrums (2) 153:19;174:7	count (3) 63:22;125:21;168:7	crime (2) 64:2,18	cumulatively (1) 279:16
contingent (1) 160:6	converged (1) 193:14	counted (3) 280:1,3;286:17	criminal (6) 146:7;159:17,17; 160:22;219:9;326:13	cups (1) 169:4
continuance (4) 51:8;52:21;155:1; 170:10	convergent (1) 193:15	counterpart (1) 97:19	criminality (7) 65:10,13;66:7,11,15, 18,21	cure (1) 90:11
continuations (1) 286:8	conversation (4) 92:11;303:8;318:8; 326:20	counting (1) 170:16	criteria (29) 19:16;43:6,13,17; 47:1;95:1;125:14; 191:12;207:5;213:7; 217:9;220:6,8;222:13; 224:6,11;235:10,13; 273:9;278:18;283:3; 288:13,14;305:13; 309:14,16;310:11; 313:1;320:2	cured (1) 163:11
continue (10) 39:21;59:22;61:3; 95:20;128:12;153:4; 240:1,1;285:7;304:8	conversion (1) 81:20	counts (1) 265:21	critical (5) 131:9;144:8;164:8; 166:17;189:20	curious (2) 34:10;64:19
continued (8) 103:6;193:18;236:15; 276:12;284:11;287:21; 289:8;296:21	convert (3) 44:17;172:16;247:19	couple (24) 5:9;6:6;8:3;23:13; 24:10;33:19;39:4;60:5; 67:5;72:19;108:11; 112:13;135:17,22; 144:5;184:10;192:19; 209:2;216:17;240:11, 13;262:12;264:7;299:7	crits-Christoph (1) 198:16	current (4) 10:2;218:15;234:14; 329:18
continuing (3) 274:11;298:17;331:2	convicted (1) 197:15	course (35) 6:6;11:17;12:18;14:4; 18:4;19:5;22:20;41:16; 43:2;52:15;55:9;64:16; 71:8;84:22;96:4;98:14; 101:5;102:3,11,20; 127:3;129:5;146:15; 168:7;171:20;221:11; 228:20;229:11;230:11, 18;235:16;240:13; 249:5;291:4;308:19	cross (1) 235:4	currently (2) 213:21;263:15
continuous (29) 109:4,9;112:21;113:1; 114:16;118:19;120:1; 122:13;132:19;139:4, 19;154:21;169:16; 173:2,17;181:1;203:14; 221:5;222:4;223:14; 225:13;227:10;229:6, 11;267:13,20;304:3; 316:1,22	convincing (2) 154:8;157:21	CPR (1) 319:9	cross-sectional (5) 30:3;138:1,3,6;241:2	Curve (14) 133:7;140:10;141:8, 11;224:3;225:14;226:6; 282:1,2,12;316:14,16, 19;320:4
contract (6) 105:14;197:21;234:1, 22;245:20;328:12	cooperation (1) 9:2	crack (3) 53:19;200:2;234:22	cross-sectionally (1) 30:6	curves (21) 120:15;141:5;259:11; 275:3,5;281:6,19; 282:12;290:19;291:21; 292:3,13;293:10,19; 295:7;298:19;316:4,6, 11;317:10,13
contrast (1) 311:20	copy (1) 38:5	cracked (1) 178:17	crude (2) 221:16;224:2	cut (12) 150:12;167:12; 171:21;188:1;193:4,13; 266:20;315:14,17; 316:4;318:10;319:10
contribute (4) 18:7,13;66:17,19	copyrighted (5) 60:9,15,17;61:1,2	crappy (1) 63:15	crummy (1) 42:5	cut-off (10) 49:11;50:17;51:10; 55:1;71:5;115:22;182:5; 191:12;192:17;193:9
contributing (1) 289:3	coronary (4) 234:18;235:1;237:16; 239:18	crash (1) 41:7	crunch (1) 138:14	cut-offs (3) 138:15;142:3;181:12
contribution (1) 240:5	correction (1) 253:13	craving (22) 38:10;44:8;45:1,7,9; 46:13;79:6;126:12,14; 136:6;209:11,11; 246:15;248:7,11; 254:17;255:12,22; 256:22;273:16;277:17; 322:22	crystallize (1) 330:17	cutting (2) 134:10;187:20
contributor (1) 208:12	correctly (2) 80:12;209:17	cravings (3) 250:5;254:3;277:16	CSSA (76) 36:22;37:4,7,9,20; 38:5;39:8;44:13;46:21; 47:13;48:4,13,16;49:10, 13,22;50:14;51:2,12,21; 52:14,19;53:22;54:6,13, 21;55:1,17;56:8,16,17; 57:12,14,17,20,20;58:3, 9,13,13;59:1,3,7;60:9; 61:2,7,9;62:18,19;63:8; 68:12;69:8;71:22;72:9, 20;73:2,9;74:20;75:2,8, 15,18;76:6;77:4,12;78:4, 8,11,14;79:7,12,17,21; 80:10;83:13;84:16	D
control (1)	cost (12) 104:5;105:8;106:20; 107:8;120:5;158:17,18; 164:16;173:22;176:10; 177:6;180:13	crazy (3) 74:10;243:1;269:19	CT (3)	DAAAP (1) 295:18

<p>97:2,8;98:2;99:19; 107:17,18;115:4;124:5; 129:8,14,15;157:8,16; 179:13;184:19;191:8; 257:8;314:8;315:6</p> <p>Dan's (3) 123:8;172:10;182:8</p> <p>darker (3) 102:3;223:10,13</p> <p>dash (1) 282:2</p> <p>dashes (1) 286:4</p> <p>data (185) 44:3;48:14;49:7;52:3; 57:3;99:12;100:2,5; 101:3;103:12,14,15; 105:11;106:5,14; 107:11;108:4;119:5,6, 16,19;121:16;123:11; 124:15;127:6;128:19; 130:2;136:14,15,17,22; 137:1,8,10;138:4,5,7; 139:18;149:18;156:5; 157:10,12,21;158:3,6; 160:12;162:16;163:5,5; 164:5,6,17,20;166:6,8, 19;167:11,12;169:14; 170:14,18,19;171:21; 174:3,13;175:14;176:10, 11,17;178:9;180:5; 181:1,22;182:4,19; 187:7;188:7,8;193:7,12, 19;196:16;197:8,9,13, 22;198:6,11,14;200:5; 203:18;208:6,9,10,19; 209:5,15,21;210:7; 211:6;213:5,15;214:19; 216:5;217:13;218:17; 219:2,13;220:4,20; 222:16;224:14;229:6, 20;230:5,8;231:17; 232:16;233:1,9;234:6,6; 236:7,8,9,12;239:3,6,6; 240:21;244:20,22;245:3, 4,16,17;247:19;250:14; 251:6,12;253:10,12; 257:20;258:20;259:6; 260:9;261:5,6,22;262:1; 263:14;264:10,11,13,18; 267:11;268:1,5,11,15; 269:4,11;270:6;274:15; 283:9;284:5;290:16; 299:1;308:11;309:2; 311:4,5,17,19;314:13; 315:1;316:21;319:18,19, 21;320:16;321:21; 322:7;324:11;329:4</p> <p>database (2) 186:18;209:16</p> <p>databases (1) 211:4</p> <p>date (1)</p>	<p>163:5</p> <p>Dave (7) 76:17;98:3;153:9; 182:7;189:7;196:3; 321:1</p> <p>David (14) 76:16;80:6;91:3; 196:8,9;198:21;201:4; 202:4;203:7;267:1; 281:15;300:20;315:6; 325:8</p> <p>Dawson (1) 106:8</p> <p>Day (44) 49:17;50:8;58:22; 59:1;84:4;96:4;99:3,4,5; 102:19;106:3;109:11,11, 18;113:9,10;115:6; 117:19,21;121:1,10; 122:19;134:2,3,7,8,11; 140:19;145:16;151:8; 172:8;179:2;191:9; 251:7;261:17;267:17; 276:7;277:7;283:9; 287:11;295:17;296:12; 313:15;330:5</p> <p>day-by-day (1) 215:4</p> <p>days (123) 6:6;41:16;47:13; 48:12;49:9,14;50:7; 53:19;75:8,9,9,16;76:3; 98:18,22;99:1,6,11; 100:7;101:10,11,20; 103:21;106:2,10;108:1, 16;109:10,12;111:9,22; 113:5,10;114:13;116:1, 10,14;117:1,5,8,9,10,13, 15,17;118:4,8;122:8; 123:4;127:21;128:1,5; 132:18;136:21,21;139:7, 8;143:6;145:9;164:14; 167:3;168:4,9;169:8,11, 19,20,21;170:1;179:6,7; 183:3;189:18;190:1; 193:9;206:6,21;215:22; 216:7;217:1,4,5,6,7,8; 219:5,7,19;221:3,4,6,18, 18,19;222:5,21;223:19; 224:15;225:11;226:1, 17;227:11,12;228:19; 229:10,10,14;230:12; 233:10,11;243:7; 251:10;263:12;276:8; 278:4,4;286:3,4;287:12; 296:13,14;299:15; 330:16</p> <p>DDT (1) 32:18</p> <p>deal (1) 40:14</p> <p>Dealers (1) 172:13</p>	<p>dealing (1) 325:20</p> <p>deals (1) 283:6</p> <p>debate (2) 141:22;196:21</p> <p>Deborah (1) 106:7</p> <p>decade (1) 129:6</p> <p>decent (1) 250:20</p> <p>decide (5) 130:3;141:13;315:14; 318:9,9</p> <p>decided (7) 7:21;52:2;115:12; 160:8;212:21;225:8; 327:4</p> <p>decision (1) 279:1</p> <p>decision-making (1) 31:12</p> <p>decisions (6) 12:9;22:20;23:2; 25:14;26:13;321:7</p> <p>declare (2) 315:11,11</p> <p>decline (2) 48:11;58:3</p> <p>declined (1) 41:15</p> <p>declines (1) 48:15</p> <p>decrease (8) 91:13;149:8,9,10; 248:19,21;251:17,19</p> <p>decreased (5) 106:18;215:16; 249:14;251:21;322:22</p> <p>decreases (2) 64:1;249:16</p> <p>dedicated (1) 96:19</p> <p>defend (1) 110:14</p> <p>define (5) 17:12;159:1;242:6; 304:7;321:11</p> <p>defined (12) 7:19;19:15,20;20:9, 20;27:6;50:18;68:9; 254:20;303:19;304:1; 315:17</p> <p>defining (5) 9:20;172:2;212:22; 291:17;304:11</p> <p>definitely (5) 77:3;102:10;114:20; 143:12;255:6</p> <p>definition (30) 26:2,9;84:10;133:22; 139:21;141:13,15,18;</p>	<p>191:6,11,19;273:5,6,22; 280:18,20;281:3;284:8; 285:12;286:12;287:18; 288:3;289:5,22;291:17, 19;304:22;319:17; 320:9,14</p> <p>definitions (10) 9:20;25:19;193:8; 273:3;283:8;284:13; 287:6;294:10;316:1,21</p> <p>definitive (1) 280:18</p> <p>Delaware (1) 198:9</p> <p>delay (1) 209:14</p> <p>delighted (1) 153:7</p> <p>delta (2) 254:6,7</p> <p>delusions (1) 40:22</p> <p>demand (1) 163:22</p> <p>demands (1) 20:18</p> <p>demonstrate (5) 151:9;205:10;293:16; 295:5;302:21</p> <p>demonstrated (4) 12:7;28:4;47:22; 198:21</p> <p>demonstrates (2) 303:6;327:2</p> <p>demonstrating (3) 291:6;292:12;326:7</p> <p>demonstration (1) 14:1</p> <p>denial (1) 215:21</p> <p>Dennis (1) 8:22</p> <p>denominator (1) 169:10</p> <p>denominators (1) 169:12</p> <p>depend (1) 92:18</p> <p>dependence (25) 44:7;47:8,17;48:1; 52:5;74:8;77:11;106:2, 11,19;107:1;165:1; 205:8,9,13;206:10; 207:2,4;213:6,17; 245:19;268:9;309:7; 324:12,19</p> <p>dependent (8) 191:17;200:3;205:6; 206:20;207:1;217:20; 218:5;316:14</p> <p>depending (5) 15:14;145:9;146:21; 164:19;214:13</p>	<p>depends (2) 145:15,18</p> <p>deposit (1) 238:17</p> <p>Depotrex (1) 308:15</p> <p>depressed (4) 38:10;40:20,20;47:2</p> <p>depression (4) 42:20;84:6,7,9</p> <p>derived (3) 14:20;15:1;84:18</p> <p>descend (2) 60:17,21</p> <p>describe (4) 21:20;119:9;225:20; 316:7</p> <p>described (6) 147:19;187:6;229:21; 275:1;277:5;321:12</p> <p>describes (2) 20:7;33:6</p> <p>describing (2) 123:16;276:16</p> <p>design (24) 25:20,22;77:2;93:13; 94:22;95:1;137:16,17; 199:9;272:16;273:11; 280:16;301:5,6;303:9; 305:10,15,20,21;306:4, 10,12;307:3,7</p> <p>designed (3) 181:13;294:14;298:3</p> <p>designers (1) 24:18</p> <p>desirable (2) 155:19;261:16</p> <p>desired (1) 135:3</p> <p>desiring (1) 92:22</p> <p>desk (2) 7:5;44:14</p> <p>desktop (1) 38:6</p> <p>despite (1) 203:16</p> <p>detail (5) 24:8;104:7;113:1; 121:19;234:3</p> <p>detailed (1) 29:9</p> <p>details (5) 11:20;129:22,22; 136:12;316:7</p> <p>detect (13) 13:1;17:22;21:3; 30:10;31:21;97:1;164:3; 220:15,18;221:2;222:1, 9;224:20</p> <p>detecting (1) 221:9</p> <p>detection (1)</p>
---	--	--	--	---

222:2 determine (6) 12:10;17:5;21:19; 93:14;230:2;267:10 determined (2) 104:12;179:5 Detox (2) 206:5;302:2 detoxification (3) 39:18;301:22;324:13 develop (14) 22:4;26:9;32:20;33:4; 40:1;92:17;118:17,20, 21;124:5;125:14;141:6; 143:9;185:17 developed (21) 5:13;7:12;20:10; 23:13;33:11;37:21;62:2; 70:16;81:16;82:14; 100:13,16;122:6,7; 123:19;181:14;187:15; 192:12;202:5;238:6,7 developers (7) 19:9;24:4,18,22; 31:20;32:20;33:3 developing (13) 24:16;29:2,21;36:22; 44:11;89:18;95:11;96:9; 123:15;129:2;313:1; 326:2;328:12 development (41) 7:15;11:5,16,21; 12:13;20:15,18;23:14, 19;24:7;25:1,17;26:15; 27:21;29:7;31:17;32:7, 8,10,14,17,18,22;33:7, 14;37:8;40:9;61:8; 84:17;85:11;89:4,13; 92:4;97:5;122:4;125:10; 153:9;176:12;329:2; 330:12,14 develops (1) 138:19 deviation (1) 157:2 deviations (2) 156:17,22 device (1) 295:22 devices (1) 295:21 devil's (2) 129:22;136:11 diabetes (2) 123:20;184:14 diagnosis (2) 81:1;84:9 diagnostic (4) 31:6;81:7;84:11;94:1 diagnostics (1) 85:4 diagram (6) 17:22;24:11;28:17,19,	19;29:9 diagrams (1) 23:13 dial (1) 148:18 dice (1) 139:5 dichotomize (1) 171:8 dichotomous (19) 109:17,22;112:22; 113:12;114:22;130:11; 132:22;134:6;173:1,18; 176:16;221:8;222:7; 225:3,11;228:11;267:13, 22;317:1 diet (1) 243:21 differ (2) 102:1;291:22 differed (1) 285:10 difference (50) 18:1,2;50:10;51:9; 58:9;97:1;101:2,16,18; 109:19,20;111:6; 113:18;114:8;115:10; 121:2;122:17;123:5; 127:14;128:9;140:19; 141:1;154:20;182:21; 184:5;192:16;201:17; 202:9;211:19;247:9; 254:6,10,13,15;270:5; 275:5;292:6,7,13; 293:10;295:8;297:12; 301:5;306:16;309:20; 310:5,8;313:18;317:21; 324:9 differences (13) 149:17;157:19; 182:13;199:1,3;248:5; 253:2,15,22;254:2,19; 255:12;300:2 different (91) 12:16;48:22;54:9,9; 68:3;73:22;97:14;99:12; 100:3;102:10;103:5; 107:6;116:2;118:10; 123:2,17;124:8,11,14; 125:14;131:19,20; 139:3;140:9,10,20; 142:2;143:11;145:10; 149:2,3,3,6,7;153:20; 159:9;162:7;163:8; 167:21;171:1,21; 183:10;186:12;190:20; 191:1;193:4,9,10,13; 199:4,6;205:4,15; 206:18;211:12,14,14; 212:3,7,8;216:17;218:7; 227:8;232:15;239:5; 245:18;246:19;247:4; 248:16;254:7;258:4;	260:3;262:3;267:9; 268:6,12;269:13; 281:11;293:13;303:14; 309:2;311:21;313:22; 314:19;319:19;324:20; 325:4,18,22,22;326:6 differential (24) 55:14;56:15;58:1; 59:7;162:16;164:18; 169:9;267:14,20;269:1, 7,17;298:22;299:5; 300:19;303:11,12; 312:11;315:3;317:14; 321:4,20;322:15;323:18 differentiate (1) 304:4 differentiated (1) 222:14 differently (7) 23:9;166:7,9;169:1; 185:2;314:10;329:13 difficult (14) 18:18;44:2;59:13,20; 94:21;161:8;182:13; 263:20;280:17;284:9; 287:2;291:20;294:11,17 difficulties (3) 176:17;297:8;307:13 difficulty (1) 177:6 digesting (1) 90:22 digestive (1) 120:15 dimensions (1) 241:2 diminish (1) 132:21 dinner (1) 331:8 Dip (1) 236:2 direct (7) 14:19,19;15:6,7;69:2; 144:21;220:21 direction (6) 65:15;94:19;157:11; 231:14,19;322:20 directions (1) 262:3 directly (6) 14:8;15:12;35:22; 65:13;206:7,17 dirty (7) 77:12;129:9;139:11; 167:21;169:17,21; 321:16 disagree (1) 88:1 disappeared (1) 321:18 disappointing (2) 58:10;72:10	disclaimer (2) 37:11;272:10 disconnects (1) 87:7 discontinuation (2) 303:20;320:1 discontinuations (1) 288:11 discontinue (2) 286:6;300:14 discontinued (11) 274:1,2;278:11; 283:20;286:1,2,10,15, 21;287:15;299:19 discreet (1) 272:15 discrepancies (1) 169:14 discrepancy (8) 168:4,21;169:3;181:8; 215:11,17,18,19 discrepant (1) 170:15 discuss (7) 24:22;72:16;113:14; 272:14,17;315:22;327:9 discussant (10) 8:7;11:8;61:6;67:2; 97:8;175:6;262:5,7,10; 266:17 discussed (5) 70:10;221:6;251:6; 279:14;305:12 discussing (3) 212:21;272:1,5 discussion (32) 6:5;10:14;11:14; 33:21;60:4;68:18;69:1, 6;70:15;72:15;77:15; 83:15,17;89:5;95:20; 123:10;143:20;153:4; 175:1;177:9,10;267:4; 272:4;275:17,19; 276:18;277:2,3;283:4; 296:4;313:8;326:22 discussions (3) 32:9;177:7;196:18 disease (12) 17:11,20;25:19;90:16; 119:6,8;120:21;122:4; 205:21;233:18;234:12; 235:14 diseases (4) 120:9,14;122:22; 123:6 disentangled (1) 92:6 disorder (10) 7:17;84:13,14;91:15; 96:17;106:12;161:18; 200:4;265:12,19 disorders (8) 7:11,14;68:20;90:18;	92:12;115:15;156:4; 186:1 display (6) 275:10,12;292:19; 293:16;295:11,13 disposition (1) 288:18 disrespectful (1) 69:17 dissecting (1) 244:21 dissed (1) 78:5 distal (6) 17:15,17;18:4,17; 120:11;263:19 distally (2) 66:12;177:2 distinction (1) 5:4 distinguish (3) 80:15;181:14;304:15 distributed (1) 58:19 distribution (4) 279:3,5,13;290:15 disulfiram (8) 217:16,19;218:4,19; 219:16;220:16;221:3; 224:6 dive (2) 68:16;170:22 divide (1) 243:8 divided (3) 57:13;99:1;251:12 diving (1) 193:6 division (4) 64:5;94:16;197:20; 260:9 divorced (1) 148:20 doctor (1) 239:2 doctors (1) 183:4 document (2) 19:9,17 documentation (2) 27:14;28:20 dollar (1) 172:17 domain (3) 60:10;247:10;261:18 domains (13) 86:8;217:2;226:2,4, 17,19;246:12;247:4,8; 249:5,10,11;254:1 done (51) 5:15;10:17;32:13; 38:2;44:20;51:18;53:12, 13;56:21;59:16;62:2,18;
---	--	--	---	--

75:22;78:13;80:1,19; 85:9;99:17;115:17,18; 119:9;120:7,8;121:20; 123:1,19;126:2;146:6; 149:16;163:11;167:15; 175:15;180:12,18,20; 181:4;189:16;198:15; 201:4;212:18;256:16; 17;266:21;267:16; 318:16,18,19;323:19; 327:4;329:2;330:19	13;82:1,9,21,22;83:7; 84:13;85:13,21;86:1; 87:8,16,22;88:11;89:14; 91:4,5,7,22;95:16;96:7; 12;129:15;143:21; 144:11,16;147:11,12; 148:9;149:2,5,6,13,14; 151:18;152:6,8,18,20; 153:3,7,12;168:16; 173:14;174:16,19,21; 175:7,12;177:10;178:7; 179:10,12,16;180:3,8, 10,15,21;181:6,7;182:7, 8;184:8,10;185:20,21; 186:3,5,14,16,17; 187:11,18;188:5,18,22; 189:6,8,9,10,11;190:12, 16;191:21;193:3,20,21, 22;194:1,6,8,10,16; 195:1;196:2,10;198:5; 209:2,10,19;210:8,17; 211:16;212:9,10,12,17; 232:7,13,19,22;238:14; 239:3;240:5,10,15,17, 18,19;241:3,6,12,13,15, 16,19,21,22;242:1,2,3,4, 8;243:4,6,11,13,14,17, 18;244:3,13,17;256:14; 257:15;258:16;259:4, 18;260:4,8,16,20,22; 261:1,3,5,12;262:4,6,11; 263:4,13;266:13,19,22; 267:2,5;268:8;269:15; 271:3,11,16;289:17,21; 290:5;296:5,5,8;297:6, 10,11,17,21,22;299:7; 300:6,20,21;301:2,3,9, 10,11,13,15,17,18;302:3, 6,7;305:16,18;306:11; 307:8,21,22;308:6; 313:6,7;314:6,9;315:6,7; 317:9;318:16,18,21; 319:7;321:1,3;323:2,3; 324:4,6,7,21;325:1; 326:20;328:9;330:2; 331:5	126:17;135:22;136:6; 137:15;139:13;140:19; 145:7,12,20;148:1,5,11, 12;150:1,9,20;185:3,3; 189:17,21;190:3,14,22; 192:4,13;328:7,7	267:14,21;269:1,8; 283:2;287:2;298:22; 299:5;300:19;303:12; 307:15;321:4,20;322:15	284:4;285:11;286:14; 287:7,7
door (1) 7:5	Drinker (2) 100:10;297:1	dropouts (4) 269:22;288:9;303:15; 324:16	drug-using (1) 207:3	drug-using (1) 207:3
dose (16) 43:16,20;183:9;276:7; 277:7;278:2,16;287:11, 14;299:10,12,14,14,16, 17;300:14	drinkers (5) 102:3,4;103:20,20; 105:18	dropped (8) 167:18;208:11;237:9; 268:22;269:21;322:3, 11;324:8	drunk (2) 192:2,6	drunk (2) 192:2,6
doses (1) 42:18	drinking (155) 98:18,22;99:1,3,4,5,6, 7,7,8,11;101:10,11,20, 21;102:10,16,19;103:2; 104:3,11,14,16,17; 105:1,7,10;106:1,1,3,10, 13,17,18,18,19,21;107:1, 1,2,5,9,14;108:1,16; 109:10,11,18;110:6,11; 111:9,21;112:2,18; 113:5,10;114:11,13; 115:2,6,8,10;116:1,2,10, 11,14,18;117:1,5,8,9,10, 13,15,17,19,21;118:4,8, 19,20;119:7;120:1,13; 122:8,8,14,15;123:3,4, 17,18;124:7,9,10;126:8; 127:21;128:1,5,10,20; 129:20;131:22;132:4,8, 18;134:19,21;135:2,10; 136:10,12,13,17,19,21, 21;137:4,6,18;139:2,3,7, 8;140:13;145:16;146:9; 147:8,20,21;148:13; 149:8,9,19;150:5; 151:20;152:5;165:3; 183:2,5,6;184:21;185:1, 13;188:20;189:18; 190:1;191:7,9,19; 233:10;257:9,10;330:16	dropping (4) 259:15,19;303:21; 321:9	DSM (1) 84:11	DSM (1) 84:11
dosing (1) 277:4	drinks (29) 99:4,5;102:19,21,22; 109:11,11;113:9,9; 121:1,5,6,9;134:2,3,7,8, 11;140:18;145:17,19; 146:17,19,20;192:1,7, 13,13,20	drops (1) 133:16	DSM-IV (3) 43:7,11;47:1	DSM-IV (3) 43:7,11;47:1
dot (1) 283:13	drive (2) 24:10;197:14	drug (123) 12:3,8,11,13;17:9; 19:9;20:18;24:4,6,22; 25:1,17;26:13;27:1,21; 29:6;31:20;32:8,10,17, 18,22;33:3,7,13,14; 47:16;52:18;53:4,22; 54:5;55:12;58:15,22; 62:14;64:6,8,10;65:15; 66:22;76:12;86:9;88:6, 14,21,22;89:4;90:1,21; 91:11;92:6;110:5,10; 125:9;139:12;151:6,16; 176:22;184:13;198:17; 199:16,19,22;200:5,14, 16,18,21;202:1,1;203:2, 12,16;204:17;205:9; 207:2;213:16;218:14; 223:15;232:20;244:18; 247:10,16,17;248:20; 249:14,15;250:2,13; 251:14,16,17,19;252:11, 15;253:19;254:14,20; 256:11;258:18;259:5; 263:8;266:1;268:8; 271:21;273:6;289:7; 295:20,22;302:6,7; 304:3;305:8;307:11,12, 15,18;308:3;325:9; 326:7,14;329:2,7	DT's (1) 41:18	DT's (1) 41:18
dots (2) 285:8;286:3	driven (3) 197:8;215:14;257:4	drug (1) 282:16	dubious (1) 5:4	dubious (1) 5:4
double-blind (2) 245:17;276:21	driver (1) 289:2	drug-negative (1) 207:21	due (3) 181:16;303:12,16	due (3) 181:16;303:12,16
double-check (1) 210:20	driving (1) 65:22	drugs (13) 22:19;32:1,3;63:20; 64:11;66:6;73:6,12; 98:17;172:17,18; 176:12;324:3	Duhig (1) 127:2	Duhig (1) 127:2
doubt (1) 210:21	drop (13) 42:2;74:5;165:17; 167:22;168:1;229:22; 259:14;260:2,18;270:4; 303:12;317:14;322:6	drug's (1) 118:8	DUI (1) 148:20	DUI (1) 148:20
dovetail (1) 129:17	dropout (17) 167:20;169:9;233:22;	drug-taking (6) 281:2;291:1,18;292:8, 10,15	DUNN (2) 91:5;188:22	DUNN (2) 91:5;188:22
down (36) 6:15;10:21;48:12; 49:17;57:20;62:19; 74:15;110:9;117:11; 121:1;126:1;127:18; 128:7,10;133:18;147:2; 150:16,17;169:3; 179:21;181:11;194:20; 205:12;209:11,12,13; 211:18;218:22;230:16; 231:8;232:1;266:7; 269:20;270:11;313:9; 329:21	draft (4) 98:7;106:16;110:12; 150:6	drug-use (11) 201:2,22;202:11; 259:6;273:7;275:7;	duration (5) 52:7;111:20;137:11; 152:1;190:9	duration (5) 52:7;111:20;137:11; 152:1;190:9
downstream (1) 66:13	drafting (1) 29:17		during (67) 40:12,15;51:8;52:22; 53:7;56:16,17;62:14,17; 76:13;77:11;97:1;99:2; 170:13;198:22;199:6, 20;200:22;202:1; 213:11;215:5;216:6; 219:3,19,22;220:3; 221:11;223:2,16;224:10, 16,18;225:5,17;227:20, 21;228:5,15,22;229:1,8, 11;230:14,18,20,21; 231:4,10,20;232:10; 245:11;248:15;249:2,13, 13,15;251:6;253:9; 255:3;265:15;272:5,20; 278:6;285:7,18;288:16; 318:20	during (67) 40:12,15;51:8;52:22; 53:7;56:16,17;62:14,17; 76:13;77:11;97:1;99:2; 170:13;198:22;199:6, 20;200:22;202:1; 213:11;215:5;216:6; 219:3,19,22;220:3; 221:11;223:2,16;224:10, 16,18;225:5,17;227:20, 21;228:5,15,22;229:1,8, 11;230:14,18,20,21; 231:4,10,20;232:10; 245:11;248:15;249:2,13, 13,15;251:6;253:9; 255:3;265:15;272:5,20; 278:6;285:7,18;288:16; 318:20
dozen (1) 108:4	drank (2) 145:10,22		Dworkin (3) 5:11;8;22;67:4	Dworkin (3) 5:11;8;22;67:4
DR (301) 5:3;8:13;10:11;11:11; 34:1,9,18,20,21,22;35:1, 11;36:10,13,20,20;37:1, 3;60:5,7,8,10,11,21; 61:4,5,9,21;62:1,8,10,12, 21;63:1,2,4,6,8,18,19; 64:4,13,20;65:2,4,5,7,8; 66:10;67:3;72:8,12,18; 73:17;74:18,19;75:6; 76:9,15,16,17;78:5,8,13; 79:11,12;80:4,12;81:12,	draw (2) 8:9;70:3		Dworkin's (1) 11:9	Dworkin's (1) 11:9
	drilled (1) 209:13		dysfunction (2) 91:5;234:5	dysfunction (2) 91:5;234:5
	DRINC (1) 100:13		dysregulation (1) 44:9	dysregulation (1) 44:9
	drink (39) 101:4,5,22;102:1,19; 103:1;117:17;118:1; 121:2,3,13;122:19;			

E

earlier (16)
194:7;201:14;210:10;
215:6,14,17;227:18;

229:21;230:17;265:9; 273:19;275:1;278:19; 279:14;287:10;288:5	3,10;224:6,21;309:3	empirical (2) 174:3;191:1	304:10	210:14
early (17) 25:1,2;32:11;55:13; 263:12;274:17;278:11; 286:6,7;287:16;288:11, 20,22;289:3;307:14; 322:3,8	efficacious (1) 88:7	empirically (1) 186:15	ends (1) 295:15	episodes (1) 164:3
earn (1) 58:21	efficacy (14) 17:4;31:3;37:9; 273:10;276:15;277:3; 278:15;280:10,13; 284:6;287:8;288:21; 290:20;303:16	empiricism (1) 178:13	engage (4) 6:5;274:17;290:8; 295:4	episodic (2) 203:12;324:18
earned (1) 58:17	effort (1) 135:2	employer (2) 152:15;184:18	engaged (1) 74:16	equal (3) 268:2;288:17;295:8
ease (1) 173:21	efforts (3) 10:7;196:6;243:19	employment (12) 86:11,18,20;87:2; 139:15;152:14;160:22; 202:19;217:5;220:12; 227:1,5	engagement (1) 74:15	equally (2) 58:19;324:17
easier (7) 35:12,22;82:5;146:13; 176:19;257:13;305:19	eight (2) 97:21;163:10	encourage (10) 24:22;29:12;32:9; 33:13,19;61:2;95:19; 209:19;210:6;265:4	enhanced (1) 234:22	equations (1) 120:11
easily (4) 44:16;159:4;171:8,20	either (18) 9:19;12:20;13:6;71:3; 82:15;93:21;113:13; 136:2;147:16;150:20; 171:18;184:21;193:8; 200:5;206:6;217:16; 218:3;263:18	encouraged (1) 169:6	enough (19) 25:2;65:12;110:11; 173:10,14;175:11; 177:3;178:14;186:21; 192:1,2;216:19;217:10; 260:21;261:14;275:6; 292:13;302:18;323:21	equivalent (2) 132:7;178:21
easy (13) 129:10;130:15; 138:12;157:17;159:12; 162:11,11;169:13; 240:15,17;320:13; 323:20;327:22	ejected (1) 309:15	end (35) 52:10;84:4;102:5; 128:3;151:8;160:13,15; 161:6;170:12,16,17,18; 173:8,11;182:4;184:16; 186:19;196:20;198:11; 199:5;201:1;222:12; 225:6;229:18;233:13; 252:16;253:3,5,7; 268:16;286:21;295:16; 301:7;313:14;322:13	enrich (1) 266:8	equivocal (1) 294:19
eat (1) 144:1	elaborate (1) 88:9	ended (5) 53:11;104:8;216:18; 219:1;287:16	enrichment (2) 80:18;94:15	ER (3) 210:9,19,21
ECCEHA (1) 234:10	elaborated (1) 147:15	end-of-study (4) 57:7;196:19;202:5; 203:6	enrolled (3) 233:19;236:5;318:1	Eric (6) 5:4;67:2;96:13; 147:15;191:6;326:19
echo (4) 76:18;91:5;194:6,8	electronic (1) 60:12	end-of-treatment (2) 230:1;231:12	ensure (4) 18:6;21:17;22:5;31:20	error (1) 168:11
economic (1) 139:15	element (2) 25:16;64:21	endorsed (2) 183:3;277:16	ensuring (1) 29:21	errors (2) 152:3;168:12
editors (1) 79:2	elements (4) 25:6,13,18;272:16	endorse (1) 205:21	enter (1) 134:8	esophagus (1) 140:6
effect (61) 19:7;28:12;41:20; 43:19;57:16;64:10; 66:14;79:15,20;94:14; 101:8;108:7;109:13,15; 110:21;111:2,12,16,19, 20;112:12;113:4,9,11, 13,18;114:9;116:19,20; 117:4,6;128:11;133:12, 20;134:14;135:3; 148:12;149:11;189:22; 201:9;208:3;211:11,13, 15;221:2;224:7;267:16; 269:14;287:7;290:11; 291:7;294:18,19;295:5; 298:20;300:18;304:16, 18,19;317:16;321:19	elevate (1) 145:18	endothelial (3) 234:17,21;308:3	entering (1) 76:3	essential (1) 228:13
effective (7) 73:20;93:18;131:8; 182:18,20;265:10,11	elevated (3) 145:13,21;146:2	Endothelin (4) 236:22;237:1,2,2	entire (13) 43:3;115:21;171:20; 207:10;215:5;216:11; 230:20;241:4;284:11; 287:21;289:9;291:11; 313:16	essentially (11) 60:22;73:19;167:7; 173:15;176:3;214:19; 215:2;221:17;269:15; 291:10;299:19
effects (27) 20:3;43:1,8,15;70:4; 93:20;110:4;112:10; 127:20;132:17;133:16; 149:3;151:20;158:16; 171:7;212:6;213:8,9; 220:15,18;221:9;222:2,	EMA (5) 97:18;122:16;125:17; 132:7;133:1	endpoint (39) 12:20;26:1,2,9,17,20, 21;27:17;28:1,7;66:9; 98:16;99:11;114:15; 150:2;153:16;155:22; 157:13;176:7,14,16; 182:19;183:2,21;184:7; 193:11;196:17,21;197:6, 16;209:9;279:2;280:14; 291:22;292:16;298:15; 316:17,18;317:4	entire (13) 43:3;115:21;171:20; 207:10;215:5;216:11; 230:20;241:4;284:11; 287:21;289:9;291:11; 313:16	establish (4) 123:16;189:18; 280:17;291:20
	embark (1) 23:17	endpoints (21) 14:21;15:2;16:14; 19:4;26:5,7,11,12,19; 27:7,10,11,19;96:15; 98:13,14;118:15; 132:22;143:10;196:12;	entry (4) 94:22;211:6;258:8; 305:12	established (4) 21:1;30:5;191:10; 203:7
	emerge (1) 171:7		environment (2) 40:8;93:3	establishing (1) 30:11
	emerged (1) 193:11		environmental (1) 135:18	esteemed (1) 89:8
	emergency (3) 40:16;105:5;160:1		envisioned (1) 281:6	estimations (1) 172:10
	emphasis (1) 21:16		enzymes (3) 144:13,17;147:1	et (1) 135:13
	emphasizes (1) 89:19		epi (1) 105:13	ET-1 (1) 239:13
			epidemiologic (2) 31:9;99:14	ethanol (3) 144:20,20;145:6
			epidemiological (1) 119:18	ethnic (1) 219:4
			epilepsy (3) 317:3;318:2,5	Europe (2) 122:11;132:7
			episode (1)	European (2) 97:18,21

<p>evaluate (20) 12:2,17;17:4;20:9,19, 21:30:6;31:3;88:15; 143:9;189:2;196:6; 199:4;226:5;231:16; 262:15;263:20;284:6; 287:8;316:3</p> <p>evaluated (8) 5:16;66:3;213:3,7; 218:2;220:14;225:2; 298:1</p> <p>evaluates (1) 19:16</p> <p>evaluating (9) 29:18;123:12;129:2; 196:12;216:21;222:19; 226:19;273:10;297:2</p> <p>evaluation (2) 30:4,9</p> <p>evaluations (1) 224:5</p> <p>even (42) 32:11;58:5;74:7; 97:10;98:10;101:17; 106:14,21;111:15; 115:16,18;117:18; 119:17,20;123:22; 124:8;125:9;126:13; 135:9;137:10;141:5; 151:18,22;155:2;166:8; 185:8;192:7,12;199:2; 210:2;264:15;284:12; 288:8;289:10;293:7; 302:19;309:18;311:17; 312:2;315:19;325:10; 329:18</p> <p>event (1) 56:1</p> <p>events (3) 18:11;121:22;303:16</p> <p>eventually (2) 141:6;329:15</p> <p>everybody (27) 52:13,16;58:21; 162:13;166:7;181:13; 187:22;199:12;200:15; 204:17;205:18;211:18, 18;212:17;217:6; 219:12;233:6;234:1; 235:10,18;236:18; 240:4;241:19;322:2; 324:15;325:8;330:4</p> <p>everyday (1) 327:21</p> <p>everyone (5) 149:7;167:17;195:1; 232:11;271:17</p> <p>everything's (1) 167:21</p> <p>evidence (31) 14:19,19,20;15:1,6,7, 10,12,15;16:9,17;19:10, 17;26:5,14;27:9,14;</p>	<p>35:7;36:2,7;62:4;99:9; 166:14;193:15,17; 209:22;239:13;284:17; 288:4;326:15;329:18</p> <p>evidence-based (1) 206:4</p> <p>evident (1) 291:1</p> <p>evolving (2) 326:22;327:1</p> <p>exactly (9) 83:12,22;84:3;145:5; 148:9;172:13;179:15; 186:15;210:5</p> <p>exaggerate (1) 304:19</p> <p>exam (1) 206:2</p> <p>examine (1) 226:6</p> <p>examining (1) 295:7</p> <p>example (29) 9:19;15:17;16:15; 18:9;27:4,21;35:16; 37:7;59:5,5;60:16; 117:16;120:14,18;122:2, 17;123:21;140:2;145:6, 15;234:7;272:19; 279:16;283:16;293:3; 306:4;307:5;316:10; 326:10</p> <p>examples (2) 108:22;165:14</p> <p>exceeded (1) 107:14</p> <p>excellent (1) 152:19</p> <p>except (6) 128:16;205:9;219:21; 226:3;249:11;308:8</p> <p>exception (2) 51:19;135:17</p> <p>exceptions (1) 58:10</p> <p>excessively (1) 204:8</p> <p>excited (6) 54:15;55:4;98:8; 131:10;144:19;212:14</p> <p>exciting (1) 146:4</p> <p>exclude (3) 50:8,11;94:12</p> <p>excluded (3) 52:7;204:3;253:10</p> <p>excluding (1) 280:22</p> <p>exclusion (1) 207:5</p> <p>exclusive (1) 38:14</p> <p>Excuse (1)</p>	<p>200:17</p> <p>exhaustive (1) 58:6</p> <p>exist (1) 316:8</p> <p>existed (1) 79:3</p> <p>existence (1) 24:9</p> <p>existing (6) 16:12,17;30:15;36:7; 196:15;229:6</p> <p>exists (2) 93:3;309:5</p> <p>expand (2) 118:15;275:13</p> <p>expect (2) 48:8;270:8</p> <p>expectation (2) 188:11,13</p> <p>expected (5) 17:2;165:22;281:12; 292:2;322:16</p> <p>expensive (1) 180:1</p> <p>experience (5) 36:22;44:4;85:1,7; 96:9</p> <p>experienced (4) 42:17;85:5;106:12; 150:11</p> <p>experiencing (2) 94:2;192:2</p> <p>experimentally (3) 42:18;43:1,8</p> <p>expert (6) 9:12;142:12,14; 178:10;184:22;328:15</p> <p>expertise (1) 92:11</p> <p>experts (3) 142:8;143:17;328:15</p> <p>explain (2) 5:7;6:18</p> <p>explaining (1) 116:4</p> <p>explanation (2) 74:20;230:16</p> <p>exploration (1) 96:14</p> <p>exploratory (6) 26:12;27:7,11;128:18; 253:11;318:20</p> <p>explore (2) 175:14;319:16</p> <p>explored (5) 193:4,7,13;234:17; 259:3</p> <p>exploring (1) 65:16</p> <p>express (1) 329:8</p> <p>expressed (3)</p>	<p>11:17;134:20;135:2</p> <p>expressive (1) 198:19</p> <p>extended (1) 309:21</p> <p>Extended-release (3) 308:15,16;309:6</p> <p>extension (1) 93:11</p> <p>extent (4) 5:18;31:19;78:9;85:10</p> <p>external (1) 231:4</p> <p>extinction (1) 41:8</p> <p>extra (2) 200:12;240:22</p> <p>extremely (7) 59:13,20;86:14,20,21; 124:18;244:5</p> <p>eye (1) 83:16</p> <p>eyes (1) 21:8</p>	<p>13;285:15;286:12,12; 287:1,5,17;288:3;289:1, 6;294:10,14,15;304:7, 11,22;305:14;320:18; 321:19</p> <p>failures (3) 278:16;289:10;322:11</p> <p>fair (1) 174:13</p> <p>fairly (8) 52:6;102:13;157:16; 201:8,9;215:18;219:18; 221:16</p> <p>FALK (22) 79:12,12;81:12;97:3; 129:8,14,15,15;148:9; 149:13;151:18;152:18; 179:12;180:3,15,21; 315:7;317:9;318:16,18, 21;319:7</p> <p>Falk's (1) 153:12</p> <p>fall (2) 75:17;305:15</p> <p>falling (1) 232:8</p> <p>falls (1) 57:20</p> <p>false (1) 21:22</p> <p>familiar (3) 39:7;99:20;310:22</p> <p>family (3) 104:21;261:10;325:7</p> <p>famous (1) 41:5</p> <p>fan (1) 153:12</p> <p>fan! (1) 153:12</p> <p>far (14) 16:7;56:19;59:6; 103:3;105:22;107:7; 108:13;114:20;126:7; 174:11,13;229:5; 293:12;316:14</p> <p>farther (1) 17:21</p> <p>fascinated (1) 155:7</p> <p>fascinating (3) 155:6;157:9;174:9</p> <p>fashion (1) 186:19</p> <p>fast (2) 144:2;251:14</p> <p>favor (1) 292:6</p> <p>favorable (1) 297:15</p> <p>FDA (59) 9:4;11:3,19;19:16; 20:6;22:21;33:15;35:2,</p>
---	---	---	---	---

F

facilitate (1)
23:14

facilitation (2)
217:15;218:3

facility (1)
218:13

fact (29)
48:7,10;57:21;64:8;
78:19;94:4;99:22;100:3;
104:16;115:15;118:5;
119:15;124:8;125:18;
145:20;177:18;181:17;
184:3,4;189:21;241:7;
261:15;263:8;264:17;
266:6;308:11;309:5;
322:19;323:7

factor (9)
46:12,14,15;121:11,
11,13;126:21;210:15;
269:2

factors (6)
46:13;63:22;77:1,8,
20;258:18

fail (1)
110:8

failed (1)
73:6

failing (1)
304:19

fails (1)
304:15

failure (36)
73:2;252:17;253:16,
22;254:4,19;255:10;
268:2;273:3,4,12,19,22;
278:11,13;283:7;284:8,

6;36:5;63:20;65:3; 66:11;72:19;79:16;80:1; 87:10;88:7,10;89:17; 97:17,19;98:6,17; 105:17;107:12;110:12; 115:16;126:11;127:6; 132:7;134:20;147:5,15; 148:3;150:6;175:9; 183:4;194:3;196:18; 197:7,14;233:7,9,15; 234:19;272:12;309:18; 313:20;314:1;315:8,16, 16,20,22;319:2;321:6; 328:22;330:11	fields (1) 155:16 field's (1) 98:8 fifth (1) 119:14 Fifty (1) 252:19 fight (1) 239:17 figure (8) 22:7;89:18;94:13; 153:15;230:9;236:18; 269:7;305:19 filing (1) 180:17 fill (2) 124:13,15 filled (1) 124:14 final (5) 30:13;170:2;244:22; 265:7;274:21 finally (15) 7:14;48:7;51:4;53:6; 59:6,10;105:8;106:5; 131:7,16;148:18;255:9; 275:9;285:6;295:6 find (35) 41:11;73:4;74:13; 86:5;88:7,15,21;91:11; 93:14;102:14;109:1,15; 112:17;113:11,13; 123:21;128:19;136:3,9; 160:19;162:20;163:16; 167:18;178:21;180:6, 18;183:22;203:10; 255:1;268:3;284:9; 312:13;320:16;323:19; 329:5 finding (6) 61:10;76:6;152:12; 157:13;202:21;231:18 findings (13) 26:20;27:9;78:15; 210:3;239:15;275:12; 281:11,18;282:20; 283:5;285:3;290:21; 295:10 finds (1) 89:1 fine (3) 65:7;143:5;323:5 finish (3) 126:5;256:2;324:13 finished (3) 119:14;236:6;239:19 First (66) 20:21;23:15;24:12,13; 29:13;32:7;34:6;39:4; 40:1;42:19;48:19;49:7, 14;54:18;62:14,17; 67:10;76:17;85:2,3;	96:18;98:6,9,11,14; 101:3;105:16;110:15,18, 19;112:13;113:3;115:1, 4;125:5,6;129:18;130:9; 131:21;139:20;145:3; 191:9;206:5;209:20; 211:10;213:15;236:5, 19;238:8,14;246:16; 251:13,21;253:15; 256:15;265:1;269:6; 273:1;274:15;275:15; 281:20;283:6,17; 290:10;292:20;328:15 Fishman (1) 239:2 fit (1) 317:7 five (4) 196:13;213:5,18; 266:15 fix (3) 61:14;86:19,20 fixed (1) 281:3 flexibility (2) 20:16;291:17 flexible (1) 167:13 floating (1) 71:5 flooding (1) 40:16 flow (1) 238:19 fluctuation (1) 133:15 flying (1) 6:21 FOA (1) 265:2 FOAs (1) 331:3 focus (11) 22:3;83:12;85:13,19; 88:12;90:19,20;148:4; 164:22;262:18;327:1 focused (4) 147:21;185:17; 205:12;306:5 focuses (1) 80:4 focusing (1) 96:16 fold (1) 177:7 folks (9) 52:19;53:9,12;161:7; 190:20;196:19;240:12; 270:11;319:3 follow (9) 101:14;102:7;103:3; 149:19,22;189:14,15; 191:5;283:11	follow-back (8) 52:15;137:2;143:1; 165:9;167:5;215:3; 259:2,5 followed (3) 233:20;241:8;324:8 following (3) 26:10;153:11;178:8 follow-up (45) 99:22;107:16;160:16; 161:16;199:8;200:5; 201:3,3,6;203:6,9;206:7; 208:10,19;213:11; 214:14,17,19;216:1,6,8, 11;219:3;220:4;222:22; 223:2,4,15,16;225:7,10, 17;226:8,15;227:20,22; 228:5;229:1,9;230:22; 233:21;237:4,10; 313:11;325:11 follow-ups (1) 312:16 food (2) 147:1;194:20 foray (1) 95:11 forced (1) 309:14 foremost (1) 20:22 forever (1) 172:5 forget (5) 24:5;76:22;141:19; 211:22;212:1 forgotten (1) 97:11 form (4) 28:5;41:4;156:17; 276:6 format (1) 211:8 formation (1) 241:10 forms (1) 26:16 formulate (1) 10:16 formulation (1) 275:20 forth (13) 87:3;122:6;123:7; 154:9;159:2;163:2; 173:6,22;174:5;185:4, 13;258:11;261:11 forward (8) 9:19;10:4;33:21; 34:13;56:12;67:15; 174:14;187:12 found (62) 27:4;38:3;41:13; 43:17;45:8;47:10,19; 50:4;56:6;57:6,11,22;	76:2;90:7;101:8;103:8, 12;104:14;105:5,22; 106:9;107:7;108:7,13, 19;111:5;112:19;113:4, 9;120:22;122:21;123:3, 4;126:7;130:16;135:14, 21;136:5;156:9;160:10; 161:11;166:7;177:20; 181:8;192:19;193:14; 199:3;200:13;201:22; 202:3,12;204:15,18; 224:4;227:16;229:5; 230:19;250:17;254:15; 255:11;284:14;287:1 founding (1) 233:7 four (14) 13:4;100:18;119:14; 145:9,12;155:18;156:3; 189:9;196:13;197:17; 259:11;272:19;273:1; 275:13 fourth (1) 252:1 frame (1) 263:21 Francisco (1) 5:14 Frank (1) 170:10 free (4) 70:20;205:20;206:12; 208:15 frequencies (1) 157:4 frequency (10) 45:2;143:6,8;156:21; 167:7;170:21;215:4,9; 230:12;317:4 frequently (2) 76:2;327:22 Friday (1) 312:21 friend (1) 133:6 front (6) 7:4;38:6;44:14; 271:13;298:13;315:11 fruit (1) 95:6 full (5) 110:5;111:10;127:8; 130:17;161:13 fully (3) 22:12;64:6;89:14 fun (2) 69:11;128:2 function (32) 12:5;14:9,22;15:4,20, 22;16:11;17:8;32:4; 35:20;36:1;67:22;79:21; 85:8;87:12,16,18;88:21; 89:20;90:20;91:7,9,10;
---	---	--	---	---

147:18;203:5;235:16; 246:21;279:3,5,13; 290:15;316:22 functional (10) 90:7,11;201:2,3; 202:16;203:15;225:10; 232:5;244:19;256:12 functioning (23) 17:15;18:14,15,15; 19:3;88:5;90:15;156:18; 157:8;159:1;173:10; 187:7;199:7,19;201:7; 213:12,14;216:16,16; 223:22;224:9;229:8; 261:8 functions (3) 14:15;148:4;316:1 funded (1) 59:14 funding (5) 9:16;59:17;197:19; 256:3,8 further (13) 43:5;69:6;71:1,2,6; 80:18;88:9;96:10; 102:11;120:17;127:18; 258:21;306:2 future (3) 77:16;186:7;245:5 fuzziness (1) 185:5	219:15 generate (1) 197:13 generated (3) 6:8;84:4;281:14 generating (2) 27:8;186:18 generation (1) 70:22 generous (1) 173:14 genetically (1) 205:3 George (12) 62:20,22;63:18,19; 144:10,11,16;198:3,4; 296:7,8;324:6 Gerry (1) 210:9 gets (12) 51:18;52:13;80:5; 93:9;97:13,15;154:12; 169:10;179:8;205:18; 219:12;306:3 GGT (1) 144:12 given (9) 24:13;25:11;34:14; 55:9;100:3,12;139:19, 21;148:7 gives (1) 108:12 giving (4) 67:12;243:4;321:14, 16 glad (1) 61:1 glance (1) 292:20 glaze (1) 21:8 glitch (1) 49:18 global (17) 131:5;216:16;225:20, 22;226:8,15;228:4,16; 246:13;247:12,21; 248:3;249:17;250:3; 285:1,5;298:7 glucuronide (2) 144:20;145:7 goal (14) 183:7,17;184:5; 187:20,20,22;188:4,13, 21;189:3,3;198:13; 199:3;327:12 goals (2) 7:8;157:12 goes (13) 62:19;76:20;78:16; 89:21;117:6,22;124:3; 133:18;165:3;188:18; 192:10;242:19;311:18	gold (1) 98:15 Good (80) 11:11;14:6;20:7;32:1; 37:3;46:9,10,16;47:4,11; 57:8,18;58:12,14;61:5; 63:9;73:3,6;74:20;76:6; 77:5;79:14;81:20; 107:18;108:11;118:1; 129:18;130:8,20;134:10, 11;136:14;137:5,6,8, 147:20;152:18;158:22; 165:4;171:13;173:10; 174:3,21;176:9;190:8; 192:17;194:8;205:19; 210:1;216:1,16,19,19; 217:9,9;222:11,13; 223:4,21;229:17;231:7; 232:19;235:16;240:6; 250:9,16;253:20; 257:18;261:13;266:11, 18;269:10;271:16; 303:9;319:9,10;320:11; 321:7;323:4;325:11 good-outcome (1) 220:6 government (1) 97:12 grace (19) 110:1,1,9,13,14; 113:15;114:20;170:6; 171:7;274:13,14; 281:10;290:6,9,18,20; 291:2,5;295:3 gradation (2) 203:10,11 grail (3) 159:6;174:10,20 grams (1) 122:2 Grant (6) 106:8;196:14;197:18; 198:7;265:6;311:19 granted (2) 28:14;305:3 granular (1) 152:21 graph (12) 116:5,6;121:8;212:3, 5;259:10;290:17; 292:17,19;293:11,15; 294:1 graphed (1) 293:20 graphical (2) 281:17;295:13 graphing (1) 293:17 graphs (7) 115:22;281:13,20; 283:22;289:7;290:14; 294:7 grateful (2)	45:21;59:20 gray (1) 223:8 grays (1) 223:10 great (32) 34:6;56:4;67:10; 77:22;79:13;85:17; 91:17;95:17;97:6;100:2; 144:2;146:6;157:20; 158:4;166:17;167:3; 169:2;176:2;178:11; 179:22;184:8;188:6; 195:2;227:17;230:7; 266:12;267:8;319:15; 320:5;324:15;330:12,16 greater (14) 43:18,19;57:7;104:14, 16;107:2,3,9;216:1; 223:11;228:5;248:8,9; 293:22 greatly (3) 67:18;68:7;175:11 green (1) 251:18 Greenfield (1) 105:13 group (80) 55:7;58:20;60:4; 76:21;80:4;83:11;89:1, 8;97:9,16;99:19;103:4, 14,19;104:10,17,19,22; 105:2,6,10;106:8;107:4, 8;121:1;127:4;130:19; 131:18;143:20;154:17; 175:12;177:9;182:15; 183:12;184:19;198:17; 199:11,12,13;200:16,18, 21;203:21;204:20; 205:2,2;206:22;207:3,4; 214:2;242:5;251:13,13, 14,15,15,16,17,18,18; 252:3,3,5,5;253:17; 257:1,18;266:6,6;267:4; 273:17;274:5;296:4; 299:1,2,5,19,22;302:15; 305:2 groups (18) 22:3;33:2;85:13,20; 100:4;103:19;238:4; 251:12;253:4;259:11; 260:1;273:15;299:9; 303:17;304:5;305:3; 309:4;310:2 group's (1) 108:4 grows (1) 241:1 growth (2) 225:14;226:6 guarantee (3) 166:5;285:14;294:15 guaranteed (2)	274:19;290:13 guard (1) 36:16 guess (24) 47:7;49:20;79:15; 82:17;143:4;180:21; 196:11;204:9;217:1; 241:7;257:10;261:9; 267:7,11;268:4;269:6; 302:20;303:5,7;307:13, 22;311:22;315:7;330:6 guessed (1) 173:4 guidance (10) 20:7,10,14;33:6;98:7; 107:13;110:12;134:21; 150:6;295:18 guide (1) 182:12 guided (4) 178:9;198:20;201:4; 214:10 guidelines (3) 21:4;30:11;138:20 guilty (1) 266:22 guy (3) 211:5,6;323:20 guys (11) 53:18;96:5;147:19; 151:16;152:22;160:4; 165:18;182:17;191:8, 13;268:4 guy's (1) 156:1
G				H
gained (2) 14:5;15:8 gaps (1) 151:13 gather (2) 215:6;292:19 gathered (1) 53:17 gave (7) 43:13;61:13;111:16; 127:5;196:15;230:16; 239:20 Gawin (3) 41:6;71:13;170:11 gee (2) 177:21;237:5 gender (1) 206:13 general (22) 18:14;29:1;50:13; 71:16;105:17;156:13, 20;159:11;168:3; 171:16;178:4;213:12, 13;218:21;219:11; 224:9;229:8;250:20; 313:8;315:15,19;319:1 generally (7) 26:19;38:15;50:22; 102:14;126:8;144:16;			half (9) 89:22;101:16;102:7; 200:7;207:12,18;209:5; 219:4,8 halfway (1) 127:19 hall (2) 6:15;10:22 hallway (1) 194:20 hand (4) 6:22;172:13;288:4; 304:18 handle (3) 267:11;268:5;269:11 handling (2) 268:10,15 hands (1) 10:5 Hank (1) 192:15 happen (5) 46:22;66:5;115:5; 261:11;308:14 happened (4)	

<p>166:22;236:9;273:14; 301:9</p> <p>happens (7) 62:17;115:9;134:5; 165:15;259:14;270:4; 285:15</p> <p>happy (5) 98:8;206:12;318:5,6,8</p> <p>hard (17) 53:1;84:1;108:8; 159:7;162:4,4;167:3; 172:9;175:21;176:5; 211:7;239:8;240:21; 262:12;297:3;298:8; 302:17</p> <p>harder (5) 17:22;19:6;66:20; 149:12;311:21</p> <p>harkens (1) 76:5</p> <p>harmonize (1) 156:5</p> <p>harmonizing (1) 166:5</p> <p>harsh (1) 45:22</p> <p>hats (1) 67:4</p> <p>HDD (1) 328:8</p> <p>head (3) 81:20;178:16;308:1</p> <p>headings (1) 26:1</p> <p>health (17) 17:16;18:20;86:4; 131:4;135:18;139:1,12; 140:3;143:11;159:11; 184:11;205:22;233:16; 18;325:15,16;326:2</p> <p>healthcare (3) 93:2;159:20;187:7</p> <p>health-related (2) 18:10,13</p> <p>healthy (1) 157:7</p> <p>hear (6) 34:10;61:1;69:11; 82:15;96:7;297:7</p> <p>heard (6) 134:22;158:12;322:4; 330:10,13,20</p> <p>hearing (2) 197:7;300:16</p> <p>heart (5) 38:12;122:4;234:3,11; 235:14</p> <p>heavily (1) 64:16</p> <p>heavy (93) 98:18,22;99:1,3,6,8, 11;101:10,11,20;102:4, 10;103:1,5,20;104:11,</p>	<p>16,19;105:1,7,9;106:1,3, 10,12,17,17,18,19,21,22; 107:2,5,9,14;108:1,16; 109:10,17;111:9,21; 112:2;113:5;114:11,13; 115:5,8,9;116:1,2,10,11, 14,18,22;117:5,8,9,10, 12,14,17,18,21;118:4,8; 122:7,8,14;123:2,4; 124:10,10;127:21;128:1, 5;132:18;136:21;139:7; 7;169:19;179:1;183:2; 189:18;190:1;191:7,9, 19;207:3;233:10,11; 257:9;330:16</p> <p>heck (1) 257:12</p> <p>hedonic (1) 44:8</p> <p>held (2) 6:16;327:18</p> <p>hell (1) 164:7</p> <p>Hello (2) 175:7;212:17</p> <p>help (33) 10:16,17;14:8;22:3,5, 6;23:3,13;24:6;25:3; 26:21;27:9;31:20;33:4, 13;36:9;40:4;51:16; 59:15;74:2,14,15;82:2; 91:12;172:20;182:11; 200:13;266:8;290:10; 291:6;295:4;306:8; 326:1</p> <p>helped (2) 67:17;330:17</p> <p>helpful (8) 15:5;24:2;28:11; 73:19;80:14;89:1;175:3; 176:21</p> <p>helping (3) 92:15;329:9,10</p> <p>helps (3) 17:12;28:16;269:18</p> <p>hence (1) 9:1</p> <p>herd (1) 142:13</p> <p>here's (6) 33:18;136:17;200:1, 11;220:4;237:6</p> <p>heroin (2) 296:10,11</p> <p>Hertz (9) 64:4,4,20;72:18,18; 81:13,13;82:1;88:11</p> <p>hesitate (1) 325:1</p> <p>heterogeneity (1) 188:16</p> <p>heterogeneous (1) 86:6</p>	<p>Hey (1) 190:4</p> <p>Hi (1) 129:15</p> <p>hide (1) 312:3</p> <p>hierarchical (1) 157:19</p> <p>hierarchy (2) 26:11;27:17</p> <p>high (39) 29:8;38:16;42:17,22; 43:15,18,22;49:10,12, 22;50:20;54:21;55:1; 56:8;57:11,15,16;62:5; 63:13;71:22;76:6;78:11; 94:5,11;124:11;125:20, 20,21,22;132:10,11; 169:15;265:6;310:7; 312:12;313:3;323:18; 324:12;325:19</p> <p>higher (24) 26:14;47:15,17;48:4; 50:18;101:5;103:5; 105:1,2,7,9;140:4;169:9; 231:20;233:12;237:14, 14;249:21,22;273:18; 282:13;283:2;293:2,4</p> <p>highest (2) 31:21;46:21</p> <p>highlight (6) 25:7;99:16;220:21; 223:12;224:12;227:14</p> <p>highlighted (1) 221:1</p> <p>highlights (1) 326:5</p> <p>highly (3) 77:21;167:13;199:14</p> <p>hired (1) 142:11</p> <p>histogram (1) 279:17</p> <p>historical (2) 55:11;71:12</p> <p>historically (1) 9:6</p> <p>histories (1) 47:15</p> <p>history (3) 31:10;69:11;192:11</p> <p>hit (2) 111:4;317:12</p> <p>HIV (2) 324:9,10</p> <p>HMO (1) 119:20</p> <p>hoc (3) 315:10;319:4,6</p> <p>hold (3) 232:10;313:6,6</p> <p>Holy (2) 174:10,19</p>	<p>home (4) 24:10;56:10;300:22; 330:8</p> <p>honest (3) 101:1;121:17;125:17</p> <p>honestly (1) 82:20</p> <p>hooked (1) 87:11</p> <p>Hooray! (1) 165:21</p> <p>hope (10) 6:5;10:12,15;153:4; 157:11;160:16;170:7; 329:3,12;331:7</p> <p>hoped (4) 281:5;282:11;320:7, 21</p> <p>hopefully (1) 8:8</p> <p>hoping (4) 74:11;96:21;129:5; 150:22</p> <p>Hospital (6) 49:18;50:8;205:20; 206:6;210:12;211:1</p> <p>hospitalization (1) 160:1</p> <p>hospitalized (1) 205:19</p> <p>hour (3) 89:22,22;145:20</p> <p>hours (1) 145:20</p> <p>housekeeping (2) 6:1;10:21</p> <p>huge (10) 51:9;157:2;172:5; 181:8;182:2,21,22; 235:22;247:18;258:19</p> <p>human (3) 13:10;44:3;97:4</p> <p>humans (1) 233:9</p> <p>hundred (3) 133:4,11;260:22</p> <p>hundreds (2) 182:4;190:5</p> <p>hung (2) 147:14,15</p> <p>hurdle (1) 23:22</p> <p>hurt (1) 270:11</p> <p>hypothesis (2) 27:7;200:12</p>	<p>205:14;207:6;209:4,16; 211:6</p> <p>Icelandic (2) 208:12;211:5</p> <p>idea (21) 53:9;91:1,1;150:2,17; 151:5,8;170:6;176:4,9; 177:14;187:12;246:16, 19;256:19;311:21; 319:15;320:6,15; 322:10;328:2</p> <p>ideal (4) 37:9;39:22;94:15; 141:5</p> <p>ideally (4) 137:16;158:17; 159:22;283:22</p> <p>ideas (5) 10:16;176:2;178:11; 245:2,3</p> <p>identical (1) 264:18</p> <p>identified (4) 18:2;72:22;93:3;328:4</p> <p>identifies (2) 28:19;63:14</p> <p>identify (16) 7:14;29:13;35:19; 40:1,3,5;52:4;54:13; 59:3;63:4,16;83:7;84:2, 15;329:10,11</p> <p>ignorant (1) 191:14</p> <p>ignore (3) 77:22;274:15;321:5</p> <p>ignored (2) 265:13;290:9</p> <p>illegal (5) 63:21,21;64:9;194:4; 201:15</p> <p>illicit (12) 172:13,18;256:11; 274:11;278:9;285:7; 288:4;302:16,20;304:3; 305:8;307:15</p> <p>illness (2) 50:9,17</p> <p>illustrate (6) 23:17;272:8,19; 276:17;280:11;285:17</p> <p>illustration (2) 279:17;283:6</p> <p>image (1) 239:1</p> <p>imagine (1) 183:12</p> <p>imbalance (2) 287:1,3</p> <p>IMBIBE (9) 127:11,12,15;151:11, 12,18,21;190:20;191:1</p> <p>immediate (1) 169:4</p>
		I		
		<p>iceberg (1) 44:5</p> <p>Iceland (9) 198:12;204:4,6,22;</p>		

impact (16) 12:3,21;14:9;17:19; 18:19;25:14;26:3;36:14; 88:6;95:4;267:15; 268:22;295:11;303:17; 304:14;306:12	61:12;88:5;309:9	248:1,20,22;251:16,19; 261:18;278:2,17	139:6	311:10;317:2,20
impacted (1) 298:11	improvement (12) 22:15,17;28:10;53:6; 135:4;246:14;252:12; 255:22;256:21;261:8; 288:18;295:1	increased (8) 42:16;47:2,3;53:14; 102:12;251:22;308:17; 309:8	influence (1) 275:10	instant (1) 215:16
impacting (1) 307:17	improvements (2) 28:12;148:22	increases (1) 141:15	inform (5) 24:6;93:5;157:13; 306:8;319:10	instead (9) 102:17;116:4;146:17; 266:2;272:4;282:15; 284:2;302:3,8
impacts (4) 18:12;19:3;65:13; 294:7	improves (2) 88:21;147:17	increasing (1) 14:5	information (18) 24:1;27:20;32:2; 88:17;92:19;95:7,9; 165:8;176:20;215:6; 272:9;275:18;293:12; 294:12;297:19;298:12; 304:9;320:19	instrument (36) 23:18,20;24:18;29:17; 30:14,15,17;31:4;37:8,9; 18;45:1,15;46:9,13; 47:6;51:17;59:16;61:11; 69:7,9,15,20;70:22;73:7; 80:3;81:17;82:17,19; 83:1,3;84:17,18;85:17; 89:19;137:15
implant (2) 276:1;299:12	impulse (1) 100:19	independently (1) 54:8	informative (2) 131:1;330:19	instruments (6) 32:13;47:6;60:15; 61:1;86:7;89:11
implantable (1) 275:20	imputation (6) 267:16;268:2;311:6,9, 10,13	index (1) 203:17	infrequent (1) 150:14	instrument's (1) 30:10
implanting (1) 276:13	imputations (1) 269:13	indicate (1) 19:12	inherent (2) 68:19;173:20	insulin (1) 184:14
implication (1) 259:14	impute (6) 207:16;303:18; 308:17,19;310:3;311:3	indicated (2) 226:16;227:10	in-house (1) 234:2	Insurance (1) 124:22
implications (3) 37:13;50:12;272:6	imputed (1) 310:19	indicates (2) 224:10,13	initial (11) 45:16;54:5,6;57:20; 71:9;78:19,21;93:10; 95:11;150:1;276:4	intake (2) 123:15;143:10
imply (2) 178:12;330:7	imputing (1) 298:22	indication (2) 26:17;126:3	initially (9) 38:1;48:21;69:19; 73:9;74:16;216:17; 220:6;277:5;303:9	integrate (3) 107:11;130:4;139:18
importance (1) 150:10	inattention (1) 38:11	indicator (11) 154:3;157:15;158:9; 160:9,19;162:14,15; 173:1;223:17;227:15; 233:16	initiated (2) 103:16,18	integrated (1) 121:15
important (67) 12:4,12;13:7;14:12; 16:1;17:18;19:5,14; 24:12;25:7,8,9;26:3; 27:17;29:3;30:22;32:2; 41:19;60:11;64:20; 70:14;76:10,13;84:22; 85:2,6;86:8,9,10,14,16, 16,20,21;89:1,6,7,9; 95:15;100:22;130:3; 131:20;150:18;151:10; 155:13;166:10;176:10, 11;178:8,12;182:12; 222:18;224:13;226:13, 18;242:9;244:3;251:7; 267:12;289:2;294:13; 295:8;310:22;312:9; 313:20;323:1,6	inaudible (1) 209:3	indicators (16) 131:5;155:20;158:22; 173:16;212:21;213:1; 220:14,19;221:1,5; 222:1,4,5,7,19;268:10	initiation (3) 73:20;104:2,12	intellectually (1) 330:4
importantly (3) 21:20;131:16;311:16	incentives (2) 35:2;311:22	indices (1) 157:3	injections (1) 207:9	intelligent (1) 321:6
impossible (2) 176:3;191:17	incidence (1) 237:16	indirect (10) 14:19,22;15:6,10,13, 14,19;16:4,7;69:2	injured (1) 237:1	intend (2) 29:22;187:1
impressed (1) 157:18	incidental (1) 202:21	individual (17) 22:3;32:8,10,17;33:2; 45:5;46:20;47:11; 128:13;154:18;199:12, 14;200:20;246:10; 276:1;291:13,15	injuries (4) 122:5,5,22;123:7	intended (9) 14:14;15:21;16:3; 21:13;23:17,20,22;24:2; 32:21
impression (8) 144:12;246:13; 247:13,21;248:3; 249:17;250:4;298:7	include (9) 17:3;26:1;38:9;65:21; 101:1;147:6;253:12; 270:6;274:14	individually (1) 227:4	injury (1) 237:2	intense (1) 40:7
impressive (2) 121:7;263:4	included (20) 9:3;30:13;44:8;52:9; 84:16;151:7;213:19; 214:5,14,17,18;217:13, 14,19;218:15,17,20; 221:8;290:17;309:2	individuals (2) 147:2;223:1	Innovations (1) 8:20	intensity (1) 45:1
improve (11) 25:4;48:9;90:15; 146:12;151:21;152:12; 274:19;289:12;290:13; 291:4;295:2	inclusive (1) 84:21	induced (1) 200:4	innovative (1) 330:21	intention (2) 40:9;188:10
improved (3)	incorporate (2) 22:21;23:11	induction (1) 276:5	inpatient (6) 78:11,13,16,18;79:5; 105:4	intention-to-treat (2) 167:15;216:2
	incorporated (1) 81:7	industry (2) 9:5;176:13	input (1) 23:2	interest (6) 9:8;29:14;81:15; 127:5;225:3;244:18
	increase (14) 42:22;96:22;117:16, 21;141:18;158:14;	ineffective (1) 163:14	insensitive (2) 161:2,8	interested (15) 13:12;32:6;42:3; 44:10;61:10;72:19; 105:18;119:5,19; 123:14;126:10;174:2; 225:19;291:12;331:2
		inevitable (1) 291:3	insertion (1) 278:2	interesting (34) 40:14;46:17;48:18; 56:13;64:21;69:11; 70:19,21;71:19;75:19; 88:2;90:4,6;101:19,22;
		infinite (1)	instance (9) 42:20;47:12;267:17; 303:15;304:16;305:14;	

112:7;113:10;122:10; 125:17;161:7;168:18; 18;174:12;187:12; 204:7;242:3;252:2,8; 264:10,13;270:1;313:4, 12;326:5 interestingly (3) 45:5;223:18;228:2 interface (1) 60:14 interference] (1) 233:6 interject (1) 67:3 intermittent (2) 197:5;203:14 internal (4) 46:5,11;70:12,12 international (1) 98:1 interpersonal (3) 100:19;139:14;217:18 interpret (14) 13:16;18:1,8;19:6; 22:10;26:21;27:9;66:20; 157:17;284:9;287:2; 294:11,17;298:8 interpretable (1) 22:12 interpretation (5) 262:1,2;292:20; 307:17;313:19 interpreted (3) 20:5;68:21;159:4 interpreting (2) 21:4;30:12 interrater (3) 46:4,10;70:11 intersects (1) 89:12 interval (2) 189:22;241:9 intervals (1) 247:7 interventions (1) 264:16 interview (4) 84:19;235:17,18; 314:19 interviewed (1) 126:20 interviewer (2) 44:15;82:18 interviewer-based (1) 83:1 interviewers (3) 328:16,19;329:9 interviews (5) 22:3;29:19,19;151:3; 170:6 into (55) 6:4;11:20;21:14;29:6; 36:1;46:13;49:18;51:17, 21;54:5;57:13;59:16; 65:3,5;67:6;68:16; 69:17;75:16;77:15; 89:16,17;95:11,16; 99:18;103:19;104:6; 121:16;146:3;154:6,14; 156:18;167:9;172:22; 177:7;193:6;205:11; 209:15;227:3;229:19; 231:2;270:12;276:8,13; 292:11;294:12;296:22; 303:8;304:10,20;305:5, 6;313:8;317:1;326:22; 327:1 intoxicated (1) 65:22 intractable (1) 318:1 intrapersonal (1) 100:20 intrigued (1) 71:21 intriguing (5) 68:1;69:5;70:1,19; 91:1 introduce (11) 5:3;11:2;36:20;37:19; 40:11;100:9;109:22; 129:7;244:15;262:6; 271:14 introduced (1) 133:9 Introductions (1) 5:2 inure (1) 176:16 Inventory (2) 100:10;190:17 invest (1) 314:22 investigated (1) 327:14 investigator (2) 277:19;279:1 investigators (9) 33:3;39:13;41:10; 107:21;168:20;278:7; 284:20;285:4;298:8 invitation (1) 11:12 invited (1) 142:7 inviting (1) 198:5 involved (7) 65:9;127:2;159:17,22; 160:4;175:22;193:6 involvement (1) 66:6 involves (2) 244:7;276:4 involving (2) 22:2;280:15 IOP (2) 49:2;206:7 IRB (2) 208:12,17 irritability (3) 38:11;42:21;47:3 irritable (1) 41:1 ischemic (1) 122:4 isolated (1) 42:19 issue (11) 94:14;152:9,11,17; 262:22;265:8;267:11; 300:3;311:2;321:4; 325:3 issues (16) 91:19;129:16;130:2; 136:11;147:15;151:17; 208:21;209:16;211:3; 229:20;230:3;263:13; 264:1;305:12;325:20; 329:10 item (4) 46:16;47:11;100:18; 225:22 items (18) 21:12,14;29:21;38:7; 44:15;45:5;46:20,22; 61:14;82:20;85:16; 100:21;127:12;128:13; 139:13;150:9,14;192:4 iterative (1) 29:1 IV (1) 206:13 Ivan (9) 62:21;63:6;153:10; 184:9;185:20;197:19; 244:15,16;265:2 J jackpot (1) 111:5 jail (1) 173:12 Jakafi (1) 28:14 JCCP (1) 225:18 JNC (1) 138:19 Joanne (3) 97:3,7;193:20 job (9) 22:21;86:22,22;146:6; 175:15;261:9;264:3; 322:6;325:6 Joe (11) 38:20;39:6,10,17; 45:13,17,17;61:13; 69:12;85:15;126:18 Johnson (2) 56:22;136:5 joking (1) 158:2 journal (4) 173:14;175:4;204:15; 238:1 judge (1) 130:12 judged (1) 286:20 judgment (4) 13:10,16;20:16;22:22 jump (1) 130:5 jumping (3) 117:20;172:22;270:12 Jurgen (1) 119:5 justice (4) 146:7;159:17;219:9; 326:13 justify (3) 27:14;98:13;118:3 K Kaiser (4) 86:1;137:5,13;325:9 Kampman (22) 34:9;36:21;37:1,2,3; 60:7,10;61:4,9;62:8,12; 63:1,8;72:8;73:17;75:6; 76:15;78:13;82:21; 85:13;297:11,21 kappa (3) 250:11,14,15 Kathleen (3) 153:6;174:16;212:13 Kathy (19) 61:22;100:14;153:5; 177:18;186:11;212:18, 20;213:12;215:10; 224:17;229:20;230:16; 250:17;258:1;264:13; 268:11;312:15;314:6; 323:15 keep (6) 7:21;14:10;83:12,16; 124:1;311:18 keeping (1) 10:7 keeps (1) 162:22 Kelly (2) 91:4;188:19 Ken (10) 34:21;68:4;89:21; 147:11,12;160:3;308:5, 6;323:2,3 Kenzie (4) 164:10;180:9;181:6; 301:17 kept (1) 200:7 Kevin (1) 207:14 key (12) 19:16;22:9;24:10; 28:7,20;96:18;129:16; 131:17;272:1,13; 278:14;294:9 kidney (3) 5:13;139:1;235:16 kids (1) 159:16 kill (1) 183:9 killer (1) 166:6 kills (1) 315:2 Kilou (6) 10:4;156:8;212:12,16, 17;268:8 kind (73) 40:13;58:9;59:11; 62:4,19;65:15;67:12; 69:17;74:11;76:5;81:9; 87:4;90:22;91:13;94:15; 96:19;97:15,17;99:15; 108:12;124:6;130:8,19; 133:16;134:14,15; 137:3;138:14,17; 143:17;151:15;158:10; 159:6;160:19;162:21; 170:8;171:8;172:14; 173:12,14;174:8;180:4; 181:3;188:22;190:21; 193:14;208:20;212:4; 213:12;218:14;219:1; 220:8;222:11;224:2,2; 227:18;228:21;231:15; 242:7;260:1,2;265:5; 297:13;310:16;315:10, 14;317:13,15;325:1,7, 17;326:18;328:14 kindergarten (1) 311:15 kinds (23) 88:12;116:1;143:11; 148:22;149:3,3,7; 156:20;159:10;164:16; 165:6,10;167:6,13; 168:2;169:8,13;173:3; 179:21;188:15;193:10; 259:2;312:4 Kleber (2) 41:6;71:14 Knights (2) 174:10,19 known (1) 12:8 knows (1) 233:6
--

<p>Kranzler (1) 192:15 Kyle (9) 36:20;37:2;45:15; 69:14;71:11;74:19; 158:12;297:10;330:13 Kyle's (2) 68:10;69:8</p>	<p>116:12;126:5;127:16; 128:4,6;155:18;158:2; 171:19;185:7;213:14,20, 22;218:18;219:7; 221:20;225:1,18; 229:15;233:13;235:7; 258:2,10;268:16,18; 271:7;289:7;291:8; 292:17;311:10;322:2</p>	<p>10:16;31:15;40:5; 73:18;81:2;82:13;108:4; 111:22;119:8;127:19; 131:13,14;135:11; 138:7;139:3;165:17; 196:13;212:20;215:1; 216:13;221:2,10,13,21; 222:9;223:14;224:16; 225:4;230:5,8;255:14; 259:8;266:8;270:14; 276:8;280:4,4,6;296:16; 327:13</p>	<p>levels (14) 55:20,21;56:4;118:21; 123:17;124:8;132:9; 140:13;146:11;179:20, 21;193:9;231:20;298:20 Lewis (1) 262:7 Li (8) 197:19;198:21;202:5; 203:7;208:7,9;260:22; 261:3 liars (3) 168:13,13,14 liberty (1) 256:14 life (20) 12:6;13:19;14:10,22; 15:20,22;16:6;17:16; 18:10,13,20;19:1;32:4; 36:1,4;69:19;85:8; 147:18;148:5;264:3 lifetime (1) 47:14 light (1) 102:2 lighter (1) 223:8 liked (2) 34:7;267:8 likelihood (2) 25:4;31:21 likely (12) 16:19;49:14;51:12; 56:2;82:4;107:16,16; 194:2;201:16;228:18; 324:1;329:5 likes (3) 53:4;147:5;234:19 Lily (4) 126:16;150:1;151:15; 190:20 limitations (6) 145:2,3;147:10; 203:18;239:12;258:20 limited (5) 77:17;135:11;138:17; 140:1;203:18 limiting (2) 277:1;291:15 limits (1) 107:14 line (5) 104:9;235:4;247:5; 261:9;283:11 linear (5) 48:11;157:19;246:22; 247:6,15 linearly (1) 41:15 lines (2) 193:15,17 lingering (1) 252:10</p>	<p>link (5) 15:12,16;16:13;17:1; 33:18 linked (3) 16:18;170:3;314:15 list (6) 25:12,15;58:6;150:17; 153:17;213:18 listed (1) 272:14 listen (2) 194:10;264:10 listening (1) 182:8 lit (1) 222:12 literature (9) 10:1;29:20;39:12; 85:17;156:13;162:10; 178:18,20;302:1 Litten (7) 96:8,11,12;144:16; 149:14;187:18;191:21 little (83) 5:8;6:14;11:13,22; 14:17;21:9;35:15;37:17; 46:17;49:18;50:17;56:9; 66:20;70:10;72:2,13; 86:3;93:20;102:8,15; 103:4;105:20;108:17; 109:21;111:1,2,3; 112:22;114:6,13;117:7; 118:6;121:7;123:9; 124:1;128:7;132:17; 133:17;135:1;138:6; 140:4,5,22;143:22; 145:10;153:18;154:19; 158:12;161:5,18;165:2; 169:7;171:6;172:8; 173:9;174:6;176:15; 178:16,19;191:13; 200:7;206:21,21;207:4, 5,11,11;208:8;209:18; 211:7;218:6;228:18; 241:17,19;244:21; 264:8;265:20;282:9; 293:8;297:2,3;314:10; 315:1;325:16</p>
L				
<p>lab (3) 181:7;234:6,6 label (1) 80:21 labeling (10) 12:9;17:9;18:6;21:21; 26:18;27:1,3,5,12;65:1 labels (1) 216:18 laboratory (2) 44:3;215:15 labs (2) 314:17,20 lack (4) 73:5;303:16;323:17; 329:6 LAD (4) 239:7;241:18,22; 242:1 lag (2) 149:14;261:7 Lai (16) 232:13,18,19;238:14; 240:17,19;241:12,15,19, 22;242:2,8;243:6,13,17; 244:3 laid (1) 34:7 Lai's (2) 263:4,13 land (1) 328:18 language (1) 172:15 lap (1) 45:15 large (11) 12:22;52:6;79:7; 99:22;119:18;122:12; 136:7;149:9;215:7; 304:16;317:21 largely (3) 191:6,17;215:13 larger (1) 292:4 largest (1) 100:1 last (46) 43:15,20;53:8;76:9; 77:11;101:6,15;109:13; 110:22;111:3,4,13,15, 16;113:22;114:2;</p>	<p>late (3) 40:13;192:12,14 latent (6) 225:14,21;226:6,14; 227:2,9 later (18) 6:14,18;8:3;101:16, 17;102:8;103:3;104:1; 137:19;143:22;156:7; 191:13;202:14;238:11, 19;242:13;244:12; 281:14 Laughter (10) 36:12;60:20;78:7; 81:22;87:15,20;168:15; 194:22;238:13;267:3 Laurie (6) 83:5,9;92:8,8,9;96:2 lawyer (1) 87:19 lawyers (4) 60:17,19,21;78:5 lay (3) 171:9;174:7;328:17 layers (1) 311:9 lead (5) 10:5;69:5;178:8; 329:9,15 leader (1) 175:8 leadership (1) 295:18 lead-in (1) 118:13 leads (3) 42:4;234:16,20 learn (7) 26:22;182:10;194:15; 230:19;231:11;313:12; 319:13 learned (24) 131:18;175:20;178:5; 233:1;271:19;272:2,5, 14;274:18,21;275:4,9, 14;276:17;280:11; 283:5;285:13;288:16; 291:8;292:11;294:9,20; 295:7;303:10 learning (2) 161:20;177:15 learnings (1) 31:20 least (40)</p>	<p>leave (5) 163:8;252:4,6;270:2; 329:17 leaving (1) 322:8 led (2) 44:4;69:8 left (8) 6:12;10:22;110:19; 234:5;281:16;282:15; 284:18;323:8 legal (15) 65:22;86:10,14,15; 152:15;201:12,13,16; 205:22;217:5;220:11; 226:22;231:3,5;261:15 lenient (3) 133:21,21;134:17 less (37) 17:18;35:7,15;94:9; 107:16;109:3;123:5; 131:15;132:4,18,19; 134:12;160:1;163:22; 165:2;170:19;176:14; 178:19;200:7;201:19, 20;204:19;223:10; 233:22;234:16,21;235:1, 3;237:17;252:17; 282:17;287:6;288:10; 315:3;320:15,19;324:18 lesser (1) 280:7 lesson (7) 283:6;285:13;288:16; 303:8;304:6;313:12; 320:22 lessons (15) 45:22;175:20;271:19; 272:1,5,8,14;274:21; 275:14;276:17;280:11; 283:5;291:8;294:9; 306:7 lethargy (2) 38:11;47:2 level (20) 6:17;26:5,14;27:13; 29:8;62:5;143:16; 152:21;157:6,6;181:14; 228:4,8;265:19;283:8; 284:14;285:17;293:18, 21;299:22</p>	<p>levels (14) 55:20,21;56:4;118:21; 123:17;124:8;132:9; 140:13;146:11;179:20, 21;193:9;231:20;298:20 Lewis (1) 262:7 Li (8) 197:19;198:21;202:5; 203:7;208:7,9;260:22; 261:3 liars (3) 168:13,13,14 liberty (1) 256:14 life (20) 12:6;13:19;14:10,22; 15:20,22;16:6;17:16; 18:10,13,20;19:1;32:4; 36:1,4;69:19;85:8; 147:18;148:5;264:3 lifetime (1) 47:14 light (1) 102:2 lighter (1) 223:8 liked (2) 34:7;267:8 likelihood (2) 25:4;31:21 likely (12) 16:19;49:14;51:12; 56:2;82:4;107:16,16; 194:2;201:16;228:18; 324:1;329:5 likes (3) 53:4;147:5;234:19 Lily (4) 126:16;150:1;151:15; 190:20 limitations (6) 145:2,3;147:10; 203:18;239:12;258:20 limited (5) 77:17;135:11;138:17; 140:1;203:18 limiting (2) 277:1;291:15 limits (1) 107:14 line (5) 104:9;235:4;247:5; 261:9;283:11 linear (5) 48:11;157:19;246:22; 247:6,15 linearly (1) 41:15 lines (2) 193:15,17 lingering (1) 252:10</p>	<p>link (5) 15:12,16;16:13;17:1; 33:18 linked (3) 16:18;170:3;314:15 list (6) 25:12,15;58:6;150:17; 153:17;213:18 listed (1) 272:14 listen (2) 194:10;264:10 listening (1) 182:8 lit (1) 222:12 literature (9) 10:1;29:20;39:12; 85:17;156:13;162:10; 178:18,20;302:1 Litten (7) 96:8,11,12;144:16; 149:14;187:18;191:21 little (83) 5:8;6:14;11:13,22; 14:17;21:9;35:15;37:17; 46:17;49:18;50:17;56:9; 66:20;70:10;72:2,13; 86:3;93:20;102:8,15; 103:4;105:20;108:17; 109:21;111:1,2,3; 112:22;114:6,13;117:7; 118:6;121:7;123:9; 124:1;128:7;132:17; 133:17;135:1;138:6; 140:4,5,22;143:22; 145:10;153:18;154:19; 158:12;161:5,18;165:2; 169:7;171:6;172:8; 173:9;174:6;176:15; 178:16,19;191:13; 200:7;206:21,21;207:4, 5,11,11;208:8;209:18; 211:7;218:6;228:18; 241:17,19;244:21; 264:8;265:20;282:9; 293:8;297:2,3;314:10; 315:1;325:16 live (4) 12:5;147:17;158:19; 262:8 liver (2) 144:12,17 lives (2) 15:9;149:11 lobby (1) 6:17 LoCastro (1) 135:13 located (1) 6:17 log (3) 249:9;250:2;260:9</p>

log-10 (1) 249:3	105:3,8,12;106:5;108:3,4,6;113:12;116:6;	270:5;284:1,2;286:7,8;287:16;296:21;299:2;	magnitudes (1) 223:11	262:3;268:6;286:6;287:20;288:5,22;
logarithmic (2) 247:19,20	135:13;142:9;173:6;	317:6;321:21;324:11;	main (6) 57:6;220:16;241:22;	295:20;296:12,13,14;
logic (2) 189:15;190:1	178:19;188:19,20;	325:2;326:11;329:4,5	272:19;273:1;291:21	319:19;320:3;331:7
long (21) 5:9;12:5,22;55:9;	192:19;201:21;202:5,7,	lots (6) 70:21;230:3;234:6,6;	mainly (4) 45:2;62:8;63:10;79:3	maps (1) 187:2
65:12;77:15;100:14;	207:14,18;208:4;210:5,	258:20;268:20	maintain (2) 189:4;219:17	March (1) 235:7
102:16;129:1;147:17;	17:211:11,16;214:8;	love (2) 39:19;135:6	maintained (1) 229:1	marginally (1) 250:6
150:13;173:15;175:11;	218:22;227:8;228:12;	loved (2) 8:22;39:6	maintenance (6) 113:17;130:18;218:6;	marijuana (4) 165:3,6;308:21;
177:3;187:8;192:11;	229:12;231:1;237:10,	lovely (2) 159:8;171:4	271:22;301:22;302:2	325:20
196:22;197:1;252:10;	16;241:20;253:5;	low (39) 49:10,12,13;51:11;	major (1) 175:20	mark (1) 282:3
302:14;327:15	268:20;279:22;302:11;	54:21;57:14;63:14;	majority (1) 324:15	markedly (1) 282:22
longer (15) 30:8;47:14;66:16;	308:18;309:19;311:2;	102:14,22;103:4;104:10,	makes (6) 100:21;129:18;130:8;	marker (5) 237:9,15;239:14;
102:12;114:6;148:18;	312:14;313:15;321:21	15;105:1,5,9;106:1,2,22;	182:13;270:5;299:2	240:20,21
170:4;264:1;274:6;	looking (73) 9:9;30:10;35:19;45:3;	107:2,6,10;124:12;	making (9) 73:13;85:3;128:22;	markers (3) 131:5;233:19;235:19
287:20;289:11;294:21;	48:19;49:9;62:3;67:15,	125:21;126:1;132:10,	177:12;193:16;259:12;	market (1) 32:1
302:2;309:22;321:18	16;68:11;75:1;81:10;	13;143:16;158:2;	270:14;280:1;298:9	Marsden (1) 179:2
Longest (1) 166:11	91:19;100:15;104:4;	181:12;185:5;201:8,9;	MALE (36) 8:12;91:9;180:16;	Martha (1) 192:18
longitudinal (4) 30:8;137:17,22;138:8	105:4;106:21;110:22;	207:15,22;215:12,19;	190:7,15,19;192:10;	Maryland (1) 83:10
long-term (13) 62:7;66:8;73:16;74:2;	119:1,17;122:20;128:13,	233:21;265:19;299:22	211:10,21;243:19;	mask (1) 304:17
83:18;120:10;158:20,	17;129:4;154:1;156:1;	low- (1) 103:19	259:10,21;260:6,13,14,	masked (1) 266:1
22;163:16;197:15;	157:3,14;163:13;	lower (13) 56:3;72:4,7;79:8;	17;267:7;269:6;289:16,	match (5) 100:16;103:8;119:12;
198:2;311:4;312:16	166:16;171:18;174:14;	106:10;120:16;140:5,	18;290:4;298:18;300:4;	126:21;193:7
look (95) 29:12;33:20,21;34:11;	185:8,9;193:2;197:21;	13;223:9;237:13,15;	309:12,17;310:4,10,11,	material (1) 266:18
39:12;50:21;54:3,5,19;	209:10,21;210:6;215:9;	246:20;283:1	17;311:7;312:7;313:4,	math (1) 38:13
56:9;65:4;66:7;77:5;	216:20;217:1;218:11;	lowered (1) 56:17	10;323:22;324:5;326:4	mathematicians (1) 242:22
78:21;81:3;89:18;90:19;	221:17;222:2;225:11,	lowering (1) 33:17	man (4) 160:9,19;173:10;	matter (4) 112:11;150:15;
93:11,16;100:22;104:1;	14;226:9;227:4;229:22;	low-hanging (1) 95:6	213:13	189:21;202:13
106:16,17;109:2,16;	230:7,12;231:16;243:11,	low-level (1) 172:6	manage (1) 300:1	matters (3) 112:9;170:12;269:14
111:8,13;113:22;115:9;	15;244:18;250:7,14,18;	low-risk (6) 99:7,7;101:21;102:3;	managed (1) 193:18	max (1) 8:1
121:10;128:12;136:18;	252:20;256:11;258:1,4;	124:7,9	management (2) 217:15;218:19	maximum (7) 38:14;41:13;170:1;
137:17,19;138:21;	267:19;268:16;282:6;	lucky (2) 127:1;320:8	managers (1) 166:8	199:11;221:4;227:11;
141:7;142:18;144:9;	290:5;297:8;300:17;	Lunch (9) 6:16;143:22;144:1;	mandate (2) 86:18;152:15	229:10
156:13,16;159:19;168:3,	313:22;315:18;317:3;	153:4;175:3;189:13;	manifestation (2) 42:10;44:6	may (75) 10:15;12:19;27:4;
16;175:19;180:6;185:4,	324:9	194:17,19;195:4	manual (2) 199:17;214:10	30:16;31:6;40:6;44:16;
11,15;188:10;199:6;	looks (7) 90:10;92:20;116:5,7;	Lundbeck (1) 122:11	manual-based (1) 246:9	50:3,15;59:3,5;68:17;
206:22;207:12;208:14;	279:15;309:9;317:15	lurcher (1) 173:5	many (40) 12:18;17:19;20:11;	69:5;71:21;73:21;79:9;
209:7,9;210:9,16;	loose (1) 164:7	lying (1) 160:16	33:1;40:11;52:3;63:12,	82:15,16;83:2;91:19,20;
212:21;216:10,15;	LORA (1) 83:11	Lynch (1) 207:14	20;66:4;77:8;97:12;	92:6;102:14;110:6,7,10;
217:13;219:13;225:8,	lose (2) 133:19;176:15	M	102:19;112:20;116:7;	118:5,9;123:22;132:20;
13;230:11;232:17;	lost (1) 127:5	magic (1) 269:11	135:19;142:17,18;	135:11;140:22;145:21;
235:21;241:18;243:20;	lot (68) 24:1,3;44:18;50:1,10;	magnitude (1) 223:9	143:14;149:9;151:17;	
246:16;247:6;251:5;	52:1;65:8;68:17;72:15;		184:16;202:20;210:21;	
252:13;256:20;261:5;	78:17;100:5;101:13;		257:21,21;258:3,17;	
268:12;269:4;281:20;	104:7,18;107:21;118:9;			
282:2;285:6;286:5;	119:6;120:3,8;121:18;			
290:6;291:11;292:18,	125:15;128:17;130:2;			
21;293:1,7;298:3,4;	131:22;136:19;148:21;			
299:2;300:10;306:19;	149:12,13;157:15;158:6,			
310:1;314:2;315:12,13	18;159:20;162:20,21;			
looked (70) 45:4;47:10;52:10;	163:5;164:16;165:1;			
53:3,7;54:20;56:20;	176:2,7;188:6;193:13;			
57:9;62:8,13;65:16;	201:18;202:2;203:18;			
77:10;90:20;102:1,17;	207:2;208:10;210:12;			
103:17;104:2,4,13,20;	220:20;232:22;257:12;			
	258:9;262:8;266:18;			

<p>149:6,8;157:20,20; 162:3,18;171:2,5;178:2, 17;183:4;189:1;196:21; 228:21;239:16;251:2; 255:2,13,16;257:12; 258:17;263:16;264:3; 265:22;272:6;274:16; 281:2;288:12;290:7; 292:21;293:7;303:21; 305:9;306:17;308:2; 311:20;314:4;316:12; 323:5;324:16;326:8; 327:18</p> <p>maybe (72) 30:7;34:16;40:11; 43:21;45:6;58:11;60:5; 63:2;70:6;72:14;79:15, 16,18;80:1,18;81:9,14; 87:11;98:10;111:3; 114:6;120:5;121:4,14; 123:17;134:8;135:18; 138:1,14;141:10;143:5, 7,22;145:8,11,12,20; 146:13;148:16,17; 150:3;152:2;161:18; 172:7;176:14,15; 177:13;186:7;188:9; 190:8;191:21;192:7; 208:5;211:22;212:5; 230:17;231:3,6;245:2,4; 266:15;297:21;308:13; 310:8;313:21;315:19; 319:8;320:12;324:15; 325:7,22;329:7</p> <p>McCann (31) 76:17,17;78:8;91:4; 98:3;153:10;182:8; 189:8,10;196:3,9,10; 202:5;208:7;209:2,19; 212:12;232:7;240:10; 242:4;243:4,11,14,18; 244:13;256:14;262:6; 266:19;267:2;300:21; 321:3</p> <p>McClellan (1) 51:16</p> <p>mean (31) 16:4;17:17;21:6,9; 36:15;58:3;65:21;69:16; 75:5,5;81:4;83:17; 90:14;91:16;94:6;131:8; 150:21;155:9;183:20; 186:8;216:7;219:5; 253:15;263:11;269:3; 274:7;289:18;305:5,5; 309:17;318:4</p> <p>meaning (3) 74:21,22;265:14</p> <p>meaningful (33) 7:13,17;15:9,13;16:5, 18;21:4,21;22:10,15; 23:4,9;31:22;36:8; 68:14,15;130:10;</p>	<p>156:12;162:18;163:15; 166:15;176:8;197:10; 198:1;209:22;251:3; 254:16;262:17,20; 281:1;291:18;317:19; 322:21</p> <p>meaningfulness (1) 316:18</p> <p>means (18) 17:18;19:15;21:10,19; 36:4,8;73:2;101:5; 140:11;179:15;194:18; 237:17;248:15;249:13; 250:22;261:19;286:19; 326:15</p> <p>meant (4) 24:3;26:13,19;191:11</p> <p>measure (119) 11:4,16,20;14:3,21; 15:2,11;16:4;17:6,11; 18:2,9;19:6,21:11; 24:16;25:9,10;27:16; 29:22;35:5,13,22;36:18; 37:5,9;38:6;47:5,21; 53:2,6,10;54:9;55:22; 58:11;62:2;64:22;65:13; 68:14;70:16,17;71:7; 72:21;73:3,8;75:14; 76:12;79:14;81:7;83:18, 19;84:1,2;89:19;90:3; 92:17,17;93:19,21;94:8, 8,19;95:2,12,13;108:19; 109:7;113:6,12;117:1; 118:1;122:13;129:19; 130:9;135:6;137:12,14; 140:7;143:1;144:13; 145:7;146:18;147:22; 160:5;161:8;177:1; 186:14;189:17,19; 191:4;213:13;214:22; 216:15;221:15;225:21; 226:14;227:7;230:1; 234:5;240:15;248:6; 255:13;258:17;265:17; 267:20;273:7,8;280:13; 285:5;301:20;307:19; 308:14;318:13,14;323:5, 6,10;327:2,22;330:14</p> <p>measured (11) 12:15;18:8;38:8,9; 43:16;46:5;48:21;49:8; 75:3;110:3;255:14</p> <p>measurement (11) 18:5;20:8,9,21;21:2; 23:16;30:4,9;31:18; 33:16;173:21</p> <p>Measures (108) 5:6;7:10,13,16;13:5,5; 15:18;16:1;27:18;31:6; 34:15,15;35:4,8,12,16, 21;37:12,21;39:2;47:12; 48:8,16;52:12;57:21; 64:1;69:4;83:13,13,19;</p>	<p>90:19;92:3,4;108:14; 109:5,9,17,22;112:21, 22;113:1,15;114:17,22; 126:7,8;131:11,14; 136:20;138:13;139:4; 140:2;142:17;146:9,16; 147:20,22;148:6,7; 152:5,5;158:5,11;161:2; 164:16;171:14;173:2,17, 18;199:7;200:22; 202:16,20;203:1,3,8,19; 212:4;213:5,11;214:16; 216:10;221:12;224:1,1; 227:10;229:7,18;230:4, 6;232:4;245:8;246:19; 248:21;250:10;255:16; 259:1;263:2;265:3,21; 267:19;285:1;306:6,8, 10,12;308:2;330:12</p> <p>measuring (19) 15:8,19;16:2;18:17; 19:22;20:2;21:10;22:6; 29:15,22;36:3;44:10; 48:17;51:7;145:6,21; 152:14;199:5,5</p> <p>mechanisms (1) 89:10</p> <p>med (1) 217:16</p> <p>median (1) 236:8</p> <p>medical (9) 60:12;69:22;115:15; 154:7;175:8;261:18,20; 263:7,18</p> <p>medically (1) 41:17</p> <p>medication (37) 40:1,3;49:5;51:4; 54:12;56:11;57:22;59:6; 80:16,21;81:9;88:4,8; 90:10;97:1;131:8; 140:17;147:16;184:1; 197:22;206:12;213:8; 220:15,16;222:2;224:7; 265:15;266:6;273:5,8, 16,20;283:3;300:11,21; 315:17;325:19</p> <p>medications (20) 54:14;56:18;58:8; 59:4;61:10;73:17,18; 90:14;97:4;100:8;153:9; 182:18;204:2;214:11; 233:8;246:4;265:10,22; 266:10;325:21</p> <p>medicine (3) 54:16;56:14;74:13</p> <p>medium (3) 57:15;125:21;132:10</p> <p>meds (2) 182:20;289:20</p> <p>meet (8) 20:17;27:13;43:13;</p>	<p>81:1;99:8;220:8;284:12; 288:2</p> <p>meeting (32) 5:5,7,12,20;6:7;7:7,8, 20;8:11;9:9,22;10:6,13; 76:14,21;77:16;82:10; 97:16;124:16;157:12; 182:15,15;232:2; 262:13;266:12;270:22; 271:18;282:7;287:17; 301:8;327:3;331:9</p> <p>meetings (7) 6:10;9:13;98:2,5; 142:7,10;182:16</p> <p>meets (1) 316:16</p> <p>Megan (2) 97:3,7</p> <p>Mehmet (1) 43:4</p> <p>memories (1) 40:10</p> <p>memory (1) 209:6</p> <p>men (2) 53:19;99:5</p> <p>mention (10) 11:7;77:1;96:18;97:2, 9;103:7;125:13;252:8; 298:6;301:16</p> <p>mentioned (18) 8:10;33:19;48:10; 64:15;198:10;215:10; 224:17;230:6;247:17; 265:2;272:17,21; 273:19;278:18;287:10; 307:1;312:8;331:4</p> <p>mentor (1) 38:21</p> <p>menu (1) 92:2</p> <p>merits (1) 199:4</p> <p>mess (1) 41:2</p> <p>message (2) 197:6,11</p> <p>met (11) 7:1;43:6;142:9;217:8; 224:11;273:21;277:11, 20,21;278:17;286:11</p> <p>meta-analyses (2) 142:15;154:10</p> <p>metabolite (1) 182:1</p> <p>metabolites (2) 144:19,22</p> <p>meta-questions (1) 95:18</p> <p>meth (1) 321:22</p> <p>methadone (8) 64:17,18;200:10,14;</p>	<p>218:5;219:17;296:20,21</p> <p>methamphetamine (2) 72:7;265:12</p> <p>method (2) 215:3;311:13</p> <p>methodical (1) 34:7</p> <p>methodologies (1) 9:3</p> <p>methodology (3) 67:14;96:20,21</p> <p>methods (7) 19:12;199:4;202:4; 311:5;312:13;313:1; 316:2</p> <p>mic (2) 186:4;233:5</p> <p>mic] (4) 174:17;190:15;209:3; 238:9</p> <p>microphone (3) 65:3,6;314:7</p> <p>microphone] (1) 237:7</p> <p>microphones (2) 6:3;88:10</p> <p>middle (2) 282:16;317:17</p> <p>might (71) 10:2;13:12;15:5,15; 16:20;17:11,13,19; 18:19,21;20:8;23:8,17; 25:14;27:7,8,13,19;42:8; 54:14;62:1;69:19;74:14; 76:20,21;79:21;91:15; 93:8;103:7;110:8;114:7; 118:10;121:3;124:8; 126:13;128:10;130:12; 132:2;134:9,10;136:20; 139:4;149:2,8,16; 176:21;185:12;188:3; 198:1;210:7;217:4; 226:21;227:1,5;231:14; 244:1;256:19;257:20; 266:7,14;267:10; 283:18;285:10;304:20; 306:13,15,22;317:11; 319:11;329:22,22</p> <p>mild (1) 186:1</p> <p>Miller (2) 100:14;126:18</p> <p>milligrams (6) 57:5;276:3,7;277:7; 287:11;299:13</p> <p>millimeters (1) 277:17</p> <p>mind (6) 14:10;76:20;189:10; 192:5;256:19;330:18</p> <p>mind-set (1) 314:11</p> <p>mined (1)</p>
--	--	--	---	---

258:21 minimal (1) 107:15 minimize (4) 141:10;270:10;311:5, 17 mining (1) 244:20 minor (2) 235:4;292:7 minorities (1) 219:5 minority (1) 180:19 minute (3) 164:20;165:12;205:15 minutes (11) 5:9;37:17;43:16;60:6; 67:5;96:1;143:5;144:5; 175:2;232:9;266:15 miserable (1) 47:22 misleading (1) 22:1 misrepresentation (1) 164:1 missed (6) 63:3;166:20;278:21; 279:10;290:1,2 missing (48) 53:1;158:3,5;164:5,6, 17,20;165:11;166:19,19; 170:14;176:10,17; 207:16;208:10;229:21; 253:9,12;262:17;267:11, 17,18;268:1,2,5,11,15; 269:4,11;283:15;286:18, 18;299:1;308:10,17,19; 309:2,3,11;310:3,19; 311:4,5,17;319:18,21; 320:13,16 misuse (1) 9:10 mix (1) 264:14 mixture (1) 187:21 mL (1) 182:5 modafinil (3) 72:4,6,9 mode (1) 9:11 model (5) 37:1;54:7;71:13; 144:7;226:9 modeled (2) 39:1,7 modelings (1) 157:19 models (3) 75:16;171:5;225:15 moderate (3)	124:12;186:2;257:10 moderately (1) 203:2 moderating (1) 196:4 moderator (8) 8:7;79:14,18;80:3,11; 82:16;196:9;232:7 modifications (2) 30:14;31:15 modified (1) 61:12 modify (2) 135:2;263:22 MOELLER (2) 210:8,9 moment (3) 68:11;90:5;216:13 Monday (1) 312:21 money (7) 125:3,7;240:22;243:1; 244:7,12;324:3 monitor (1) 154:11 month (15) 53:21;103:21;111:4, 16;112:17;114:2;123:5; 127:16;179:6,7;206:21; 219:6;221:20;236:19,20 monthly (1) 312:20 months (51) 101:7,16,17;102:8; 103:7,17;104:1,1,12,13; 109:14,16;110:8,20,22; 111:3,14,15;112:13,14, 16;113:22;114:7; 116:12;117:2;149:15, 16;167:8;171:16; 199:10,20;200:20; 203:3;214:20;222:22; 236:5,7,15,17,20; 237:20;238:5,11,19; 243:7;274:10,15; 275:22;276:12,14; 290:10 MONTOYA (21) 63:2,6,6;185:21; 186:5,16;197:19;244:15, 16,17;257:15;258:16; 259:4,18;260:4,8,16,20; 261:1,5,12 Monty (2) 174:18;232:14 mood (3) 38:10;47:2;200:4 more (182) 14:17;15:15;17:13,15, 17,19;18:17,22;26:22; 29:5,9;30:20;40:6,7; 41:21;42:1,5,9;43:8; 44:18;46:17;47:8,17;	49:13;50:16;51:3,12; 55:14;56:2;62:13;66:12; 68:6;69:18;71:3;75:10, 11;76:2,11;86:3;87:4; 94:3;96:16;99:3,4; 101:6,13;104:7,18; 105:17;106:14;108:17; 109:21;111:1,16,20; 112:2;113:1;114:13,17, 19;117:14;118:1,2; 119:8;121:7,19;123:9; 126:9;128:1;129:21; 132:8;133:2,20,21; 134:1,17;135:22;138:6, 8;141:19;144:18,21; 145:13;146:2,13;147:6; 149:8,13,19;150:4; 152:2,4;154:21;155:1, 16;156:3;163:3;166:11, 12;169:16;170:10,18; 171:2,6;173:3,7;174:14; 177:2,13;178:4;181:1,2, 4;200:19,21;201:15,16; 206:22;207:12;208:4; 216:22;225:4,13; 226:22;227:1;228:1,21, 22;229:14;231:16; 242:16,17,17;248:11; 250:1;251:21;252:15; 257:1,2,5;261:19,20; 263:1,19,20;264:7; 265:7;267:10;270:11; 271:2;274:4;277:14,16; 278:4,4;280:3;282:4,9, 11;284:17;288:8,13; 292:2,7;294:2,5;296:13; 299:5;303:15;308:13; 311:16;313:8;315:1,19; 318:12;323:22;324:1, 18;329:12,12,13;330:7 morning (10) 6:14;7:4;8:3;11:11; 37:3;95:22;135:1;195:2; 247:17;330:13 MOST (42) 9:1;12:12;13:15,18; 38:16;41:5;48:18;54:3; 56:20;84:21;95:14; 99:20;125:19;128:15; 130:2,6;132:11;135:16; 138:18;146:4;151:20; 161:9;163:21;173:16; 178:7;180:3,19;182:9; 188:8;200:2;201:12; 207:22;214:20;217:4; 242:21;247:8;249:11; 263:15;270:2;285:9; 296:14;312:9 mostly (3) 203:14;255:11;312:8 motivation (1) 13:10 mouth (3)	120:18;140:4;297:21 mouthful (1) 98:19 move (15) 9:18;17:21;34:13; 60:12;88:2,10;119:22; 148:18;151:1;152:7; 153:3;154:13;231:15; 262:4;263:1 moved (1) 209:17 movement (1) 186:20 moves (1) 86:2 moving (5) 67:6;154:6;156:18; 254:12;313:8 MRI (1) 234:4 much (64) 11:12;45:6;49:13; 51:12;58:4,21;66:1; 74:19;78:17;79:8;83:2; 96:13;102:1;103:9; 104:15;106:10;107:2,6, 15;112:9;121:3;127:2; 142:20;144:14;145:4,4, 5,9,16;146:17;147:13; 157:4;158:14;175:18; 183:16;186:20;200:8; 202:2;203:11;223:19, 21;233:12;237:3;240:8; 242:7;244:13;255:4; 257:3,5;274:4;279:14; 287:20;288:2;294:6; 296:9,11;297:3;303:11; 314:22;319:4,6;320:15; 321:12;327:20 multicenter (1) 51:20 multiple (10) 18:19;27:18;32:22; 36:6;69:21;253:11,14; 268:11;269:3;311:13 multiplicity (1) 135:20 multisite (2) 108:5;112:5 must (1) 301:6 mutually (1) 38:14 myelofibrosis (2) 28:1,5 myriad (1) 139:22 myself (4) 5:3;41:11;90:7;177:20	179:14 naivete (2) 189:14;194:2 nalmafene (3) 122:11,18;123:5 naloxone (1) 91:16 naltrexone (16) 101:8;110:17;111:6, 11;116:19;117:3; 198:12;204:5,9,16,18, 19;208:3;296:20; 308:15,16 name (2) 34:20;126:14 nanograms (1) 182:5 NAS (1) 193:12 nasty (1) 314:18 national (4) 105:15;206:2;208:15; 311:1 natural (1) 31:10 NCIG (1) 119:12 NDA (1) 81:11 near (5) 281:8;282:14,21; 293:1;314:7 neat (1) 121:20 necessarily (20) 11:18;36:14;50:15; 63:16;65:1;73:2;79:17; 88:6;160:22;169:19; 192:4;272:11;289:12; 291:6;295:2,4;297:13; 323:12,13;327:9 necessary (4) 19:9;88:14;176:19; 311:9 need (60) 6:15;12:22;15:12,15; 16:8;17:6,9;18:6,10; 21:17;22:18;23:11;27:2, 6,13;28:21;29:13;30:16; 34:12;35:7;36:2;61:18; 77:17;78:3;80:19;83:21; 114:20;143:8;145:17; 154:3,5,9,11;155:6,13; 183:14;184:3,6,14; 190:13;197:2,8;209:6; 233:12,17;247:6; 274:16;275:6;287:16; 288:1;290:7;292:14; 295:9;299:11;302:21; 305:4;307:6;314:7; 319:16;323:16 needed (10)
--	---	--	--	---

<p>13:16;20:16;26:5,14; 27:19;40:6;277:20,21; 288:14,15 needing (1) 305:2 needs (21) 9:21;10:3,17;30:13; 32:12;68:20;79:22; 105:20;138:6;194:12; 196:22;197:1;258:21; 273:5,9,18,20;276:10; 277:11;287:18;316:15 negative (28) 53:1;54:20;93:16; 112:10;163:19;165:16; 205:10;212:1;222:6; 229:13;242:11,14,16; 243:5;246:7;257:16; 279:8,10,21;280:3,6; 282:4;283:13;293:18, 21;294:3,5;310:15 negatively (2) 39:21;268:22 negatives (1) 108:11 negotiate (1) 320:10 Neither (2) 289:5;304:5 NESARC (7) 106:5;119:15,15; 128:18;137:5,12;193:19 network (1) 119:13 Networks (2) 8:21;119:21 neurobiologic (1) 42:11 new (15) 30:15,18;118:14; 119:15;129:2,5;144:19; 154:14;164:3;232:19; 239:6,16;240:12; 250:19;271:20 newly (2) 48:2,3 news (1) 253:20 next (19) 5:8;6:6;11:2;37:17; 61:7;70:22;76:21,22; 85:10;118:13;129:6; 131:7;212:12;217:12; 239:21;242:15;244:7; 288:16;328:18 next-door (1) 271:5 NHLBI (1) 142:10 NIAAA (11) 79:12;96:15;97:2; 98:1;106:6;129:15; 153:1;179:13;275:2;</p>	<p>330:16,18 nice (21) 49:15;57:19;101:14; 137:12;147:8;151:19; 158:9;159:15;162:15; 166:13;167:19;170:3; 171:1,3;173:1;176:4; 179:20;182:17;214:1; 216:5;255:7 nicely (3) 67:11;68:10;69:8 nicotine (1) 205:9 NIDA (20) 59:10,12,20;63:6; 76:17;98:3;153:9; 196:11;198:6,14; 199:17;212:19;233:6; 19;240:8;245:20;265:6; 328:10,11;330:21 NIDA's (1) 244:17 night (1) 158:2 NIH (2) 9:4;239:4 Ninety (1) 133:15 nobody (2) 116:14;154:22 Node (2) 198:9,9 non- (1) 278:11 non-abstinence (3) 112:11;183:2,21 non-compliance (4) 278:14;289:3,19,22 non-compliant (2) 278:21;289:20 non-drinking (10) 118:22;126:6;129:21; 131:22;134:18,20,22; 135:5,6,15 non-drug (1) 226:3 none (4) 53:1;58:8;135:21; 238:6 non-medication (1) 264:12 non-significant (1) 223:7 non-specific (1) 47:20 non-starters (1) 269:22 non-substance (1) 143:10 noon (1) 6:19 nor (2) 25:16;289:6</p>	<p>normal (1) 124:1 normalize (1) 181:18 normative (1) 156:18 Northwestern (1) 328:17 nota (1) 69:21 note (6) 13:7;26:7;29:3; 194:16;226:18;271:4 noted (1) 67:19 notes (1) 163:5 notice (2) 117:6;140:9 noticed (1) 112:12 notion (2) 157:7;232:2 novel (1) 232:17 nuances (2) 31:17;298:16 number (42) 55:3;75:8;85:18; 98:22;99:1;108:16; 109:10;116:1,9;117:17; 121:22;122:8;127:21; 130:22;136:20;139:6; 146:19,20;165:19; 168:7;178:13;196:13; 198:8,16,22;202:6,7; 203:19;215:13;221:10; 228:19;234:15;257:8, 15;260:10;284:10,19; 285:6;292:4,22;303:13; 317:21 numbers (7) 125:16;138:5,14; 142:8;154:1;260:5; 269:21 nurse (1) 85:14 nuts (2) 129:11;330:6</p>	<p>13:19 observation (3) 13:17;311:11,11 observe (2) 14:1;177:4 observed (5) 247:13,14,22;249:18; 254:9 observer (4) 13:21;246:13;284:22; 298:6 observers (1) 13:6 observes (1) 84:8 obsess (1) 270:9 obsessed (1) 90:1 obsessive (1) 168:17 obtain (1) 264:19 obtained (1) 277:22 obtaining (1) 176:11 obviate (1) 319:16 obvious (2) 128:8;131:9 obviously (1) 158:21 occasion (1) 200:1 occurred (3) 149:20;303:22;313:5 occurring (4) 42:12;140:4,5,12 odd (1) 161:16 off (16) 107:20;124:10;125:7; 130:5;131:21;139:20; 174:17;190:15;209:3,3; 237:6;238:9;266:20; 306:2;311:3,18 official (2) 11:19;329:20 often (19) 13:1;18:22;21:7; 22:11;31:13;34:15; 40:21;42:1;135:2; 150:11;152:10;160:19; 162:9;165:15;270:21; 273:21;302:14;307:10; 317:4 old (3) 39:3;53:15;98:15 once (8) 59:8;73:3;161:18; 231:5;274:1;286:15; 299:16;305:11</p>	<p>one (198) 8:22;12:12;21:14; 23:8;34:1,2;38:7;45:4; 47:7,7,8;48:8,22;50:14; 53:4;54:15;56:14,18; 61:6,16,20;63:21;64:17; 65:10;66:1,7,11;67:19; 73:15;75:6;76:9;77:12, 22;79:2;82:10;94:3; 98:9,11,14;99:15;100:1; 102:17;105:11,13,16; 106:6;109:2,9;110:18; 113:6,13;115:5;117:20; 118:11,18;119:14; 120:18;121:3,13; 122:19;124:5;125:1,18; 126:11,12;133:8;134:1; 136:7,7;137:21;138:2, 18;140:3,11;141:7,10; 144:11;145:7,9;146:5; 148:10;157:12;161:4, 11;163:19;165:16; 166:1,13,17,19,21; 169:20;172:21;174:4; 175:20;177:12,13; 178:14;181:7;182:14, 17;184:11;186:11; 188:6,14;198:6,9; 201:12;202:13,18; 203:17;209:13;213:20; 214:5,17;216:3,9;218:1; 222:12,18;224:3,16,20; 225:2,7;227:4,9;230:15; 231:15;232:8;234:15; 235:8;238:1,4,5;239:9, 10;240:14;242:4,13; 243:8;245:6;246:5; 247:6,9;248:7;249:9; 252:3,21;253:15;256:4; 257:11;260:6;261:2,17; 263:13;264:6,7,9;265:1, 12;266:3;267:12,21; 269:4,16;270:21; 277:20;280:21;283:17; 288:15;293:13;295:9; 296:8;297:7;298:6; 299:8;300:7;301:16; 306:12,17,22;307:1,22; 308:8;309:15;310:5; 311:15;313:4,6,6,11; 319:13,17;320:13; 321:9;325:13;328:11 one-quarter (1) 261:4 ones (20) 51:2;58:6;76:4;108:6; 114:19;128:14;135:10; 141:7;143:13;182:9; 191:9;207:20;217:3; 223:19;224:12,13,22; 229:9;267:10;285:20 one's (3) 41:18;140:5;166:17</p>
		O		
		<p>objections (1) 93:7 objective (8) 25:22;35:4,12,13; 36:3;76:12;94:10; 234:14 objectives (3) 25:20;234:15;326:6 O'Brien (2) 51:15;98:4 observable (1)</p>		

<p>one-third (3) 51:1,2;55:17</p> <p>one-year (2) 160:15;161:15</p> <p>ongoing (4) 51:22;196:6;235:10; 304:2</p> <p>only (53) 8:4;10:20;52:10; 56:14,18;57:11,15; 71:20;74:3;92:1;102:22; 108:20;124:18;130:18; 136:14;140:2;141:4; 143:6,8;151:14;160:2; 163:13;164:13,14; 194:14;205:6;207:13; 214:6,18,18;218:15; 233:16;236:16,17; 247:9;249:20;254:13, 14;257:22;269:16; 270:15;272:8,9;275:17; 276:16;277:3,20; 287:18;297:19;299:20; 302:8;306:14;309:2</p> <p>open (11) 51:5,5;72:14;177:11; 197:7;256:4;296:1,6; 297:7;300:16;328:2</p> <p>open-label (1) 277:1</p> <p>operant (1) 262:16</p> <p>operationalize (1) 176:3</p> <p>operationalized (2) 268:9;269:4</p> <p>opiate (4) 322:14;324:12,19; 326:12</p> <p>opiates (3) 321:13;324:14;325:19</p> <p>opinion (2) 185:22;328:15</p> <p>opioid (20) 60:16;207:4;271:22; 277:14;278:9;279:8; 280:11,16;284:3,17; 287:4;288:5;297:2,9; 306:21;308:19;309:7; 313:13;327:19,20</p> <p>opioid-dependent (1) 276:22</p> <p>opioid-negative (8) 279:6,15,18;281:21; 282:9;283:19;290:16; 293:5</p> <p>opioid-positive (1) 286:20</p> <p>opioids (8) 274:11;279:22;282:5; 285:7;287:21;289:8; 302:16,20</p> <p>Opportunities (2)</p>	<p>8:21;257:21</p> <p>opportunity (8) 68:17;144:8;210:1; 256:3,8;271:18;304:4,13</p> <p>opposed (6) 95:2;183:14;191:2; 225:10;259:16;310:6</p> <p>opposite (1) 276:13</p> <p>optimal (2) 20:14;117:10</p> <p>optimistic (1) 271:3</p> <p>optimize (1) 9:2</p> <p>oral (3) 120:18;204:16,18</p> <p>oranges (1) 270:20</p> <p>order (7) 12:8;13:1;20:17; 94:17;192:6;285:22; 310:13</p> <p>ordered (1) 6:20</p> <p>orderly (1) 23:18</p> <p>organizations (2) 96:19;97:14</p> <p>organizes (1) 24:3</p> <p>oriented (1) 199:13</p> <p>orienting (1) 7:6</p> <p>original (2) 189:3;293:15</p> <p>originally (1) 209:15</p> <p>originated (1) 69:13</p> <p>others (10) 94:12;120:6;125:11; 162:19;197:7;206:16; 209:19;211:20;270:12; 293:14</p> <p>otherwise (2) 194:13;329:17</p> <p>ours (3) 268:20;269:5;289:14</p> <p>out (119) 6:19;8:9,17;9:11,15; 22:7;34:8;42:2,15; 44:13;46:15;49:19;52:5; 54:7,21;57:2;61:9; 69:13,21;70:3,14;74:5; 75:18;76:8;77:6,9; 78:20;80:13;87:5,6; 88:15;89:18;92:15,16; 93:14;94:13;98:7,9,10, 11;100:3;103:6;104:8; 18;108:2;112:16;114:6; 138:5;146:11;150:7,12;</p>	<p>153:15;165:17;167:18, 19,22;168:1;172:14; 174:7;176:2;178:16; 180:14;183:11;187:2,9, 13;188:11;192:16; 193:1;196:15;197:12,17, 22;198:3;200:13; 208:11;211:3;214:4,16; 215:12;218:16;219:7; 221:2;223:14;225:18; 229:22;230:9;233:3; 234:13;235:18;237:3; 259:14,15,19;260:2,18; 263:14;265:2;268:8,22; 269:5,7,21;270:4,22; 276:11;300:8;303:12, 21;305:19;317:14; 320:6;321:9;322:3,6,11, 17;324:8;328:5</p> <p>Order (188) 5:6;7:10,13,16;9:22; 11:4,16;12:10,16;13:2,3, 4,5,8,15,17,21;14:3,11; 19:16,19;20:4,7,13,15; 22:10;23:15;24:7,16,20; 25:1,5;26:4,6,7,8,15; 28:6,18,22;29:2,30;21; 31:2,14,18;32:6,20;33:5, 8;34:15;35:5;37:13; 41:21;45:3,10;48:20,21; 50:6;52:12,17;53:10; 54:4;55:22;57:21;58:11, 14;62:2,6,12;64:1; 69:3;70:16,17;72:21; 73:6;76:7;77:21;79:13, 18;80:5,11;85:11;86:3; 88:4;89:19;90:3,7,11,19; 92:3,4,17;93:21;94:14, 19;96:9;108:14,19; 109:4,6;110:2;113:6; 114:17;117:1;118:19; 120:2;126:6;129:19; 130:9,11,20;131:11,14; 132:1;134:7,12;136:17, 19;137:3;138:12; 139:20;140:2,7,17,21, 22;141:3;142:17; 146:16;147:21;148:7, 13;159:11;160:10; 165:4;173:21;186:13; 188:22;189:19;191:18; 194:4;199:1;200:11,11; 201:14;203:17,19; 211:21,22;212:2,3; 213:4;216:19,19;217:1, 9,10;222:11,13,19; 223:4;225:3;228:11; 243:21;244:2;246:11; 248:11;250:3;263:12,18, 19;265:2;267:18,20,22; 270:21;297:17;298:15; 301:20;306:5,8;316:12; 317:1,12;318:8;323:10;</p>	<p>327:2;328:13;330:11</p> <p>outcomes (94) 10:2;14:4,7;17:4; 20:11;30:22;35:17; 43:14;45:8;52:20;54:3, 10;64:14;72:1,9;82:10; 89:7;93:12;118:22; 125:18;128:21;129:3,20, 21;130:1,3;131:1,22; 132:4,19;134:17,18,19, 20,22;135:5,7,15,15; 136:10,12,13;137:18; 138:10,21;139:1,1,3; 141:4;148:17;151:1,20; 152:14,15;154:16; 158:21;161:15;162:7; 163:17;186:6,12;189:2; 199:5;201:2,2,3,6,22; 202:2,11,11,16;204:1; 211:13,14;212:7,8; 219:11,13;221:8; 225:10;244:19;256:12; 262:19;264:18;267:9, 14;285:2;297:15;298:1, 5;308:13;328:3;329:7</p> <p>outlier (1) 219:18</p> <p>outline (1) 69:7</p> <p>outpatient (12) 37:13,15;39:17;49:3; 58:14;79:10;151:5; 206:8,15,16,17;218:13</p> <p>outpatients (1) 151:4</p> <p>outside (5) 7:5;32:16;59:12; 210:19;226:11</p> <p>over (67) 5:8;6:6,12;14:5;21:8; 38:22;41:16;43:16; 48:11;58:3,9;62:12,19; 67:16;96:3;105:3;106:6; 111:20;112:16;113:2, 17;115:21;117:7;129:5; 145:19;146:1;151:16; 153:4;171:5,19;172:2; 196:8;197:12;206:21; 207:11;209:17;210:8; 213:1,16,22;225:16; 226:8;228:20;230:11; 235:6;236:6,19;239:21; 241:10;242:13;243:9,10, 12;263:5,8;265:13; 274:19;278:5;279:6; 283:12;289:12;290:13; 291:4,12;295:2;298:17; 312:17</p> <p>overall (10) 56:3;170:1;199:7,19; 215:18;227:21;258:15; 284:1;290:20;292:9</p> <p>overlap (3)</p>	<p>54:8;157:15;272:16</p> <p>overlaps (1) 164:10</p> <p>oversee (2) 97:4;328:22</p> <p>overview (6) 96:8;208:8;217:12; 218:21;272:13;280:9</p> <p>owe (1) 232:22</p> <p>own (2) 11:18;69:19</p> <hr/> <p style="text-align: center;">P</p> <hr/> <p>package (2) 115:17;118:6</p> <p>page (1) 178:4</p> <p>paid (1) 24:18</p> <p>pain (8) 9:7;115:15,17;303:14; 311:20;318:2,6;325:19</p> <p>pair (3) 11:8;34:4;144:3</p> <p>pancreas (1) 122:6</p> <p>panel (2) 9:12;178:10</p> <p>paper (15) 9:10;10:1;71:15; 78:19;105:19;162:6; 173:13;189:1;190:5; 198:21;204:21;233:2; 238:1;268:8;319:8</p> <p>papers (5) 69:21;79:4;133:9; 175:17;234:13</p> <p>paradigm (1) 305:13</p> <p>paradoxical (2) 72:3,13</p> <p>parallel (2) 91:14;178:2</p> <p>parameters (3) 67:14;202:14;295:13</p> <p>paranoia (1) 38:12</p> <p>paranoid (1) 40:21</p> <p>parent (1) 199:9</p> <p>part (33) 25:13;42:12,14;44:1; 46:22;57:18;64:15;66:2; 76:19;79:7;86:3;92:11; 96:15;118:13;131:19; 150:1;186:10;192:15; 209:20;234:4;236:15; 240:21;248:4;265:8; 271:18;281:2;285:11; 304:21;306:4;317:4;</p>
---	--	--	---	---

<p>326:22;327:7;328:11 partially (1) 56:5 participant (3) 98:3;242:10;249:2 participants (6) 218:8,17;219:2;234:4; 236:14;242:21 participate (1) 325:17 participated (3) 51:6;199:15;295:21 participating (1) 188:14 participation (5) 13:11;31:8;88:16; 314:14,16 particular (17) 26:15;42:3;50:5;59:4; 75:1;82:17;163:17; 193:11;279:9;301:18; 309:12;310:5,12;317:2; 319:17;327:8;330:14 particularly (13) 73:1;82:6;104:20; 105:4;108:6,15;112:13; 144:21;222:7;281:9; 282:17;294:18;304:5 partners (1) 75:22 pass (2) 79:1;206:2 passionate (1) 270:17 past (11) 25:4;47:14;51:22; 56:1;117:20;185:13; 196:7;197:12;262:18; 271:2;325:15 path (2) 232:1;329:21 pathway (4) 16:21;23:19;32:16; 33:1 pathways (1) 32:5 patient (59) 13:14;14:4,7,15;17:3, 4,7;20:6,11,15;21:12; 22:16;23:2;25:19;28:6; 29:19;30:22;33:2,35:16; 36:4,16,19;50:3;69:3; 79:18;85:6;90:13;91:21; 92:20;130:12;148:4; 150:4;151:9;163:4; 168:9;169:6,16;208:13, 16;226:1;238:9,15,15, 16,16,20;239:9;243:2; 250:22;251:2;263:7; 274:1;283:16;286:2,3; 316:13;325:22;329:8,11 Patient-Focused (1) 23:15</p>	<p>patiently (1) 321:2 patient-reported (2) 216:22;328:12 patients (171) 12:4,12;13:7;14:9,22; 15:3,9,21;16:10;17:8; 18:18;22:2;23:5,8,10; 28:12;31:7;32:1,3; 35:20;36:1,8;37:14,15; 39:15,20;40:2,6,15; 41:13,21;42:4,17,21; 43:6,11,12,17,21;44:1; 47:16;48:1,3,5,9,12,14; 49:8,10,13;50:8,11,16; 51:1,6;52:9,11;53:16; 54:14,21;55:1,14,16; 56:7;57:5,11,16;58:19; 59:19;65:19;66:14; 67:22;71:17;74:9;75:10; 76:2;78:15;79:5;80:15, 17;82:3;84:19;85:7,15, 18;86:5;87:5,12;91:6, 18;94:2,4;101:15; 103:15;107:13;122:1; 123:1;124:21;126:20; 150:9;151:3;160:11; 163:7;164:1;176:19; 183:4;184:21;199:18; 200:19;204:1;205:3,5; 207:18;210:12,18; 217:17,20;218:5;248:17, 19;249:14;261:20; 264:2;273:21;274:8,9, 16,19;276:22;277:12; 278:1,8,10;279:17,20; 280:1,2;282:1,8,10,13, 20,21;283:12;284:10; 285:7,8;286:5,10,15,19; 287:10,19;288:6;289:8, 11;290:7,12;291:3; 292:5,22;293:3;294:4; 295:2,3;309:15;313:16; 314:14;319:22;320:13; 328:18 patient's (5) 16:5;28:2,10;170:17; 200:1 pattern (7) 50:19;110:6,10; 228:13,14;291:1;324:20 patterns (12) 65:16;66:4;118:21; 123:18;128:21;172:4; 176:22;177:19,22; 275:7;280:22;306:15 Paul (1) 198:16 pay (14) 117:14;163:1;235:20, 20;236:21;240:22; 242:12,14,15,16;244:10; 323:21,21,22</p>	<p>payer (1) 197:14 payers (4) 124:22;154:9;159:5; 194:12 payment (1) 242:19 payments (2) 208:13,16 peak (1) 117:7 peculiar (1) 241:16 peer-reviewed (1) 10:1 penalize (3) 305:1,3,5 Penn (4) 38:20;39:16;54:19; 63:19 Pennsylvania (4) 49:2,6;51:14;326:11 people (162) 5:19;6:5;7:22;8:2,2,4, 15;9:4,4;15:19;35:15; 38:15;40:12;41:8;55:7; 59:14;61:16,19;62:4; 63:12,15,16;64:8;74:2, 16;86:11,12,13;87:1; 88:10;89:8;94:11;95:5, 19;107:21;115:2,7; 125:11;126:3;127:9; 132:1,12;134:7;142:10, 12;144:6;147:17;149:2, 6,8,9,12;151:6;155:8; 159:10;160:6;161:9,12, 17,22;162:22;163:21; 167:2,11,18,22,22; 171:3,10,15;172:7,18; 176:8;179:5,7;180:12; 183:14;185:2;187:6,19; 188:5,8,15;192:12; 202:2;203:15;205:6,7; 206:9;208:11;209:12; 220:2,5,9;221:9;222:12; 223:3;226:11,21;227:5; 228:9;229:22;230:19, 19;231:2,11;235:15,19; 236:5,6,6,16,16;237:8, 19;239:19,20;242:12; 256:7,22;257:1,4,4,6,9; 259:14,19;260:2,15,18, 18;266:1;268:21; 269:19;270:2,4;275:2; 300:13;302:1,12;309:21, 22;312:2,4;317:22; 318:5,6,7,12;320:14; 322:5,8,10,12,16; 323:19;324:8;325:4,5,8; 327:21;328:10 people's (2) 181:11,15 per (26)</p>	<p>99:4,5;109:11,11; 113:9,10;121:5,6,9,21; 122:1,3,8,22;134:2,3,7,8, 11;140:19;182:5;208:7; 233:22;276:7;277:7; 287:11 perceived (1) 275:11 percent (139) 53:3;63:10;74:9; 98:15,18;99:10;107:22; 109:10,12,17,19;110:16; 111:8,21;112:1;113:5, 10,16,20;114:10,12; 117:3;130:18;132:18; 133:4,4,4,11,13,16,17, 18;136:21;154:20; 155:7,10;160:12,14,15; 161:9;163:19;165:22; 166:2,3;167:3,17;168:4, 6,10,11,21;169:8,11,19, 19;171:9,10,10,11; 173:9;176:4;188:9; 193:9;200:6,19;207:21; 212:1;215:13;216:2; 219:8,14,19,22;221:6, 13,13,21,21;222:5; 224:21;229:10,12,13; 233:22;235:1,3,4; 237:18,18;238:11,19; 245:12;250:22;252:11, 15,18,19,19,20,21,21; 254:20;255:9,20;257:1, 2,5,14;258:6,12,14; 279:20,21;280:1,2,4,5,6; 282:4,8,8,10,10;290:15; 293:3;294:1,3,4,5; 312:17;315:4;317:3,18, 22;318:2,3,12,13,14 percentage (8) 50:22;111:9;143:6; 149:9;220:5;227:11,12; 279:5 percentages (2) 258:4;293:2 perception (1) 295:12 perceptions (1) 131:20 perfect (1) 150:16 perfectly (2) 25:15;158:4 perform (2) 224:14;230:4 performance (7) 13:4;14:3;15:17;16:1, 2;154:12;229:17 perhaps (17) 69:18;70:5;71:3;73:7; 79:19;83:12;94:10; 119:17,20;124:11; 161:17;192:3;208:5;</p>	<p>261:13;266:8;271:3; 310:22 period (61) 73:15;105:3;110:1,1, 2,9,13,14;113:17; 114:20;130:18;137:18; 146:1;148:16;159:13; 170:7;171:7,15;196:22; 197:2;213:11;214:15, 17;216:6,11;219:3; 220:3;223:2,16;224:10, 17,19;225:6,17;227:20, 22,22;228:5,15,22; 229:9;230:20;233:13; 236:7;241:11;243:14; 268:17,18;281:10; 283:13;284:12;287:22; 289:9;290:6,9,18,20; 291:2,5,5;295:3 periods (3) 113:15;274:13,14 Permanente (1) 86:2 person (7) 66:5;81:8;126:22; 146:22;152:13;238:12; 304:8 person's (1) 189:3 perspective (7) 11:5,15;17:3;19:8; 80:1,2;330:11 persuasive (1) 88:7 Petullo (1) 281:15 pharma (2) 125:10;270:20 pharmaceutical (5) 97:20;124:19;125:4,5; 197:14 pharmacotherapies (1) 245:19 pharmacotherapy (4) 37:10;264:15,17,20 pharmacy (1) 278:1 phase (17) 41:8;79:19;151:7,14; 214:5;245:17;266:4; 276:20;301:5,6,7,8; 315:12;318:21;319:1,10, 11 phenomenon (2) 37:12;42:3 Phil (6) 153:10;261:17;262:6, 9,10;301:3 Philadelphia (1) 49:3 philosophical (1) 163:12 phones (1)</p>
--	---	---	---	--

6:2 phosphatidyl (3) 144:20;145:10,17 physical (5) 18:15;100:18;131:4; 135:4;139:12 physician (3) 118:7;183:13,18 physicians (1) 185:15 PI (1) 198:17 pick (8) 109:20;114:7;128:11; 141:7;147:22;149:16; 176:14;308:14 picked (2) 140:2;186:4 picking (2) 109:18;143:13 picks (1) 133:17 picture (2) 238:3,8 pictures (1) 185:1 pieces (1) 319:19 pill (1) 265:21 pilot (1) 218:9 pink (1) 293:8 pioneer (1) 39:17 pitfall (1) 24:17 pitfalls (1) 25:3 pivotal (3) 96:16;112:15;266:4 place (3) 27:16;204:6,7 placebo (65) 56:9,16;57:8;58:1,19; 110:18;111:7,11;112:12, 17;114:4;116:16;117:2; 121:1,9,11;122:18; 123:6;127:15;128:3,4; 140:16,19;206:11; 214:11;217:20;218:4, 20;266:5;273:12,17,21; 274:4;277:3,8;282:2,10, 22;283:16;285:15; 286:5;287:1,5,13,13; 288:9,22;293:7;294:4, 13,15;299:1,2,5,18,19; 300:10,18,19;302:14; 303:13,16;305:2; 309:22;313:18 placebo-controlled (1) 276:21	placebos (1) 322:18 places (3) 314:19;320:4;326:12 plain (1) 48:4 plan (3) 86:4;271:6;285:17 planned (2) 9:22;22:4 planning (1) 318:22 plans (2) 325:15,16 plant (1) 34:16 plaque (8) 234:18;237:17;239:9, 9;240:22;241:1,10,17 plate (1) 127:9 platform (1) 218:20 play (2) 112:16;170:6 playing (1) 171:12 Please (4) 6:2,3;83:4;308:5 pleasure (1) 96:13 plenty (1) 144:1 plot (2) 120:12,12 plotted (2) 117:16;293:4 plug (2) 59:10;175:4 plummet (1) 134:14 Plus (9) 118:5;149:2;198:18, 18;199:12;203:20; 218:3,12;283:14 point (44) 5:15;51:8;52:22; 60:11;62:6;70:1,7; 97:11;152:18,19; 157:11;167:20;170:13; 177:12,13,18,19;178:4; 188:18;190:8;191:5; 193:14;242:5;261:13; 266:9;273:11;274:2,12; 283:10,21;286:2,9; 303:8;304:6,13;310:22; 312:7;315:14,17;316:5, 10;317:2;319:10;326:14 pointed (1) 192:16 pointing (2) 92:16;187:9 points (19)	8:9;24:11;68:7,8;69:5; 72:19;184:10;193:4,13; 216:8;222:22;223:5; 226:16;253:8;272:13, 19;273:1;274:21;281:7 police (1) 64:18 policy (2) 184:11;208:15 policymakers (2) 159:5;194:13 ponder (1) 327:10 pooled (2) 156:4;218:17 pooling (1) 213:5 poor (3) 17:14;58:18;63:11 poorer (1) 230:4 poorly (1) 63:12 popular (2) 109:9;180:8 population (23) 13:13,20;17:7;20:1; 21:11;22:16;31:9;53:17; 80:22;90:13;92:20; 105:17;151:2;160:13; 205:4,14,21;206:18,19; 210:11;311:20,20; 318:11 populations (4) 130:20;184:12;266:8; 325:22 portion (1) 213:15 pose (1) 34:8 position (2) 11:19;315:8 positioning (1) 26:2 positive (49) 12:3;56:22;57:1;72:5; 108:9,10;112:10; 165:11;168:8;181:9,12, 15;204:19;207:13,17; 215:21;227:13;229:9,12, 15;242:12,18;243:3,8,9; 244:8;273:13;274:3; 279:11;283:14,20,22; 284:3;285:16;286:19; 294:16;298:15;308:18, 20;309:3,11;310:3,16, 20;311:11;312:3;318:3; 323:9,11 positives (1) 181:20 possession (1) 66:1 possibilities (2)	95:9;317:7 possible (8) 23:7;32:11,12;115:22; 165:21;194:3;234:13; 315:14 possibly (2) 118:14;255:5 post (3) 315:10;319:4,6 post-approval (1) 16:22 post-dropout (1) 270:6 post-treatment (7) 213:10;222:20; 223:21;224:8,10;227:16, 19 potency (1) 172:15 potential (14) 5:16;30:19;72:16; 110:5;131:11;196:12; 210:9;231:10;233:18; 243:20;245:2;285:14; 298:2;327:14 potentially (10) 21:22;80:16;150:19; 170:4;180:17;184:2; 210:15;263:6;307:17; 308:4 power (3) 152:9;158:15;176:15 powered (2) 150:20;298:4 powerful (1) 173:3 powering (1) 150:21 practical (2) 20:18;66:8 practice (4) 25:21;31:12;206:4; 312:6 practitioners (1) 85:15 preaching (2) 154:4;194:14 predict (11) 16:9,19;48:20;50:21; 54:10;72:9;158:20; 162:20;188:21;201:1; 320:5 predicted (5) 42:21;45:7;127:22; 202:14,18 predicting (7) 54:12;63:11;76:6; 201:6,21;202:11;223:15 prediction (2) 16:13;50:7 predictive (13) 45:8,9;46:6,19;49:15; 50:3,15;57:19;70:13,18;	73:8;77:21;158:15 predictor (11) 45:3,10;52:17;58:14, 16;62:9,10,13,16;71:3; 231:14 predictors (5) 52:4;54:2,4;57:10; 229:7 predicts (6) 57:22;62:6;137:19; 158:11,13;188:15 preface (1) 190:12 preference (1) 314:1 pregnant (1) 235:15 pre-hypertension (1) 124:2 pre-IND (1) 32:11 premature (1) 239:18 prepared (1) 175:10 prerogative (1) 177:12 present (7) 96:14;97:17;98:1; 115:1;198:6;209:1; 244:22 Presentation (22) 11:10,17;37:2;70:15; 74:21;79:13;83:22; 96:11;129:14;153:6; 182:9;198:4;209:21; 212:16;232:8,18;244:16, 21;257:20;267:8; 271:15;295:15 presentations (6) 8:5,6,10;76:19; 147:13;210:2 presented (11) 92:14;209:5;240:11; 242:5;256:18;258:1; 259:7;264:13,14;274:9; 312:15 presenters (4) 195:2;197:17;266:16; 271:8 presenting (3) 106:15;262:2;294:7 presents (1) 251:1 pressure (12) 16:16;123:20,21; 124:3;131:5;136:1; 138:9,11,20,22;142:5; 231:4 PRESTON (4) 180:10;181:7;301:18; 302:6 pre-treatment (1)
--	---	--	--	---

<p>188:20 pretty (51) 6:10;10:11;46:15; 47:4;48:22;50:6;51:11; 53:20;58:4,21;63:14; 64:16;75:7;78:17;89:8; 98:21;102:9;103:9; 107:6,10;116:8;123:3; 128:8;134:10;137:5,6, 13;138:12;144:13; 147:20;148:1;181:12; 200:8,18;202:2;207:19; 215:11;219:15;224:2, 22;229:4,15;231:13; 247:1;250:20;252:2; 257:16;285:20;309:1; 323:20;324:14 prevalence (1) 259:22 preventative (1) 159:22 prevention (2) 73:21;162:1 previous (3) 197:21;199:2;232:14 prey (1) 305:15 price (1) 117:13 priest (1) 87:21 primarily (8) 9:16;40:21;53:18; 58:17;98:2;99:19;206:9; 207:19 primary (26) 9:11;26:11,12,16,20, 21;27:10;28:1;99:11; 113:6;118:15;148:6; 150:21;154:6;184:22; 214:22;218:16;279:2; 280:10,12,14;291:22; 297:17;301:20;315:18; 317:12 principles (2) 20:8,12 print (1) 322:2 prior (10) 53:21;75:3,9;76:3; 188:13;196:6;215:22; 219:6;221:19;286:7 priori (5) 141:13,17,21;317:11; 318:18 priority (2) 95:11;265:6 prisoner (1) 327:19 private (1) 9:17 PRO (5) 20:7;79:17;80:1;</p>	<p>81:16;82:7 PRO-805 (1) 276:18 PRO-806 (1) 276:19 probably (37) 8:5;35:3;41:5;44:18; 52:10;58:5,16;65:11; 67:20;68:6;90:12;99:20; 114:15;125:15;135:9; 137:11;145:12;146:16; 160:5;178:22;179:2; 180:18;183:18;190:5; 192:1,7;210:19;226:10; 234:19;257:18;283:1; 300:13;305:4,6;308:12; 312:9;327:3 problem (21) 77:6;86:9,10,11,15,17, 21;87:2;135:10;148:14; 172:8;175:16;177:21; 204:11;205:22;206:1; 238:14;308:11;309:5; 311:6;312:18 problematic (3) 24:21;163:13;230:13 problems (40) 47:16;51:3;65:22; 104:21;165:10;169:9; 190:17;192:17,20; 201:16;206:10;217:2,5, 5,6;220:11;225:12,16, 20,22;226:2,8,15,17,22; 227:1,6,21;228:1,4,6,8,9, 16,19,20;229:4;231:21; 233:17;261:20 probuphine (37) 271:21;272:4,7,18,19, 22;273:3,14,18;275:14, 16,17,20;276:4,15,18; 277:2,8;281:11,16; 282:1,8;284:2,16; 287:13,19;288:6;289:1, 11;290:12;292:7;294:2; 297:16;299:18;302:13; 307:14;316:10 procedure (2) 5:15,17 procedures (1) 277:4 proceed (1) 94:18 proceeding (1) 272:10 proceedings (1) 8:11 process (15) 29:2;32:19;33:7; 36:14;42:13;81:6; 143:13;183:22;191:2; 328:21,22;329:3,20; 330:11,18 produce (2)</p>	<p>9:18;40:4 produced (3) 9:10;88:5;174:13 produces (1) 201:18 producing (1) 240:1 product (3) 27:1;89:13;305:11 production (1) 230:7 productive (1) 159:15 products (3) 12:8;14:9;175:8 professional (2) 324:1;328:16 profile (15) 274:22;275:4;279:4; 280:21;281:5;291:9,10, 14;292:12;295:6;302:4; 306:18;313:14,22; 325:19 profiles (3) 315:9,19,20 prognosis (1) 58:18 prognostic (1) 31:7 program (20) 8:21;25:2,17;27:22; 32:10,17,19;33:4,10,13; 127:2;200:10,14; 245:20;256:10;272:7; 309:13;313:13;329:12; 331:3 programming (1) 322:1 programs (6) 24:7;31:17;32:8,22; 184:15;205:17 progress (2) 119:2;129:1 progression (3) 234:19;235:3;237:17 prohibitively (1) 12:22 project (5) 100:16;103:8;156:2; 162:8;188:19 prolong (1) 326:20 promise (1) 82:8 promising (1) 329:19 prompted (1) 250:10 pronounced (1) 79:9 proof (2) 113:7,7 proper (2)</p>	<p>89:5;304:10 properties (5) 20:21;21:2;30:4,9; 33:16 Proportion (15) 115:13,21;116:17; 130:14;133:2,7;220:2; 222:5;281:21,22;282:6; 293:5,17,20;319:9 proportions (2) 275:3;282:13 proposed (7) 32:13;133:1,1,2; 277:4;316:8;317:11 Propranolol (12) 55:12;56:2,6,7,8,11, 13,17;58:11;59:4,8;70:4 pros (1) 162:9 protocol (5) 77:6;221:4;223:20; 224:15;303:19 protocols (1) 176:1 protocol-specified (12) 273:4,9;277:10; 278:18;284:8,13; 286:11;287:17;288:3; 289:5,22;320:1 prove (3) 197:2;231:8;315:16 provide (8) 12:11;25:2;27:19; 32:1,5;88:17;96:8; 239:16 provided (5) 99:10;206:11;278:9; 295:18;323:8 providers (1) 194:12 provides (5) 20:14;166:14;239:13; 275:21;280:9 providing (2) 275:17;286:16 proximal (3) 17:13;19:3;263:2 proximally (1) 177:1 PSNHDD (1) 98:20 psych (2) 201:11,17 psychiatric (10) 49:21;50:9,16;104:21; 201:8,19,20;204:1; 217:6;220:12 psychiatrist (2) 45:13;189:11 Psychiatry (3) 71:16;84:6;204:15 psychological (2) 18:14;156:13</p>	<p>psychometric (3) 81:19,19;328:21 psychometrically (1) 157:22 psychometrician (2) 45:12,19 psychometrics (2) 45:21;330:15 psychosocial (13) 66:18;74:14;245:8,10, 14;246:19,21;248:15,21; 252:12;262:19;263:18; 329:6 psychotherapy (8) 40:7;49:1,7;198:15; 199:10;200:8,9;211:17 psychotic (1) 40:21 psychotoxic (1) 201:18 psychotropic (1) 204:2 PTSD (1) 50:3 public (1) 60:10 publication (2) 180:20;309:1 publications (2) 100:5;104:8 publicly (4) 33:4;272:9;297:18; 301:12 public-private (1) 9:2 published (13) 39:4;59:19;105:16; 112:6;121:17;175:16; 204:14;213:14,16,20; 233:2;246:7;256:10 pull (2) 155:15;197:22 pulled (1) 256:18 pun (1) 9:12 punish (1) 267:21 punishes (1) 299:2 pure (2) 205:12;258:11 purple (1) 116:16 purpose (3) 37:6;95:4;328:13 purposes (7) 29:10;31:5,6,7,13; 55:11;80:3 pursue (2) 33:14;56:11 push (1) 60:15</p>
--	---	---	--	--

<p>pushed (1) 188:15</p> <p>pushing (1) 105:20</p> <p>put (28) 6:8;21:16;25:12;41:8; 51:17;52:3;61:9;75:16; 79:5,19;94:20;95:10; 98:7,10,11;110:12; 121:8,16;146:11;198:7, 11;208:16,18;299:12; 300:11,13;303:7;328:5</p> <p>putting (4) 58:7;95:2;98:9;330:22</p> <p>p-value (1) 249:7</p> <p>Python (2) 174:18;232:14</p>	<p>questionable (1) 130:19</p> <p>questionnaire (3) 21:14;75:1;328:14</p> <p>quick (8) 149:22;152:6;184:10; 258:5;289:16;292:18, 21;327:3</p> <p>quickly (2) 145:18;198:12</p> <p>quit (15) 183:5,15,15,22;184:5; 237:8,11,19;238:5; 240:3;257:3,5,7;259:12; 324:2</p> <p>quite (12) 40:19;73:13;82:19; 100:22;101:1;108:14; 109:20;112:15;146:8,9, 21;157:5</p>	<p>rare (1) 180:4</p> <p>rate (17) 38:12;112:17;155:1; 168:4,11,19,20;169:3; 181:19;207:16;215:17, 19;233:22;247:22; 254:9;283:2;303:12</p> <p>rated (3) 82:19;285:1;298:7</p> <p>rates (9) 72:7;216:1;219:13; 282:22;312:12;313:3; 323:18;324:12;325:11</p> <p>rather (13) 19:4;28:15;71:4; 80:11;90:11;93:22; 169:4;215:15;216:20; 226:18;227:3;230:11; 311:10</p> <p>ratings (1) 214:11</p> <p>Raye (18) 96:8,10,11;129:17; 131:2;132:6;133:9; 135:12;140:15;144:4; 155:7;157:8;182:8; 184:19;187:17;191:8, 21;257:8</p> <p>RCI (1) 179:4</p> <p>reach (7) 185:9;242:17;276:7; 277:6;287:10;299:10,12</p> <p>reached (2) 244:14;287:14</p> <p>reaching (1) 299:14</p> <p>read (4) 128:16;133:9;142:6; 175:18</p> <p>readily (1) 95:3</p> <p>reading (3) 153:22;179:20;189:10</p> <p>readmissions (2) 210:22,22</p> <p>real (16) 67:13;90:13;132:14; 137:9;146:9;149:22; 152:6,17;157:21; 171:17;181:19;182:12; 205:4;269:8;296:8; 330:4</p> <p>realize (6) 10:14;69:10,12; 147:10;220:20;226:10</p> <p>really (240) 5:18,22;9:15;14:6,8; 22:18,21;23:16;24:2,6, 12,20;29:1;30:1,33:19; 40:19;41:11,19;44:4,9; 46:9;49:21,22;50:6,9;</p>	<p>55:4,5;57:19;63:9,9,15; 67:17;68:16,16;70:17; 72:10,22;74:4,6;78:10; 80:8,15;83:16,18;87:9; 88:13,16;90:17;91:1,13; 92:14;93:14;94:19; 96:15,19;97:6,6,13,15; 99:12;103:8;104:18; 105:17;106:4,16; 107:12;108:20;109:9; 114:3,18;116:6,15; 118:9,16;119:4,5; 121:20;126:13,19,22; 127:5,20;128:12,20; 131:10;134:21;136:9, 14;139:16;140:22; 141:8;144:2;146:3,5,18; 150:14,15;153:8,21; 154:1,5,5,11;155:5,5,13, 22;156:12,19;157:18; 158:4,9,14;160:14; 162:4,11,15;163:15; 164:6,8;165:4;166:4,10, 13,13,18,18;167:13,19; 168:1,13,14,16,21; 169:10,15,22;170:14; 171:3,12,13,13;172:3,9, 9,11,11,16,16,19,21; 173:19;174:2,12,12; 175:3;177:14;179:8,14, 22;181:13;184:20; 185:1,3,12,16,16; 187:15;188:3,16;190:9; 194:2;196:16;203:16, 20;204:6,22;205:12; 206:3,18;208:2;212:14; 215:8;221:16;230:7; 232:16,21;257:14; 259:20;263:4,11,16,20; 264:3,19,21;265:13; 266:11,18;267:15,19,21; 268:1;269:8,16;270:1,6, 10,10,15,19;275:10; 299:1;301:20;303:17; 310:7;313:11;314:11; 317:19;319:15;320:5,6, 11;322:20;324:2,14; 325:4,11,17,18;326:1,5, 8,9,14;327:3;329:5,19; 330:9,17</p> <p>reason (12) 44:1;89:2,15;162:3; 184:15;229:2;287:9; 299:4;312:8;319:6; 320:2;325:13</p> <p>reasonable (2) 53:5;173:4</p> <p>reasonably (1) 16:19</p> <p>reasons (13) 161:1;162:17;163:8; 167:2;173:3;190:11; 257:11;259:19,22;</p>	<p>268:14;278:12,14; 288:20</p> <p>receive (3) 150:5;210:18;277:12</p> <p>received (7) 7:7;210:18;212:19; 246:9;253:17;278:3; 287:12</p> <p>receiving (2) 283:3;288:1</p> <p>recent (8) 14:5;27:21;138:18; 156:3;164:14;181:16; 182:9;192:22</p> <p>recently (9) 9:7;29:5;56:20; 121:17;229:14;234:7; 256:9;258:10;262:8</p> <p>recess (3) 96:6;195:4;271:10</p> <p>recognize (2) 39:8;70:14</p> <p>recommend (4) 18:22;22:2;175:19; 204:6</p> <p>recommendations (2) 98:12;193:16</p> <p>reconvene (3) 96:1;194:17;271:6</p> <p>record (1) 57:2</p> <p>recorded (2) 6:7;43:15</p> <p>recording (3) 8:11;34:22;63:5</p> <p>records (2) 60:13;137:3</p> <p>recruit (1) 235:10</p> <p>recruited (1) 235:7</p> <p>red (11) 101:9;111:18;114:10; 116:19;224:13;251:16; 283:14;284:3;285:8; 286:3,7</p> <p>reduce (13) 50:3;79:6;118:11; 121:13;125:19;150:5; 183:6,16,16;184:1; 189:4;209:22;263:8</p> <p>reduced (27) 28:4;64:18;66:15; 67:1;179:5;183:12; 185:9,10,11;197:5; 232:4;236:16,21;237:12, 22;242:6;243:2,4; 252:15;256:22;257:2,4, 6;265:3;308:18,20; 329:7</p> <p>reducing (3) 58:1;59:7;121:12</p> <p>reduction (66)</p>
Q				
<p>Q&A (5) 60:4;143:20;177:9; 267:4;296:4</p> <p>qualification (2) 32:19;33:7</p> <p>qualified (2) 33:9,12</p> <p>qualify (2) 32:21;33:4</p> <p>qualitative (2) 151:3,14</p> <p>quality (7) 17:16;18:10,13,20; 19:1;258:18;308:12</p> <p>quantifiable (2) 179:14;180:22</p> <p>quantified (2) 12:7;23:1</p> <p>quantifies (1) 20:2</p> <p>quantify (1) 162:7</p> <p>quantitative (27) 55:21;146:10,14; 164:2,15;171:14; 172:19;179:19;180:5, 11;181:10;245:7,9,13, 21;246:18;247:15,16; 248:14;250:7,19; 252:13;254:22;255:10, 15,21;258:13</p> <p>quantity (9) 143:2,2,3;156:21; 167:8;170:21;172:11; 215:7;221:17</p> <p>quartile (8) 251:22;252:1;260:6,8, 8,10,11;261:3</p> <p>quartiles (2) 251:13;261:2</p> <p>quest (1) 159:6</p>	<p>quits (1) 319:5</p> <p>quitting (1) 183:17</p> <p>quote (1) 87:13</p> <p>quoted (1) 192:18</p>	R		
	<p>R21 (1) 256:10</p> <p>Rachel (3) 271:11,15;315:8</p> <p>radiographic (1) 28:9</p> <p>radiology (1) 239:4</p> <p>ran (2) 49:18;54:19</p> <p>random (1) 171:4</p> <p>randomization (8) 59:1,2;100:6;112:8, 18;199:21;214:21; 251:10</p> <p>randomized (10) 156:3;199:18;205:11; 206:9,10,14;213:6; 245:18;269:22;276:20</p> <p>range (7) 115:21;181:22;204:1; 219:20;270:4;291:12; 317:17</p> <p>ranged (1) 214:12</p> <p>ranked (1) 245:21</p> <p>rant (1) 262:7</p> <p>rapidly (2) 175:9;251:21</p>			

28:1,8;53:3;112:20; 118:19;122:14,14; 132:8;133:3,11,18; 147:8;148:21;170:21; 171:9,11,19;172:3; 173:8;176:4;221:12,13, 14,15,21,22;223:22; 224:1,21;230:6,11; 234:20;236:13,22; 237:11,13,14;239:15; 242:7;243:21;244:2; 245:12;250:1;251:14; 252:11,17;254:6,20; 255:9;257:14;258:6,13, 15;259:1;260:11; 263:10;296:17;298:20; 317:3,18,22;318:2,3,12, 13,14	249:7 regrets (1) 5:21 regrettably (1) 193:5 regular (1) 98:3 regularly (1) 241:14 regulations (2) 19:11;22:22 regulators (2) 21:16;266:9 regulatory (11) 11:5,15;19:8;20:17; 26:3;31:18;35:18;97:19; 124:18;180:17;319:5 Rehm (8) 119:5;120:7,11; 121:15;136:17;137:8; 138:3,5 reinforced (1) 39:21 reinstated (1) 186:22 rejected (1) 205:7 relapse (9) 73:16,21;74:3;106:19; 107:1,16;115:7;162:1; 324:12 relapsed (2) 324:10,16 relapsing (1) 161:18 relate (3) 158:22;263:5;278:15 related (27) 7:11,16;15:3;17:10, 16;19:1;66:12;67:15; 69:3,4;83:20;139:13; 152:13;163:16;202:17; 212:15;223:15,20; 227:16,20;228:4,17; 229:3;231:1;288:21; 289:14;303:21 relates (1) 285:13 relationship (11) 76:11;174:4;222:20; 223:3;224:8,9;225:9,16; 275:7;292:14;295:9 relationships (5) 213:10;223:1,12; 319:16;326:2 relative (10) 120:20;140:8,20,22; 141:16,17,19;142:1; 259:22;288:11 relatively (4) 7:22;161:8;203:13,16 release (1) 275:21	released (1) 237:1 relevance (5) 118:18;124:14;143:9; 150:10;189:19 relevant (4) 17:8;129:3;150:18; 316:10 reliability (12) 21:3;30:7;37:22; 44:20;45:16;46:4,5,10, 11;68:12;70:12;78:21 reliable (11) 19:14,15,20;20:10,20; 27:6;68:9;157:3;158:1; 172:10;255:18 reliably (1) 20:3 reliance (1) 34:14 relied (1) 203:20 rely (1) 13:10 remain (3) 75:18;248:22;274:9 remaining (2) 294:21;321:8 remains (1) 44:22 remarks (3) 175:10;262:12,13 remember (17) 31:1;100:15;113:19; 145:21;158:18;171:17; 179:4;206:15;210:21; 260:5,21;276:17; 286:10;291:9;297:14,18, 19 remind (5) 7:8;99:3,5;194:21; 330:10 renal (1) 139:1 repeat (1) 186:19 repeated (2) 48:16;267:18 replenished (1) 6:16 replicable (1) 158:1 replicate (3) 55:8,9;212:4 replicated (3) 56:5,12;228:10 replication (2) 76:1;204:9 report (6) 13:13,20;147:7;168:9; 233:4;311:1 reported (21) 13:6,14,17,21;14:4,7;	17:4;20:6,11,15;28:6; 30:22;35:16;39:13; 43:18,19;79:18;217:7; 220:11;226:1;228:19 reporting (3) 39:15;85:19;322:13 reports (2) 9:13;10:1 represent (7) 11:18;16:3;21:15; 223:6;281:1,7;286:2 representation (2) 281:17;293:11 representative (1) 110:5 represented (1) 283:10 represents (7) 29:1;30:1,2,18; 115:20;283:2;318:10 reproduce (1) 212:2 request (1) 277:18 requested (1) 277:18 require (1) 112:8 required (5) 33:9;100:6;112:14; 278:1,20 requirement (3) 16:21;231:5;232:2 requirements (1) 323:17 requiring (2) 204:2;322:12 rescue (25) 273:5,8,15,18,20; 276:10;277:13,22; 283:3;285:18;286:3,9, 13;287:16,18;288:2,10, 13;299:21;300:11,21; 304:2,17;305:2,4 research (26) 7:15;9:20;10:3;29:20; 35:1;60:14;61:18;86:4; 94:7,10;95:10;100:4; 119:20;155:15;162:19, 21;163:2;169:2;185:6; 214:2;239:17;265:5; 325:18;327:19,20;328:4 researchers (4) 97:22;98:1;124:20; 126:20 residential (2) 206:7,16 resist (1) 9:12 resolved (1) 231:6 resonate (1) 150:3	resonated (2) 68:10;70:5 resonates (1) 68:4 respect (3) 70:2;89:15;95:21 respected (1) 329:12 respond (3) 21:12;54:14;306:1 responded (1) 76:4 Responder (27) 115:13;133:7,21; 139:21;141:13,15,18; 193:8;273:2;280:18,20; 291:16,19;294:10; 298:19;315:9,18,20,22; 316:1,21,21;317:10; 319:14,17;320:9,14 responders (3) 115:21;275:3;288:7 responding (1) 264:2 response (28) 10:10;19:13;54:12; 55:2,14;58:1;59:7; 130:10;273:10;274:22; 275:4;279:4;280:21; 281:3,4;283:7;284:21; 291:9,10,14,16;292:12; 295:6;302:4;305:17; 306:18;313:14,22 responses (5) 148:1;291:11,12,13,15 responsibility (1) 100:19 responsive (2) 59:4;81:8 rest (5) 218:7;219:18;254:1; 283:21;317:13 restless (1) 41:1 restricted (1) 203:22 restrictive (2) 208:4;288:13 result (10) 66:6;139:19;140:15; 141:1;212:19;215:16; 250:18;273:14;285:16; 294:16 resulted (2) 69:20;293:17 results (61) 10:6;18:9;35:14;68:5; 90:2,2;101:2;103:9; 105:12;106:7;109:15; 112:19;130:4;169:5; 180:11;212:14;215:20; 231:18;236:4;245:7,10; 246:18;247:3;248:14;
---	---	---	--	--

252:13,22;254:22; 258:3;262:2;275:10,11; 278:8;279:16;280:10; 283:12;284:9,18,22; 285:10,21;291:22; 292:3;293:16;294:8; 295:11,12;298:10; 302:11;303:10;307:12; 309:10,20;310:2; 312:14;321:5;323:10; 327:1,5,12;328:1,3	67:16;257:20 rid (1) 53:8 riff (1) 90:4 right (62) 6:12,12;7:5;17:21; 19:22,22;21:10;22:6; 53:14;57:18;64:20;72:2, 4;87:13;119:2;123:13; 129:4;133:14;134:2; 135:10;143:8,21;164:4, 4;184:3;185:14;186:16; 188:5,21;190:6,22; 191:8,10;232:22;236:4; 241:11,14;244:6,7; 251:1;256:4;260:7; 261:11;270:19;281:9, 19;282:19;289:21; 297:6;304:17;307:20; 311:3,7;316:12,14; 317:9;320:17;323:12,13, 13;327:4;329:21 right-hand (3) 133:10;282:12;292:4 risk (45) 22:17;33:17;68:15,15, 16,21;102:14,22;103:4, 20;104:10,15;105:1,6,9; 106:2,11,18,22;107:2,6, 10;119:7;120:13,20; 121:11,11,13;122:3; 123:15;124:11;140:8,10, 20;141:1,16,17,19; 142:2;210:15;233:16; 234:10;263:10;324:9,10 risks (8) 12:8;22:19;23:1,5; 68:19;140:12;141:10; 233:18 risks- (1) 123:16 road (2) 74:15;266:7 Roadmap (4) 23:15;25:6;28:16; 92:14 robust (2) 70:17;71:3 Rochester (1) 9:16 rod (6) 276:11;277:9;278:2, 17,20;299:18 rods (6) 276:2,2,8,11;277:8; 287:13 room (10) 6:11,14,16,17;60:19; 95:8;105:5;226:11,12; 328:10 rooms (2) 40:16;160:1	Roosevelt (1) 6:17 roots (1) 39:8 roughly (4) 103:15;117:2;219:4; 270:13 round (1) 101:10 routine (1) 6:10 routinely (1) 50:11 row (3) 166:21;278:22,22 run (4) 9:15;65:12;77:6; 269:12 running (2) 95:16;235:17 runs (1) 53:15 Russian (1) 324:7 roxolitinib (3) 27:22;28:3,14 Ryan (1) 97:3	samples (31) 222:6;257:16;264:4; 274:2;278:6;279:11,21; 280:6;282:4,9;283:20, 21;286:17,17;293:5,19, 21;294:3,5;308:18,20; 309:11;310:3,19;312:18, 19,20,21;315:4;323:9; 325:9 San (1) 5:14 Sanchez (1) 192:18 SAS (1) 321:22 sat (1) 124:5 Satel (1) 41:11 Satel's (1) 79:4 satisfied (1) 280:7 save (2) 176:20;243:1 saving (1) 125:3 saw (16) 57:16;181:10;209:4; 227:18;262:7;280:21; 282:15;285:21;287:20; 288:5;289:7;291:3; 295:10;300:19;302:11; 322:19 saying (13) 46:9;107:13,22;115:3; 184:4;187:9;298:21; 302:10;307:18;317:17; 321:17;325:8;326:4 scale (16) 38:8,18,19;44:11,17; 45:10;47:18;48:7,8; 246:15;248:7;250:6; 254:3,17;277:15,17 scales (6) 38:14;39:19;45:1,7; 255:22;256:22 Scandinavian (1) 205:2 scared (1) 232:21 schedule (1) 166:1 scheduled (1) 271:6 scheme (1) 268:2 schizophrenic (1) 50:2 science (1) 22:22 sciences (1) 29:5	Sciences' (1) 311:1 score (36) 16:4;20:1;21:14,15, 18,19,20;22:13;26:8; 28:4,11;30:1;38:15,15; 45:4,4;47:17;51:10; 53:22;55:18;59:1;71:4, 5;78:12;79:21;84:4; 101:5;117:18;127:22; 135:18,22;136:6; 249:15;253:19,20; 254:14 scored (3) 48:4;51:1;277:14 scores (43) 38:16;46:21;47:12,16; 49:11,12,13,22;50:19, 21;51:11;53:4;54:6,13, 22;55:1;56:8,16,17; 57:12,14,15,15,17,20; 58:2,3;59:8;71:22;75:8, 15,18;76:6;78:11;79:8; 94:5;101:4;102:1; 216:21;249:16;253:16, 21;254:17 SCRAM (1) 146:6 screen (2) 54:6;58:22 screened (3) 199:15,15;205:8 screening (1) 77:11 screens (3) 52:18;58:16;62:14 Screw (1) 322:17 SE (1) 200:17 second (19) 28:17;32:16;49:2; 57:3;59:9;119:10; 177:22;234:17;236:20; 238:15,16;239:10; 248:12,13;255:3;256:9; 273:11;313:6,7 secondary (15) 26:12,19;27:10;28:7; 59:18;64:21;135:14; 150:22;198:14,20; 285:2;297:15;298:1,5,14 Secondly (1) 118:20 Section (2) 27:4,5 seed (1) 34:16 seeing (9) 114:1,3;140:12; 149:18;152:16;241:8; 284:6;303:1,10 seek (1)
	S			
		safe (1) 157:5 safety (1) 276:15 sake (1) 174:22 salient (2) 8:9;217:4 Sally (1) 41:10 same (39) 27:13;59:14;65:4; 75:18;86:19;97:13; 103:9;107:7,9;153:21; 166:9;178:22;179:1; 205:2;212:3,5;214:2; 222:4;227:22;228:9,12; 231:18;238:12;247:12; 248:20,22;249:17; 254:8;258:3;270:13,19; 271:2;273:7;278:17; 282:20;295:1;302:15; 309:5,9 sample (28) 53:11;55:6;57:13; 152:17;161:10;163:17; 200:1;203:11;205:4; 207:11;208:5;216:2; 218:6,22;219:17;246:5, 8;258:7,9,14,14;260:20; 261:1;279:7,8,10; 283:14,19		

<p>12:2 seeking (3) 92:20;206:9;261:21 seeks (1) 9:18 seem (8) 48:16;66:8;117:10; 121:3;170:9;188:2; 223:14;229:15 seemed (16) 48:5;49:15;55:2,13; 72:2;127:17;138:1; 193:1;203:15;221:1; 224:22;229:7;230:4; 231:13;287:6;323:1 seems (23) 37:12;53:5;71:1,5; 72:21;73:9;84:9;108:16; 117:7,11;138:5;144:8; 147:20;148:1;176:8; 183:17;192:16;219:17; 223:18;241:16;289:2; 301:21;320:18 seizure (1) 317:4 seizures (2) 41:19;318:1 select (2) 31:7;82:2 selected (4) 17:7;52:21;205:5; 217:3 selecting (4) 24:16,19;27:16; 153:19 selection (7) 11:5,16,21;23:14,18; 26:6,15 Selective (2) 37:4;39:1 self-correct (1) 169:6 self-identified (1) 93:4 self-medicating (1) 172:7 self-rated (5) 246:14;247:13;248:1; 249:19;254:9 self-report (25) 35:9;44:17,21;52:16; 61:15,17;71:7;76:11; 83:2;147:7;167:4;168:5; 169:17;181:9,20; 199:21;203:21;208:20; 216:12;250:19;265:21; 278:9;279:9;284:5; 321:15 self-reported (13) 53:7;75:3;215:1,19, 21;233:9;249:5;250:8, 13;255:6,17;259:4,6 self-reports (1)</p>	<p>200:6 self-taught (1) 211:6 selling (1) 152:10 send (1) 238:3 sends (1) 5:21 sense (8) 55:15;61:18;67:12; 118:9,10;219:12;241:6; 305:1 sensible (1) 148:2 sensitive (39) 108:1,14,17;109:2,3; 112:2;114:14,16,17; 118:22;126:8,9;128:20; 129:2;131:7,12,14,15; 132:3,5,14;143:9,14; 144:13,18;158:15; 162:3;164:17;165:2; 171:5;176:15;178:19; 182:19;192:5;220:18; 244:6;255:13,15;267:10 sensitivity (18) 63:7,8,13;94:6;96:22; 129:20;131:21;135:11; 151:22;174:5;176:9; 211:12;212:8;213:8,8; 224:6,7;269:10 sensors (1) 146:6 sent (4) 120:11;238:1;239:3; 306:20 separate (3) 104:18;252:22;281:6 separated (2) 54:21;111:1 separately (1) 226:20 separates (1) 13:8 separation (10) 111:12;114:1,3; 282:11,15;292:3;316:3, 5,11,16 sequence (1) 307:20 series (1) 201:5 serve (1) 11:7 session (5) 195:3;196:4,5;266:11; 271:7 sessions (5) 165:16;199:11;200:8; 278:22;290:3 set (26) 11:1,14;62:6;93:6;</p>	<p>100:2,5;105:11;130:11; 142:10;154:11;158:3; 160:12;164:4;182:14; 188:7;193:7,12,19; 212:20;217:13;224:14; 232:11;289:7;290:19; 291:8,21 sets (15) 99:13;103:15;108:4; 119:5,20;124:15; 128:19;136:15;138:8; 166:6;182:19;196:16; 231:17;244:20,22 setting (8) 6:13;26:3;103:12; 214:13;306:21;316:20; 317:8;318:15 settings (7) 25:21;48:22;78:16; 99:13;154:7;318:6; 326:18 settled (1) 110:9 settles (1) 46:15 seven (2) 182:15,16 several (4) 133:1;221:5;225:12; 226:4 severe (15) 40:2;41:21;42:5;47:8, 17;49:19,21;50:9,16; 55:14;75:11;94:9; 124:12;151:6;186:2 severely (1) 75:11 Severity (17) 37:5;39:2;47:7,12,15; 49:21;75:4;158:11; 186:14;246:14;247:10, 14,22;249:12,19,20; 255:4 sex (1) 172:17 sexy (1) 320:20 SF12 (2) 131:6;135:17 shaded (1) 223:7 shadings (1) 223:6 share (5) 11:15;30:20;31:19; 172:18;271:18 Sharon (5) 64:4;72:16,18;81:13; 93:17 sheet (1) 7:4 Shengan (2) 232:13,18</p>	<p>short (9) 137:11;148:16; 152:11;189:21;190:2,16, 17;263:16;276:20 shortened (2) 190:21;191:3 shorter (3) 150:17;152:1;251:20 shortly (1) 38:22 Shou-Hua (3) 197:19;256:18;260:21 show (36) 19:6;48:14;64:1; 109:5;114:21;116:5; 118:18;122:15;127:13; 147:16;148:10;149:2; 165:13;181:21;189:22; 190:3;198:1;223:18; 236:4,18;237:5;238:3; 242:18;243:3;257:9; 264:4;290:11,14; 296:17;298:2;307:10; 310:13;327:5,15;328:6; 329:4 showed (13) 42:19;43:6;56:15; 58:8;71:14;109:12; 192:22;241:10;252:21; 257:9;275:2;308:16; 309:3 showing (12) 16:9;42:15;47:22; 223:19;275:5;279:17; 281:14,18;291:15; 292:17;322:12;324:11 shown (6) 12:11;48:13;59:7; 70:18;322:22;329:4 shows (9) 29:13;36:2;197:9; 199:1;247:10;279:12; 282:19;283:8;294:6 shrinking (1) 28:2 shut (1) 297:21 side (13) 16:7;98:4;129:9; 133:10;134:2;184:11; 185:8;281:16;282:12; 284:2;287:19;292:4; 317:9 sign (2) 6:2;283:14 signal (6) 170:9;204:9;208:3; 246:17;266:1,7 signals (1) 72:5 signed (1) 7:3 significance (9)</p>	<p>111:17;114:5,21; 136:9;156:12;201:7; 202:19;223:6;228:14 significant (70) 22:11,14;41:18;54:7; 105:2,7;108:18,20; 109:13,18;110:21;111:3, 5,13,14,15;112:20,21; 113:4;114:2,8;121:14; 128:9,11;132:17;135:8, 17,21;136:1,2,4,7; 148:12,15;151:22; 179:4;189:22;190:10; 201:9,11;202:15; 204:19;211:19;223:9; 227:17;228:7;235:5; 237:8,20,22;238:6,7; 247:9;248:4;249:20; 250:6;251:4;253:2,22; 254:2,5,10,13,15,18,18; 263:12;292:6;293:10; 313:18 significantly (3) 79:6;234:11;254:7 sign-in (1) 7:4 signs (10) 38:8;39:14;83:14,19; 84:7,15,20;85:4;93:8,10 SILVERMAN (12) 34:18,21,31;35:1; 36:10;147:12,12;308:6, 6;323:3,3;324:4 Silverman's (3) 68:4;89:21;160:3 similar (17) 40:19;84:10;104:22; 105:5,9;109:15;123:18; 205:3;212:6;228:13,14; 250:17;284:15;285:20; 290:21,22;305:15 Similarly (1) 193:12 simple (7) 98:21;116:6,7,8; 140:1;240:18,19 simply (5) 42:7;43:22;46:3; 60:12;183:12 single (5) 51:17,21;291:16; 311:10;320:14 singling (1) 286:8 SIP (3) 190:17,21,21 sit (1) 313:9 site (2) 301:1,2 sites (1) 119:13 sitting (1)</p>
--	--	--	---	--

44:14 situation (5) 176:18;183:10; 305:15;310:15;314:3 situations (2) 116:2;316:13 six (6) 97:20;112:14,16; 199:9;226:16;236:20 size (21) 28:2;110:21;111:2,12, 19,20;113:18;114:9; 116:19,20;117:4,6; 146:22;148:13;152:17; 211:13;234:8;246:8; 260:20;261:2;269:14 sizeable (2) 130:14;269:21 sizes (3) 201:10;211:15;246:5 Skeete (20) 271:15,16;289:17,21; 290:5;296:5;297:6,17, 22;299:7;300:6;301:2,9, 11,15;302:3,7;306:11; 307:21;313:7 Skeet's (1) 271:12 sketch (1) 77:6 skid (1) 186:19 skids (1) 187:6 skinning (1) 268:6 Skolnick (9) 232:22;240:6;262:6, 10,11;301:3,3,10,13 Slagle (8) 11:3,10,11;35:11; 36:13;66:10,10;80:4 Slagle's (1) 263:1 slavishly (1) 153:11 sleep (3) 38:10;41:1;47:3 slice (3) 92:5,6;139:5 slide (10) 17:12;148:10;162:4; 222:16;259:18;279:12; 280:9;281:17;283:8; 290:14 slides (8) 8:12,14;67:16,17; 144:11;217:12;257:8; 262:11 slight (1) 102:12 slightly (2) 117:4;166:9	slip (1) 230:18 slope (9) 140:10;228:17;229:3; 249:3,4,9,22;255:19; 260:16 slopes (3) 157:20;249:18;260:10 slow (2) 209:18;211:2 small (7) 7:22;22:13;55:5; 145:8;220:2;257:16; 328:11 smaller (2) 112:12;113:19 smoked (1) 53:19 smoking (1) 173:6 snapshot (1) 265:18 sobering (1) 160:18 social (7) 18:15;29:5;100:18; 104:21;135:4;261:8; 297:1 soft (1) 239:9 Sofuoglu (1) 43:5 solid (1) 282:1 solve (1) 326:1 somebody (10) 73:10;78:10;83:4; 90:8;92:8;167:9;183:8; 192:2,5;325:10 somebody's (1) 165:15 someone (7) 23:17;82:5;152:15; 307:1;311:17;315:11; 323:7 sometimes (17) 12:14;21:8;24:5; 27:18;35:21;40:20,20; 45:22;87:7;98:19; 105:20;168:12,12; 276:19;296:19;321:6; 322:5 somewhat (9) 15:18;71:4;104:22; 107:3;122:19;168:19; 203:22;255:17;324:19 somewhere (9) 7:22;38:17;62:5; 113:20;117:8;181:19; 191:15;271:1;317:16 soon (2) 127:8;234:13	sorry (6) 63:1;75:20;149:5; 179:13;249:22;265:1 sort (50) 11:14;44:5;48:11; 54:1;55:15;61:9;87:7; 88:16;90:2;92:2,15; 95:10;103:6;118:3,13; 123:18;126:18;144:7; 145:13;153:13;159:13; 163:4;173:20;177:15; 181:2;186:22;187:21; 192:11,11;193:6; 194:14;205:1;211:2; 212:7;214:8;218:13; 224:19;229:1;251:17; 265:13;268:22;270:3; 300:1;303:3;304:12; 306:3;307:16;320:20; 326:7;330:5 sorts (2) 7:2;305:9 sound (5) 23:18;154:3;157:22; 318:7;326:8 sounded (2) 303:9;320:6 sounds (8) 35:6;69:16;77:5; 81:20;121:6;167:3; 179:22;319:15 soup (2) 330:6,6 sources (2) 9:17;258:10 SPARENBORG (4) 74:19;76:9;328:9,9 speak (6) 6:4;11:12;65:3,5; 201:10;315:21 SPEAKER (53) 8:12;87:21;91:9; 149:21;151:11,12; 180:16;190:7,15,19; 192:10;211:10,21; 212:12;243:19;258:5, 22;259:10,21;260:6,13, 14,17;261:7;267:7; 269:6;289:16,18;290:4; 298:18;300:4;303:7; 309:12,17;310:4,10,11, 17,21;311:7,8;312:7; 313:4,10;315:21; 317:20;318:17,19,22; 319:12;323:22;324:5; 326:4 speakers (4) 67:10;95:22;267:6; 331:6 speaking (2) 36:21;266:21 speaks (2) 34:9;326:2	special (5) 79:22;142:9,11; 146:11;240:5 specific (11) 18:22;47:19;48:6; 71:4;89:12;94:1;269:5; 283:4;291:19;306:7; 310:18 specifically (7) 19:12;20:10,19;21:9; 261:14;297:8;309:19 specification (1) 316:4 specificity (3) 63:7,10,14 specified (1) 179:17 specify (1) 313:13 spend (1) 279:13 spent (1) 197:20 spider-web (1) 226:9 spirit (1) 244:17 spleen (3) 28:2,2,9 spoke (6) 29:13,17;30:3,8,13,18 spokes (3) 28:19;29:9;137:22 sponsor (1) 301:6 sponsored (1) 8:16 sponsoring (1) 328:11 sponsors (2) 32:9;274:14 sponsor's (1) 293:16 spurring (1) 153:10 stabilized (2) 299:13,14 stable (4) 110:11;228:21;229:4; 248:19 staff (3) 206:1;314:13,18 stage (6) 11:14;32:11;41:6; 123:22;124:2,2 stages (1) 124:11 stakeholders (5) 32:2;33:1;87:6; 131:17,19 standard (13) 6:1;53:20;90:3;98:15; 152:3;155:15;156:16,	22;157:2;172:12,14; 319:1,2 standards (2) 20:17;154:12 stands (1) 97:10 start (20) 60:9;77:8;94:13; 114:1,3;116:22;140:12; 143:22;146:15;149:18; 166:5;171:12;182:18; 192:2;198:3;209:3; 244:20;253:18;271:1; 299:9 started (14) 5:10;48:19;111:14; 126:13,17,19;156:10; 192:21;193:16;196:2; 299:8;311:3;329:1; 330:22 starting (8) 42:15;119:14;161:22; 205:19;219:6;221:19; 256:15;266:9 state (6) 10:3;34:20;73:10; 90:16;141:5;221:15 stated (1) 188:13 statement (3) 26:17;87:13;265:8 statistical (5) 281:15;295:22;316:2, 17;319:3 statistically (6) 22:11,14;148:12; 251:3;292:6;293:9 statistician (3) 197:20;207:13;322:1 statisticians (4) 77:7,14,19;78:6 status (3) 18:20;172:22;206:13 stay (5) 74:12;75:17;240:10; 252:7;322:18 stayed (4) 207:20;209:12; 287:19;313:16 staying (4) 294:21;302:12,13,19 steeper (1) 140:11 steepest (2) 141:8,11 stemmed (1) 287:4 stenosis (11) 235:2,3,5;237:20,22; 238:6,7,10,11;239:8; 241:20 step (7) 11:21;43:5;61:7;85:3,
--	---	---	--	---

10;120:17;328:18 step-down (1) 253:13 steps (3) 70:10;177:15;226:4 Steve (3) 74:18;328:8,9 Steven (1) 72:17 stick (2) 51:21;145:11 sticking (1) 163:6 still (38) 27:2;45:22;79:8; 100:4;101:16;102:13; 110:6;111:2;121:18; 123:8;129:1;132:20; 151:21;179:7;181:21; 185:8;196:21;218:7; 230:9,15;231:8;237:21; 257:6,17;263:12; 274:11;275:6;278:17; 289:12;292:13;298:11, 17;300:18;302:9,20; 307:2;310:17,18 Stimulant (25) 5:7;34:12;130:6; 142:20,21;153:16,19; 154:5,15;172:1,4; 177:20;190:13;191:4; 196:7;262:16;272:6; 305:10;306:6,9,19,22; 307:5;314:5;327:8 stimulant-dependent (1) 86:13 stimulants (4) 144:8;164:13;165:2; 178:6 stimulant-use (4) 7:11,17;68:20;90:18 stimulated (1) 196:12 stimulating (1) 330:5 stinks (1) 63:10 stomach (1) 147:1 stone (2) 5:13;329:17 stop (12) 10:8;60:2;64:8;72:14; 74:5;87:1;165:5;177:8; 185:6,19;235:19,20 story (2) 75:20;293:13 straightforward (2) 10:12;247:1 STRAIN (98) 5:3,4;8:13;10:11;34:1, 20,22;36:20;60:5,8,11, 21;61:5,21;62:21;63:4,	18;67:2,3;72:12;74:18; 76:16;78:5;79:11;82:9, 22;83:7;84:13;85:21; 87:8,16,22;89:14;91:7, 22;95:16;96:7;143:21; 147:11;149:5;152:6,20; 153:3;174:16,21; 177:10;179:10;181:6; 182:7;184:8;185:20; 186:3;187:11;188:18; 189:6,9,11;190:12; 193:20,22;194:8,16; 195:1;196:2;212:10; 240:15,18;241:6,13,16, 21;242:1,3;262:4; 266:13,22;267:5;271:3, 11;296:5;297:10; 300:20;301:17;305:16, 18;307:8,22;313:6; 314:6;315:6;321:1; 323:2;324:6,21;326:19, 20;330:2;331:5 Strain's (1) 173:14 strategy (1) 80:18 stratification (7) 77:1,8;80:7;82:16; 189:6;264:9;265:14 stratified (1) 206:13 stratify (1) 266:5 straw (4) 160:9,19;173:9; 213:13 street (1) 183:8 strengthen (1) 76:10 strengths (2) 136:16;155:21 stress (1) 272:3 stressed (1) 311:17 stretch (1) 330:8 stretching (1) 193:20 stricter (1) 283:2 strikes (2) 189:13;307:9 striking (1) 5:18 stroke (1) 122:4 strong (3) 16:8;166:14;224:22 stronger (3) 35:7;127:18;223:12 strongest (1)	137:20 struck (1) 241:7 structure (5) 7:20;34:11;67:13,18; 317:5 structured (1) 10:13 struggle (1) 305:22 struggling (1) 95:19 stuck (1) 75:21 stud (1) 111:10 studied (5) 49:4;55:12;56:15,19; 64:16 studies (48) 14:21;15:2;16:22; 19:21;27:5;31:9;42:15; 64:3;72:4;73:2;93:16; 96:10;97:4;99:14,16; 105:13;125:8;144:3,15; 151:7;180:19;185:13; 190:2;192:19;196:7; 213:20,21;215:6,14,17; 216:3,4;217:13;219:10; 246:2,2,6,6,7;288:21; 292:5;297:2;308:9; 312:11;322:22;324:7; 325:3,12 study (137) 18:21;25:21,22;38:21; 55:6;75:21;93:11,13; 94:11;99:21;109:8; 112:1;114:12;119:16; 120:7,21;121:18; 127:13;137:16,17; 177:3;198:11,15;199:3, 5,7,9,16;200:13;203:1,1; 204:4,13,21,22;205:11; 206:19;207:7;209:4; 210:19;211:17;214:6,13, 18;215:5;217:14,18; 218:1,9,10,18;219:7,14, 16,21;221:11,19,20; 229:12;233:7;234:4,14, 15;235:9,10,15;236:6; 237:5,10;239:13,16,19, 22;240:4,7;242:21; 244:6;250:18;258:7; 272:18,22;274:1,7,13; 275:14;276:19,22; 277:15,20,21;280:12; 282:18,22;283:1,9; 284:15,16;285:8; 287:20;288:8,9,11,14, 15,15;289:12,15;290:7, 19,22;292:8;294:13,21; 298:3;303:9;304:9,15; 305:20,21;306:9,10,11;	307:3,13;308:7;309:6, 13,15;310:12,18,19; 311:4,18;313:16;319:1; 321:5;329:15 studying (5) 42:3;73:18;121:18; 123:8;184:12 study's (1) 239:21 stuff (10) 46:7,17;168:17; 184:17;208:21;227:19; 240:6;301:11;319:6; 327:19 subclinical (1) 234:11 subgroup (1) 40:6 subgroups (2) 59:3;80:2 subject (7) 98:18;108:1;283:8,10; 284:14;285:17;288:18 subjective (3) 35:16;42:22;43:8 subjects (43) 50:22;57:5;98:15; 99:2,10;106:9;109:17; 110:16;111:8,21;112:1, 7;113:16;114:11,13; 115:1;130:14,17; 132:18;133:2;200:7; 209:8;241:9;244:1; 246:9;252:3,14,14; 253:9,11;260:11; 261:19;277:5,14; 278:15;282:6;285:22; 287:14;288:22;293:17, 20;294:2;324:2 subject's (1) 19:13 sublingual (6) 276:5;277:1,6,10; 287:11;299:9 submit (1) 167:2 submitted (6) 28:21;127:7;165:19; 256:7;293:18,21 subpopulations (1) 25:19 subscale (1) 100:20 subscales (1) 100:18 subsequent (3) 38:2;56:6;258:8 subset (3) 80:22;313:15;314:2 substance (11) 159:12;160:10; 172:13;194:5;214:15, 22;215:1;246:15;248:7;	250:5;254:3 substances (2) 7:12;65:10 substance-use (5) 7:14;186:1;216:9; 218:13;265:18 substantial (1) 19:9 substantially (4) 88:6;184:1;291:4; 309:8 substantiate (1) 71:15 substitute (1) 14:15 success (19) 52:20;57:10;73:16; 74:10;125:22;159:12; 179:6,8;252:14;253:16, 21;254:4,19;255:10,17, 21;321:12,13;322:13 successes (13) 182:11;312:5 successful (6) 25:4;93:2;203:17; 265:22;304:5;310:13 successfully (1) 7:12 sudden (1) 74:5 suffer (1) 311:6 suffering (1) 101:13 sufficient (1) 316:17 suggest (4) 143:21;148:5;210:6; 309:18 suggested (2) 322:4,21 suggesting (2) 192:13;228:14 suggestions (2) 297:7;300:7 suggests (2) 149:18;163:6 suicidal (1) 40:21 suitable (1) 64:12 summarize (5) 67:5;189:20;203:17; 222:17;229:5 summarizes (2) 224:4;288:19 summary (10) 104:6;106:16;114:15; 128:22;206:5;254:21; 281:19;282:19;288:19; 294:9 summer (1) 175:22
--	---	---	--	--

super (2) 150:13;329:19	12:18,19,21;13:1; 14:21;251:9,11;259:11	122:7,7,16,21;123:13	179:17	185:20;195:1,1;196:8; 198:5;209:1;212:9; 240:5;271:7,14;279:15; 290:4;314:6;331:8
supplement (5) 153:13;198:8,13; 212:19;307:14	survive (12) 15:3;16:11;35:20; 36:2;67:22;87:12,17,17, 18;91:8,10,11	tabular (2) 281:19;282:19	tend (13) 8:6;47:17;49:22;50:1, 20;51:2;58:3;131:10; 158:6;164:22;167:16; 180:3;324:17	theoretically (2) 116:13;296:16
supplemental (5) 276:9;277:10,12; 278:3,19	survives (1) 14:16	talk (56) 14:17;21:8;34:6;37:4, 6,17,21;38:2;46:8,17; 67:12,20;68:10,10;69:8; 71:11;77:3;78:3;87:4; 98:6;99:14;109:21; 110:15;112:4;119:22; 123:9;129:16,19,21; 134:18;153:18;154:7; 155:17,20;156:2; 159:10;161:4;164:10; 168:19;170:16;177:10; 190:19;191:13;212:20; 224:18;263:1,4;266:9; 271:12,13;272:8; 295:19;296:6;325:15; 328:19;330:12	tendency (1) 262:18	therapeutic (3) 303:14;312:1;316:9
supplemented (1) 39:14	susceptibility (1) 158:3	talked (9) 71:11;74:22;152:9; 157:16;173:19;213:12; 264:8;268:11;308:10	tends (4) 136:18;164:13; 179:22;324:19	therapies (7) 100:8;214:9,9;222:3, 10,15;224:8
supplements (4) 196:14;198:7,10; 256:6	susceptible (2) 163:22;166:18	talking (21) 11:4;76:20;129:17; 131:3;132:6;137:21; 140:16;155:7;156:6,8; 157:8;159:9;161:3; 174:6;176:12;210:10; 212:18;261:16;281:8; 306:13;309:18	term (8) 21:7;66:16;81:19,21; 102:16;170:4;263:14; 302:2	therapy (11) 198:18,19;199:13,14; 200:13,17;213:9; 217:19;246:10;264:14, 19
support (19) 16:14,20;18:6;26:4,6, 13,14,20;28:7,21;60:1; 66:18;89:11;131:17; 193:11,18;197:13; 210:3;233:19	suspicious (1) 299:6	talks (7) 11:8;34:4;67:5,11; 71:10;290:5;330:16	termed (1) 216:17	therefore (3) 16:8;80:17;289:10
supported (4) 106:6;193:15;197:21; 240:7	sustained (1) 275:21	tally (1) 142:8	terminology (3) 9:9,10,20	thinking (24) 24:4;62:1;82:18;90:8, 22;92:3,5;94:21;95:5; 118:16;119:4;120:1; 125:12;131:10;147:3; 156:10;160:3;177:20; 224:5;225:8;229:2; 305:10;306:18;314:5
supporting (1) 27:11	Sweden (1) 204:14	target (13) 7:12;19:3;160:22; 171:2;233:18;276:7; 277:7;287:10,14;299:10, 12,14,16	terms (35) 9:19;14:18;15:5;16:4; 21:21;89:6;92:3,12,21, 22;95:6;102:6,15;107:5; 113:15;136:16;137:6, 16;146:10;147:4; 148:18;155:19;159:1; 173:19;179:20;180:5; 184:6;213:7;216:6; 218:22;219:11;261:8; 305:12;306:9;307:6	thins (1) 52:13
supportive (4) 27:8;40:7;163:3; 198:19	Swedish (3) 206:19,22;208:5	targeting (1) 160:21	terrific (1) 147:13	third (12) 49:4;77:12;118:21; 124:22;200:2,3;219:4, 21;234:20;245:12; 252:9;257:18
supports (2) 258:2;322:10	switch (2) 67:4;187:3	taught (2) 45:20;290:12	tertiary (1) 150:22	Thirdly (1) 274:6
suppose (1) 120:18	switched (1) 299:17	taxis (1) 6:19	tertiles (1) 57:14	though (30) 29:11;34:3;55:10; 66:2;70:8;101:1;107:3; 109:15;114:3,18; 116:14;121:15;125:13, 15;126:10;144:18; 174:9;190:8;191:5; 262:22;264:15;281:5; 284:12;285:22;289:10; 293:7;302:9;313:15; 316:9;329:18
supposed (1) 268:19	symptom (3) 28:4,5,11	team (5) 97:2,6;107:19;175:8; 272:2	test (24) 15:18;16:2;45:16; 68:5;78:14;93:15; 132:20;137:20;169:4; 184:16;186:7;212:8; 235:12;236:2;240:18, 19;242:10,14,19;243:8; 244:11;248:2;296:18; 325:9	thought (40) 25:18;42:8,9;54:17; 58:7;67:10,17;68:9; 69:1,19;70:3;71:20; 72:10;74:6;76:7;81:4; 90:17;100:21;101:13, 19;110:4;120:6;128:2; 129:16;148:8;162:8; 166:8;174:17;177:21; 189:8;205:1;210:1; 217:3;231:7;233:1; 252:8;287:9;305:19; 309:12;319:15
supports (2) 258:2;322:10	symptomatology (1) 43:3	teasing (1) 87:5	tested (6) 59:6;108:19;151:19; 184:14;246:5;308:22	thoughtful (1) 309:1
suppose (1) 120:18	syndromes (1) 41:4	tech (1) 61:18	testing (10) 38:1,2,22;44:20; 78:22;143:14;181:17; 184:13;214:12;215:15	thoughts (9) 34:11;71:9;80:10;
sure (42) 8:21;18:11;25:10; 36:10;58:18;60:7;64:5, 22;70:20;73:1,5;80:9; 81:5;83:16;84:20;85:3; 89:10;95:8;104:6; 112:16;115:18;116:7; 123:22;126:9;132:21; 143:13;151:14;157:5; 184:20;187:4;192:8; 211:8,16;220:7;244:5; 260:4;270:2;298:11; 301:16;307:8;308:8; 324:14	Syndrome (7) 41:7,12;43:4,7,18,22; 94:2	technically (1) 305:3	tests (3) 135:19;200:6;243:7	
surprising (8) 108:15;200:11,16; 201:14,17;220:9; 224:19;322:20	synonymous (1) 26:8	technology (1) 146:12	Thanks (28) 61:21;72:18;74:19; 76:15,18;81:12;87:8; 96:5;147:11,13;174:16, 16;179:10;184:8;	
surrogate (10) 34:15;35:8,21;64:12; 69:4;75:14;134:21; 233:16;292:16;303:3	system (5) 146:7;159:17;219:9; 231:3;326:13	telephones (1) 208:20		
surrogates (5) 14:13;16:12,17;36:6; 177:2	systems (1) 326:3	tells (4) 36:7;94:5;116:17;		
survey (1) 105:21	systolic/diastolic (1) 138:13			
surveys (2) 105:16;119:18	T			
survival (8)	table (7) 121:16,22;124:6; 237:6,6,12;238:3			

178:4;179:11;186:5; 245:1;300:16;305:16 thousands (1) 182:5 threat (1) 308:12 Three (39) 41:6;48:21;57:1;77:9, 14,20,20;78:1,2;99:12; 103:19;109:16;118:16; 122:12;129:4;145:9,11; 154:21;155:1,18;164:9; 166:21;169:16;171:16; 177:15;181:17;185:22; 196:15;197:18;215:22; 225:4,5;227:10;234:15; 241:1;245:6;277:21; 288:14;307:16 three-quarters (2) 205:7;207:1 three-stage (2) 41:12;71:13 threshold (8) 130:11;192:8;202:7,8; 203:7;232:7;244:14; 282:7 thresholds (1) 273:21 threw (3) 45:15;54:4;266:2 throughout (3) 284:11;287:21;289:8 throw (3) 55:10;76:7;183:11 thus (2) 33:17;59:6 tight (1) 32:14 timeline (8) 52:15;137:2;142:22; 165:9;167:4;215:2; 259:1,5 timelines (1) 32:15 times (16) 33:19;52:14;97:18; 116:7;159:20;164:9,15; 165:1;166:2;181:17; 190:6;214:12;245:22; 274:10;278:7;296:12 timing (4) 164:5,8;166:16; 174:22 tip (1) 44:5 title (3) 196:5;271:13,16 titration (1) 113:4 today (23) 5:21;11:13,14;29:10; 37:4;46:8;83:10;96:14; 103:13;127:1;153:8,18;	175:16;192:22;194:7; 265:9;272:1;292:18; 306:14;308:10;327:10; 329:4;331:6 toes (1) 330:22 together (15) 8:8;25:12;41:4,9;52:3; 54:2;58:7;94:20;95:10; 97:7;102:13;107:11; 142:13;155:16;256:19 toilet (1) 266:2 told (3) 105:19;240:6;293:9 Tom (4) 51:15;105:13,19; 192:14 tomorrow (9) 5:21;6:19;8:4;87:4; 164:11;181:22;325:16; 327:11;330:8 ton (1) 222:16 tonight (1) 331:8 tons (2) 165:6,13 took (23) 38:22;43:5,10;45:14; 49:17;54:2;56:7;69:18; 101:6;102:18;103:15; 120:21;127:19;128:2; 150:1,9;187:5;218:13; 220:13;235:8,9;236:1; 266:1 tool (18) 7:15;24:3,9;32:18; 33:7,17;36:22;39:2,3,6, 10;80:14,14,19;82:2,5; 234:9;329:3 tools (2) 33:5;95:3 tool's (1) 20:21 top (5) 55:6,17;136:16; 226:14;290:17 topic (1) 67:15 topiramate (19) 56:20,21;57:2,6,7,10, 12,16;59:5;75:20,21,22; 76:5,7;130:16,19;133:8; 134:4;136:5 total (22) 28:4,10;45:3;46:16; 99:1;110:16,17;111:19; 112:2;114:10;133:5,11; 134:3,4;136:18;143:7; 207:10;219:1;236:12, 21;246:8;317:9 totally (2)	77:22;154:13 touch (1) 10:20 touched (2) 68:13;69:2 tough (2) 77:13;172:18 toward (4) 180:17;183:14; 285:16;294:16 towards (5) 88:10;150:4;263:1; 273:13;282:15 toxicities (1) 18:12 toxicology (11) 245:22;278:8;283:9, 12;284:5,14,22;285:2, 21;298:10;302:5 track (2) 107:20;175:10 tract (1) 120:16 trade-off (1) 176:21 trade-offs (1) 35:12 traditional (3) 16:15;28:14;265:20 traffic (1) 122:5 train (2) 314:13,14 trained (3) 45:13;199:16;244:10 training (1) 206:3 trajectories (2) 167:22;248:16 transcript (1) 6:8 transformation (1) 182:3 transition (1) 81:17 transitioned (1) 82:7 translate (7) 35:22;65:18;142:2; 156:14;292:10;302:22; 303:3 translation (1) 211:4 Translations (1) 8:20 transmucosal (1) 276:6 transparent (1) 270:15 trashed (1) 233:1 travel (1) 5:14	treasure (1) 233:3 treat (9) 44:2;54:17;64:7; 66:14;73:12;74:12; 90:14;91:16;96:16 treated (3) 105:18;277:6;322:11 treating (6) 42:7;74:1,3;159:12; 162:2;233:8 treatment (317) 12:2,13,17;14:17,18, 20;15:1,7,7,10;16:5; 17:12,14,21;18:1,1,21; 19:2,7,10,17;20:5;21:21; 24:15;25:8,15;27:22; 28:17;31:22;35:19; 37:13,15;38:17;40:5,16; 41:14,21;42:1,6;47:21; 48:20,21;49:3,9,14;50:7; 51:3;52:5,20;55:19; 56:3;58:15;66:13;74:6, 13,14;79:15,20;80:16; 86:8,15;87:6,7;91:20; 92:12,21,22;93:2,9,15; 94:14;99:2,13,21;101:7; 102:5,12,20,22;103:12, 17,18;104:2,4,13;105:3, 8;106:20;107:8;109:14; 110:4,20;111:1;116:13; 120:5,5,22;127:17; 128:4;132:9,17;133:12, 16,20;134:14;135:1; 151:19;152:13;154:16, 18;158:16;159:21; 160:2,13;161:13; 162:14;163:8,9,14; 169:12;170:12,13,17,18; 173:8,11;184:12,15; 186:6,20;199:1,11,20; 201:1,1;202:12;205:16, 18,19;206:15;207:20; 208:11,14,15;209:13; 210:18;211:11;212:6; 213:4;214:5;218:2,2,11, 11;219:20;220:1,3; 221:4;223:20;224:15,17, 19;225:1,6;228:15,22; 229:18;230:14,18,20; 231:2,5,11,21;232:16, 20;245:9,11;246:22; 248:15,17,18;249:2,6, 14,15;250:1;251:10; 252:4,5,6,16;253:1,1,3,4, 5,6,7,8,9,16,17,18; 254:11,12;255:1,3,14, 16,19,21;256:1;258:2; 261:13,21;264:2; 267:15;268:16,17,18,21; 269:14,18;271:22; 272:16;273:2,4,10,19, 22;274:6,7,12,17,17;	276:3,4,12;278:11,13, 16;279:7,19;283:7,7; 284:8,11,13,20;286:11, 12;287:5,17,22;288:3,6, 17;289:1,6,9,10;290:8, 11;291:5,6,11,13,16; 294:10,17,19,19,20,21; 295:4,5;298:14,20; 299:9,20;300:18; 301:19;302:2,8,10,11, 18,19,22;303:4,17,21; 304:1,4,7,11,16,18,21; 305:14;307:2,4;309:22; 310:6;311:18;314:15; 317:16,21;320:18;321:8, 10,14;323:8;325:5; 326:12;329:11 treatment-failure (1) 285:11 treatment-predicted (1) 202:1 treatments (17) 72:22;93:1,18;152:11; 154:14;158:16;160:21; 171:6;176:1;185:9,10, 17;198:17;199:2;207:7; 210:17;303:13 treatment's (1) 205:20 tree (1) 241:20 trees (1) 241:5 trend (3) 102:14;247:10;248:8 Trial (125) 8:20;12:20;18:8; 24:17;25:20;49:1,8; 50:5;51:18,22;52:22; 53:8,12;54:18,19;56:6, 16,18,22;57:4,6;59:9; 62:17;65:12;66:9;72:1; 74:10;76:1,3;77:2; 79:19;80:20;84:1,88:4; 93:7,7;94:12,15,22;97:2; 99:20;109:1,3;110:2,8, 19;112:5,5,6,15,15; 113:7,8;127:19;130:16; 133:8;134:4;136:5,7; 137:1;139:19;140:15, 18;141:1;144:17;147:6; 161:6;162:1;165:15; 167:9,10,17;168:7; 170:19;177:5;179:3; 191:16;196:20;197:1; 214:7,18;217:22;218:1, 9,12;222:13;232:16; 233:14;263:21,21; 264:20;265:15;266:4; 269:17;273:11,13,15; 274:9;280:16;281:18; 285:14,15;286:1,16; 294:16;297:14;301:18;
--	---	--	---	---

<p>302:13;306:5,7,19,21, 22:307:5,6;308:16; 313:2,14,21;314:16; 315:12;318:21;319:22; 320:9;329:16</p> <p>Trials (165) 5:7;7:10,18;9:3;12:1, 7,22;14:7,13;17:5;18:5; 19:4,11;22:5,8;23:16; 24:21;27:15;31:3,8,14, 22;32:7;33:9;34:12,16; 35:5;37:10;38:4,17; 42:19;49:5;50:11;51:4, 5,5,9,20;52:1,3,6;53:13; 54:11;56:21;57:1;58:2, 4,22;59:16;60:16;62:15, 15;63:13;71:6;72:6; 74:8;80:11;96:16,20,22; 99:13;103:10;108:5,9, 10,18,21;114:19;118:16; 119:11,12,13;122:12; 130:7,21;132:12,20; 134:8;135:7;136:4; 137:9,14;142:20,21; 143:15;148:16;149:10; 150:19;153:16,19; 155:8;156:4;158:1,7; 162:19;168:5;178:14; 180:4,7,16;183:19; 187:5,19,22;188:14; 191:4;196:7;197:22; 211:10;213:6,18;214:1, 6,14,16;218:21;219:2, 12;220:17;231:17; 245:18;257:13;262:16; 263:14,15,22;264:11,12, 14,15,17,19;265:16,19; 268:3;270:20,20; 271:19;272:6;273:4; 274:14;275:16;276:16, 21;277:2,5;278:6; 280:12;282:13;284:18; 285:19;288:19;291:14; 294:14;305:11;306:6,9; 314:5,22;315:3;319:10, 14;321:11,22;323:16</p> <p>tricky (1) 154:2</p> <p>tried (11) 25:12;41:3,8;108:2; 156:5;197:11,13;215:6; 220:21;265:17;268:21</p> <p>trip (1) 192:7</p> <p>tripled (1) 52:10</p> <p>tripped (1) 172:2</p> <p>trite (1) 326:8</p> <p>trivial (1) 122:22</p> <p>trouble (4)</p>	<p>73:13;208:9;235:22; 325:6</p> <p>true (3) 28:3;167:14;324:4</p> <p>truly (1) 232:16</p> <p>trust (1) 35:14</p> <p>truth (1) 156:2</p> <p>try (20) 71:1;76:10;78:1; 94:13;130:5;142:13; 143:14;181:15;183:15; 186:3;196:16;197:22; 222:17;243:20;263:1; 268:4;269:9,20;270:10; 312:20</p> <p>trying (26) 12:1;44:11;59:11; 64:11;83:22;89:16,17, 18;91:14;118:17; 126:10;138:4;142:5; 146:5;148:10;153:15; 182:10;183:22;186:7; 230:9,15;231:8;258:6; 297:19;307:10;312:3</p> <p>T's (1) 8:18</p> <p>turfed (1) 151:16</p> <p>Turk (1) 8:22</p> <p>turn (8) 13:2;80:13;88:20; 176:2;178:15;196:8; 296:22;320:6</p> <p>turned (2) 44:13;52:5</p> <p>turns (4) 49:19;167:19;178:16; 188:11</p> <p>twice (7) 161:19;164:8;182:16; 264:4;288:21;302:13,14</p> <p>two (79) 24:13;25:6;32:5;34:2, 2;38:14;43:2;45:1,6,7; 46:13;54:10;56:21;57:3; 62:14,17;67:5;71:10; 73:21;77:10,18,18;78:1; 79:4;95:22;98:13; 101:17,18;102:7; 103:15;104:8;105:12, 15;108:20;109:14; 113:13,14;115:11; 116:20;124:8;125:19; 126:11;128:9;132:8; 138:12;140:2,2;143:5; 145:11;147:12;152:22; 156:16,22;165:15; 169:20;177:15;193:15; 205:10;206:3;211:10;</p>	<p>225:1;227:8;234:13; 236:1,5;238:4;241:8; 250:10;253:4,8;256:3; 259:19;265:1;278:14; 290:14;293:10;304:4; 309:4;310:2</p> <p>two-group (1) 218:10</p> <p>two-hour (1) 146:1</p> <p>two-parter (1) 153:14</p> <p>two-shift (1) 132:11</p> <p>two-thirds/one-third (1) 54:22</p> <p>type (10) 20:13;29:4;81:10,18; 115:19;152:4,5;280:14; 311:6;316:11</p> <p>types (14) 12:16;13:2,4,9;14:11; 15:22;99:12;124:15; 129:12;139:3;176:1; 257:21;258:3;309:2</p> <p>typical (3) 296:13;328:14,21</p> <p>typically (1) 80:4</p>	<p>326:21</p> <p>unethical (1) 300:12</p> <p>Unfortunately (3) 55:5;198:7;244:4</p> <p>unique (2) 97:17;305:20</p> <p>unit (2) 140:20;172:12</p> <p>units (2) 172:14;276:1</p> <p>universal (1) 58:4</p> <p>University (8) 9:15;49:1,5;51:14; 83:10;235:22;326:11; 328:17</p> <p>unless (4) 84:2;152:14;240:13; 318:9</p> <p>unpublished (2) 193:5,5</p> <p>unrealistic (1) 65:11</p> <p>unrelated (1) 188:12</p> <p>unstable (1) 110:6</p> <p>unsuccessful (1) 304:1</p> <p>untorned (1) 329:18</p> <p>unusual (2) 22:20;168:19</p> <p>up (128) 6:13;8:14;10:6;41:5; 53:11,17;55:10;61:14; 72:15;75:19;84:8;93:6; 101:14;102:7,8,11; 103:3;104:4,8;106:4,8; 109:18,20;110:13; 111:2;112:17,18;114:1, 7;116:11,14;117:6,18, 21,22;123:12;124:3,6,7; 125:16;126:5,18;127:4; 128:1,11;129:18; 131:12;132:1,7;133:17; 138:14;139:8;140:4; 142:8,10,13;144:4,14; 145:7;147:14,15;149:17, 22;153:5,17;158:3; 159:7;160:9;162:5,8; 164:4;165:3,3,4,16; 167:12;170:11;171:20; 172:9;173:1;175:1; 178:11,17;179:21; 182:4;186:4;189:9,13; 190:7;191:2,5,9;194:14; 196:3;198:8;199:20; 204:11,22;212:20; 214:16,20;216:18; 219:1;220:6;222:4,12; 223:19;230:10;231:6;</p>	<p>232:12;233:20;242:18; 262:8;264:4;265:9; 268:14;270:18;275:22; 280:1;286:9;287:16; 300:13;310:13;315:11; 317:17;324:8;326:19; 328:14</p> <p>update (1) 119:3</p> <p>upon (11) 60:18,21;90:21;130:4; 280:14;292:1;306:5; 307:11,12;312:10;327:1</p> <p>upper (5) 50:20;51:1,2;120:15; 276:9</p> <p>urge (1) 126:14</p> <p>urinalysis (4) 35:4;309:10,19; 323:10</p> <p>urinary (3) 55:19,21;56:3</p> <p>urine (104) 52:18;54:5;58:15,22; 62:13;68:5;77:11;90:2; 165:16;166:20,20,20; 167:2;168:8;169:5,14, 18;170:15;180:11; 181:19;200:5;203:20; 214:12;215:15,20,21,22; 216:13;222:6;229:17; 235:12;236:2;242:10,12, 18;244:11;245:7,9,13, 21;246:18;247:15,17; 248:2,10,14;250:7,12; 252:13,16;254:6,22; 255:15,20;257:16;258:7, 8;264:4;274:2,9;278:6,8, 21;279:7,8,9,21;281:21; 282:4;283:8,12,13,19, 21;284:4,14,21;285:2, 21;286:16;290:2;293:5, 18,21;294:3,5;296:18; 298:10;302:4;307:12; 310:14,14;312:3,17,21; 321:14,16;322:2,3; 323:8;327:1,12,21;328:3</p> <p>urines (47) 52:14;53:9;55:3; 153:20;155:2,4;158:19, 20;163:19;164:2,15,22; 165:18;166:12,16; 168:6;169:21;170:5; 172:19;179:14,16,18; 181:9;199:21;204:19; 205:11;207:9,10,12,16, 21;212:1;215:11; 219:14;227:13;229:12, 22;243:5;279:6,18; 280:2;284:3;286:18,20; 290:16;318:3;322:12</p> <p>urine's (1)</p>
--	---	--	--	--

<p>53:1 use (285) 9:9;12:10;14:12; 19:20;21:7;22:4;25:5, 11,13;27:14;28:21; 29:14;30:16,18;31:2,14; 32:21;35:8;36:5;37:7; 39:21;42:8;45:2;47:14, 15;50:12;53:7,20;54:13; 55:22;58:17,17;60:22; 64:10;65:17,18;66:4,22; 72:7;75:4,9,10,14,17; 76:12;77:19;80:9,20; 81:19;82:4,5;84:13,14; 86:6;88:6,22;90:21; 91:13,16;92:6;94:22; 95:7,12;96:17;97:13; 98:13;106:11;126:3; 137:2;141:4;144:17; 145:1,14;147:4;149:10; 156:4,21;157:7,20; 160:20;161:15;164:14; 165:4;167:8;168:9; 170:4,21;171:9,11; 172:4,8;173:5,6;174:4; 177:1,19,22;179:1,6; 181:14,16,19;182:1,11; 183:13,16;184:1;185:9, 10,11;189:5,16;190:18; 191:15;197:5,5;199:6; 192,22;200:5;201:1,19; 202:1,1,14,14;203:1,3,4, 12,16;204:11;206:3; 207:3;209:8,22;210:11, 14,14;212:15;213:10; 214:15,22;215:1,4,7,9, 20,22;216:7,22;217:8; 218:14;219:5;221:18,18, 19;222:21,21;223:15,16, 21;224:9;225:9,15; 226:3,7;227:7,15,17,19, 20;228:1,3;229:8; 230:12,18;231:10;232:4, 17;233:11,15;234:10,20; 235:12;236:13,15,16,19; 237:11,12,14,15,21; 239:5,15;242:6;244:18; 245:4;246:20;247:16; 248:9,18,20;249:6,14; 250:2,8,13;251:15,16, 17,19,21,22;252:11,15; 254:20;255:6,18,20; 256:11;257:14;258:15, 18;259:5;263:3,9,9; 265:3,12;273:6;274:11; 278:9;280:22;281:4; 282:17;284:11,17;285:7, 18;286:3,5,9,13;287:21; 288:5,10;289:7,8; 296:14,17,18,21;297:9, 12;298:17;302:6,7; 303:2;304:2,3,13;305:8, 14;306:15;307:2,11,12,</p>	<p>14,15,18;308:3,19; 310:7,12;315:2,20; 321:15;322:13;324:18; 326:17;327:9;328:13; 329:7 useable (1) 44:18 used (62) 12:17;14:3,14;16:14; 23:21;26:9;27:8,19; 28:6;31:6,7,8,11,12; 33:8;35:9;53:5,10;61:4; 72:20;73:12;76:2;80:17; 81:10;83:2;89:3;98:16; 100:17;115:14,16; 146:7;162:9;163:20; 167:5;173:17;179:3; 187:14;199:21;202:4; 212:6;215:14;216:4; 220:16;229:6;236:17; 238:5;239:14;246:22; 248:6;250:19;256:5; 258:10;273:9;284:5; 287:8;293:15;295:13; 302:8;303:2;309:6; 328:7;330:21 useful (26) 14:8;23:3;25:17; 29:20;46:1;73:1,9; 83:16;92:15;93:20;95:2; 124:20,21;144:5; 158:21;159:4;160:18; 178:2,11;183:21;184:2; 187:15;226:10;304:21; 305:10;329:22 usefulness (1) 38:3 users (18) 156:19;159:12; 160:10;167:16;172:1,4, 6;177:20;203:13,14,14; 204:10;218:16;234:22; 235:8,11;236:11;328:19 using (59) 22:2;30:15;36:22; 54:22;64:8,11;80:10; 87:2;93:22;98:13; 122:13;146:15;159:22; 161:18;163:10;165:5,5; 167:1;169:4;172:6; 179:7;186:6;199:5,19; 200:2;201:15;206:21; 216:8;220:10;225:14, 22;226:4,5;229:14; 235:19,20;236:2;237:9; 239:6;241:13;269:13; 272:9,17,18,21;275:14; 280:10;283:5;285:17; 292:12;296:10,12,13; 302:4,15,20;316:22; 320:17;321:17 usual (6) 53:11,18;218:2,3,11,</p>	<p>12 usually (8) 14:14;40:19;68:3; 98:16;112:14;167:1; 201:19;289:19 utility (1) 285:4 utilization (7) 104:5;105:4;106:20; 107:8;120:5;159:20; 187:8 utilized (1) 226:4 utterly (1) 188:12 <hr/> <p style="text-align: center;">V</p> <hr/> VA (1) 49:3 valid (3) 154:3;177:1;262:19 validate (19) 118:17,18;120:2,3; 126:10,19;131:3;136:10, 20;138:10,21;139:9,18, 21,22;140:7,15;141:12; 317:18 validated (7) 31:5;130:22;136:15; 138:16;147:9,22;191:18 validating (8) 7:9;80:2;126:17; 130:1,3;135:9;136:12; 192:21 validation (6) 125:16;136:13; 137:22;147:6,19;148:6 validity (25) 20:22;21:1,3,6,7,17; 29:18;30:5,6;37:22; 44:20;45:16;46:6,6,18, 19,20;49:15;50:4;57:19; 68:12;70:13;78:22; 244:11;308:13 Valley (1) 198:9 Valorie (4) 6:21,22;7:1;271:5 valuable (4) 71:8;93:9;124:18; 177:17 valuation (1) 186:9 value (16) 65:1;70:18;71:2;82:2, 15;84:2;90:13;101:10; 122:20;128:3,6;151:9; 172:17;189:18;308:2; 316:13 values (7) 113:17,19,22;116:17, 19,20;247:20</p>	<p>varenicline (13) 109:2;112:4;114:4; 120:21,22;121:10,12; 127:13,15,17;128:6; 149:15;151:19 variability (7) 149:13;152:2,4; 219:10;226:21;247:18; 258:19 variable (8) 58:18;130:10;135:11; 177:19,22;181:2;189:7; 220:7 variables (11) 17:19;18:7;52:17; 66:19;75:7;80:8;174:5; 179:1;223:14;243:20; 246:11 variance (1) 156:20 variation (1) 258:10 varies (3) 146:21;149:11;172:15 variety (4) 9:17;65:20;135:16; 190:11 various (10) 31:16;64:2,14;65:9; 66:3;120:9,14;128:20; 193:8;320:4 vary (6) 71:5;79:21;128:13,15; 147:1;172:4 Vaver (1) 192:14 venue (1) 61:3 verifiable (2) 158:8;170:5 version (7) 29:9;39:5,5;82:13; 190:22;191:3;311:15 versions (1) 39:5 versus (24) 73:20;94:14;106:17, 22,22;120:13;127:22; 191:19;217:18,19;218:2, 11,18;221:13;226:22; 250:8,19;253:7;254:4; 255:10;257:10;267:13, 21;301:22 vetted (1) 81:5 view (2) 29:8;289:14 views (2) 11:17;272:11 Virtually (1) 214:8 virtue (2) 287:18;321:19</p>	<p>visit (1) 204:7 visits (6) 210:10,19,21;274:10; 278:22;290:2 Visual (1) 277:17 Vivitol (15) 206:11,11;207:8; 209:4;309:6,7,8,13,20, 21;313:13,17;320:8; 321:13;322:14 Vogur (2) 206:17;211:1 voice (1) 6:3 Volpicelli (6) 38:20;45:14;61:13; 69:13;85:16;126:19 volume (4) 28:9;106:1;241:1,4 vouch (1) 125:11 vulnerable (4) 319:18,21,22;320:15 <hr/> <p style="text-align: center;">W</p> <hr/> wait (1) 177:21 waiting (3) 62:21;169:5;321:2 walk (4) 15:18;29:11;226:12; 232:12 wall (1) 185:2 wandered (1) 284:19 water (1) 331:1 wave (3) 6:22;10:5;137:18 way (69) 20:1;21:12,22;22:7; 61:12;67:13;69:17;71:3; 75:2;86:22;93:21;103:6; 109:13;113:6;119:1; 127:5,14;138:12; 153:21;154:8,13; 159:15;166:9;167:12; 175:21;176:20;182:10; 194:20;212:7;225:13; 230:7,10;232:1,17; 242:19;244:8;268:5,12, 14;269:5,11;270:13,16, 19;273:14;275:9; 280:21;285:9,9;286:21; 291:10;294:14;298:2, 22;299:8;300:4,5,10,17; 306:14,20;311:3,16; 314:12;315:10;320:7, 21;321:12;322:15</p>
---	--	---	--	---

<p>ways (23) 69:16;92:7;129:1; 139:6;153:20;159:10; 165:17;171:1,21;199:6; 210:6;227:9;263:22; 268:6,12;269:3;270:7; 300:17;312:5;314:21; 323:19;325:22;327:18</p> <p>weakness (1) 44:16</p> <p>weaknesses (4) 50:14;123:11;136:16; 155:21</p> <p>website (8) 6:9;8:14;24:10;28:18; 29:10,12;33:18;199:17</p> <p>Weddington (2) 41:10;79:4</p> <p>Wednesday (1) 312:21</p> <p>week (21) 113:3,3;121:5,5; 164:9,9,16;166:1,2; 169:5;181:17;214:12, 13;224:16;239:21; 242:13,15;246:1;264:4; 274:10;278:7</p> <p>weekly (2) 52:15;246:10</p> <p>weeks (64) 51:7;52:7,21;53:8; 62:15,18;113:2;117:20; 128:5,7;145:11,12; 154:21;155:1;161:13; 163:10;166:11,12; 167:9;169:11,17;170:2, 10;171:19;173:7; 198:22;202:6,8;203:6; 205:10;221:10;222:8,9; 223:17;225:1,4,5; 228:11;229:15;231:13; 246:3,4;248:18;253:1,1, 6,17,18;254:10,12; 255:11,11;258:2; 261:13;263:15,16; 268:17,18;277:9;278:4, 5,10;279:6;322:2</p> <p>weigh (4) 12:6;22:16,22;23:5</p> <p>weighing (1) 22:19</p> <p>weird (1) 118:6</p> <p>Weisner (7) 86:1,1;103:13;119:19; 152:8;184:10;325:1</p> <p>welcome (1) 5:5</p> <p>Welcoming (1) 5:2</p> <p>well-controlled (2) 19:11,21</p> <p>well-defined (1)</p>	<p>19:14</p> <p>well-established (1) 16:13</p> <p>weren't (11) 103:3;110:9;186:15; 191:8;220:7;221:9; 223:19;285:3;286:16; 297:14;298:9</p> <p>what's (27) 17:5;29:15;45:17; 48:13;63:7;89:6,9; 94:21,22;122:10; 123:18;131:20;139:2; 153:15;156:11,12;157:5, 6;162:9;168:18;177:16; 179:1;191:19;292:20; 311:3;328:6;330:19</p> <p>wheel (2) 28:19;29:8</p> <p>whenever (1) 125:4</p> <p>whereas (5) 75:18;101:11;148:13; 149:7;299:21</p> <p>Whereupon (4) 96:6;195:4;271:10; 331:9</p> <p>whichever (1) 83:11</p> <p>whole (18) 38:16;44:18;45:10; 50:1;53:9;54:19;94:13, 15;95:4;110:19;113:17; 162:20;167:11;193:13; 241:4;297:14;325:3; 326:16</p> <p>whopper (1) 317:16</p> <p>who's (7) 11:3;36:21;62:16; 96:8;103:13;126:22; 197:20</p> <p>who've (3) 210:13;257:2;322:11</p> <p>wide (1) 135:16</p> <p>widely (5) 163:20;167:5;172:4; 187:13;229:6</p> <p>wife (1) 325:10</p> <p>willing (2) 163:3;176:13</p> <p>Winchell (10) 65:2,2,8;80:12;175:6, 7,7;193:3;194:6,10</p> <p>wind (1) 194:14</p> <p>window (3) 145:8;190:2;286:22</p> <p>winner (1) 165:21</p> <p>wisdom (1)</p>	<p>178:16</p> <p>wish (4) 5:22;18:9;132:2; 134:16</p> <p>withdrawal (53) 37:6;38:7;39:3,13,22; 40:2,13;41:6,7,12,14,17, 20,22;42:7,10,16;43:3,7, 11,13,21;44:5,10;47:9, 20;48:8,17,19;54:18; 55:15;71:12,18;73:10, 15;74:1,4,12;75:11; 78:10,14,15,20,22;79:3, 9;83:14;93:10;273:16; 277:13,15;288:20;300:1</p> <p>withdrawals (3) 42:5;287:4;289:4</p> <p>withdrew (1) 288:22</p> <p>within (22) 16:12;17:6;25:22; 31:18,22;32:7,10,14; 33:3;35:18;84:14;89:8; 145:8;189:1;196:11; 202:12,14;203:1;214:2; 237:20;257:4;296:16</p> <p>within-study (1) 203:4</p> <p>within-treatment (7) 202:10;225:9,15; 226:7;227:7,15;228:3</p> <p>without (14) 16:17;31:15;36:18; 66:21;88:22;90:15; 96:10;172:6;186:9; 199:10;204:17,18; 232:5;266:20</p> <p>women (2) 99:4;235:15</p> <p>wonder (7) 34:19;42:4;181:3; 239:22;264:17;266:14; 306:6</p> <p>wondered (3) 161:21;178:3;285:10</p> <p>wonderful (6) 55:2;59:11;76:19; 135:8;167:6;175:15</p> <p>wonderfully (1) 164:3</p> <p>wondering (6) 148:3;180:22;187:21; 188:2;257:3;301:8</p> <p>Woody (20) 63:19,19;64:13;65:4, 5,7;144:11,11;149:2,6; 198:3,4,5;209:10; 210:17;211:16;212:9; 296:8,8;324:7</p> <p>word (2) 262:16;283:18</p> <p>words (3) 110:7;276:5;302:3</p>	<p>work (44) 7:9;8:16;29:4;32:12, 20;33:1;59:12;75:15; 77:14;80:19;81:14,18; 82:11;89:12;90:10;97:7; 100:2;107:19;118:9; 127:18;131:2;153:11, 12;157:4;159:1;174:8, 11;175:12,13;183:14; 193:1;196:12,15; 197:13;212:13,18; 230:9;241:3;257:13; 266:10;318:20;320:12, 21;326:11</p> <p>worked (12) 9:6;94:4;103:13; 177:16,16;180:14; 197:18;204:10;309:13; 320:10,11;330:15</p> <p>working (13) 86:4;105:19;110:10; 155:19;159:14;160:4; 170:2;173:11;196:11; 204:21;208:22;219:8; 240:20</p> <p>works (3) 9:2;73:4;279:13</p> <p>workshop (2) 160:6,7</p> <p>world (3) 29:6;100:4;161:19</p> <p>worse (5) 47:9;102:15;248:10; 259:16;299:3</p> <p>worst (1) 161:19</p> <p>worth (5) 91:19;147:3;205:10; 236:1;257:17</p> <p>Wrap (1) 326:19</p> <p>wrapped (1) 308:1</p> <p>write (1) 56:10</p> <p>write-ups (1) 83:13</p> <p>writing (2) 10:6;204:22</p> <p>written (2) 38:20;79:1</p> <p>wrong (1) 233:5</p> <p>wrote (3) 39:1;78:19;162:5</p>	<p>Y</p> <hr/> <p>Y-axis (6) 101:4;211:22;212:2; 281:22;283:10;293:2</p> <p>year (19) 101:17;121:6,6,21; 122:3,9;167:11;174:4; 182:17;187:7;209:5; 213:14;214:16;225:18; 233:22;235:7,8;236:1; 251:11</p> <p>years (25) 14:5;29:4;52:1;53:13, 15;59:22;69:10;97:16; 104:4;155:18;170:11; 175:21;182:16,16; 187:5;193:16;196:13, 14;197:12;198:16; 206:3;213:22;233:21; 265:13;311:2</p> <p>yelled (1) 314:18</p> <p>yellow (3) 102:4;110:18;111:11</p> <p>yes/no (2) 145:5;181:5</p> <p>young (1) 45:14</p> <p>younger (1) 40:12</p> <hr/> <p>Z</p> <hr/> <p>zero (10) 38:8;116:2,11,22; 134:3;141:15;217:7,8; 220:1;225:11</p>
		<p>X</p> <hr/> <p>X-axis (8) 116:9;134:1;281:7,21; 282:3,16;292:4;293:6</p> <p>X's (1) 286:1</p>		